STAR-IDAZ
International Research
Consortium on Animal Health

1. Roadmaps for the development of diagnostic tests and therapeutics for helminths

2. Roadmaps for the development of candidate vaccines and control strategies for liver fluke and nematodes

3. Roadmaps for the development of candidate vaccines, diagnostic tests and control strategies for FMD

4. Roadmap for research to underpin the development of control strategies for ASF

SIRCAH Deliverable 3.4

30/09/2019

Interactive versions of the roadmaps in this report can be found at https://roadmap.star-idaz.net

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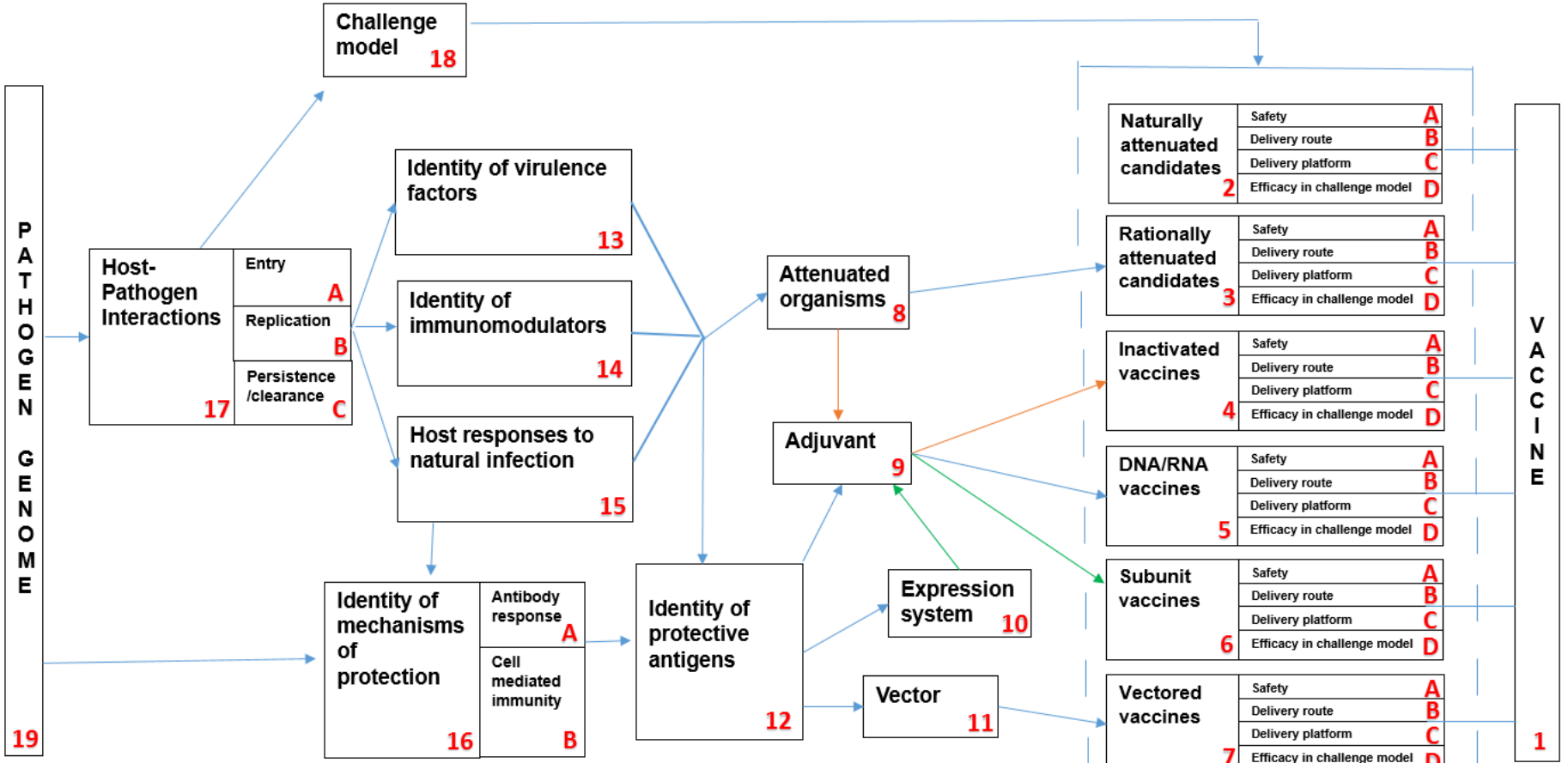
3a) Roadmap for the development of candidate vaccines for FMD



FMD roadmap lead summaries are in draft form until validated by the GFRA

FMD Vaccine - Lead Summary 1

Title:	Development of a genetically stable, effective, FMD DIVA vaccine inducing fast and long-lasting protection and preventing infection after vaccination, for all species, with one inoculation.

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Highly efficacious.
Rapid onset of immunity (0 to 4 days).
Long term immunity.
Prevention of infection after vaccination.
Reduce the need of applying high doses of immunogen produced in the new platforms.
Protection of pigs from FMD.
The development of intradermal vaccines, stimulating dendritic cells in the epidermis to initiate a wide range of immune response, and possibly obtaining "sterile" immunity.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Cross-protection of vaccines.
Better efficacy.
High potency vaccines.
Antigenic variation.
Capsid stability.
Difficulty adapting field strains to cell culture for vaccine production.

Solution Routes

What approaches could/should be taken to address the research question?

Establish protection levels with various candidate vaccine options, including priming with one vaccine and boosting with a different vaccine.
Conduct field studies in endemic situations.

Dependencies

What else needs to be done before we can solve this need?

Development of a cross protective/multivalent vectored vaccine.
Development of a cross protective rationally attenuated vaccine.
Development of cross protective/multivalent killed vaccine.
Development of a subunit vaccine.
Development of DNA/RNA vaccines.

State of the Art

Existing knowledge including successes and failures

Current commercial FMD vaccines consist of inactivated (killed virus) formulated with various proprietary adjuvants formulations. Several new vaccines technologies are being applied to develop new FMD vaccines (marked vaccines, use of vectors to deliver complete empty capsids of FMD and peptide-based vaccines).

Projects

What activities are planned or underway?

Lead Summary 3

Title:	Development of a rationally attenuated vaccine that doesn't persist or is excreted.

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Replicating organisms are likely to give the most appropriate immune response but wild-type virus manipulates the host response. The aim is to reduce the virulence of the organism so that the vaccinated animal can mount a protective immune response.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Generate GM organisms that are viable but lack virulence.
Identify strains that give the greatest cross protection.
Ensure no reversions to virulence.
Ensure that vaccination results in sterile immunity.

Solution Routes

What approaches could/should be taken to address the research question?

Monitoring the immune response following immunisation with the various candidates.
Challenge experiments with the various vaccine candidates, including challenge with other strains.

Dependencies

What else needs to be done before we can solve this need?

The generation of stable genetically modified organisms.
Identity of virulence factors in FMD.
Identity of immunomodulators in FMD.
The availability of a standardised challenge model.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 4

Title:	Development of effective, genetically stable, rapid, DIVA inactivated FMD vaccine that provides long-lasting protection with one inoculation and prevents viral transmission.

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of a highly efficacious inactivated vaccine that provide rapid and long-lasting protection and is safe.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Ensure cross-protection of vaccines, considering antigenic variation.
Improve efficacy.
Develop high potency vaccines.
Improve capsid stability.
Generate a Th1/CTC without a replicating organism.
Improve adaptation of field strains to cell culture for vaccine production.
Prevent infection after vaccination.
Reduce the need of applying high doses of immunogen produced in the new platforms.
Ensure pig protection.

Solution Routes

What approaches could/should be taken to address the research question?

Generation of a range of recombinant viruses expressing protective Antigens from a range of strains.
Monitoring the immune response following immunisation with the various candidates.
Challenge experiments with the various vaccine candidates.

Dependencies

What else needs to be done before we can solve this need?

Identifying protective antigens for pigs.
Identify antigens or administration routes grating “sterile” immunity.
The availability of suitable adjuvants to stimulate strong and fast CTC and VN-Ab responses.
The availability of a standardised challenge model.

State of the Art

Existing knowledge including successes and failures

Current commercial FMD vaccines consist of inactivated (killed virus) formulated with various proprietary adjuvants formulation. Significant steps have been made to improve the quality of vaccines, but there are significant differences between different manufacturers, and vaccines distributed for use in either FMD-endemic regions *versus* FMD-free countries. Three main adjuvant formulations available worldwide: emergency use (high potency) vaccines; oil emulsion vaccines; aluminum hydroxide-adjuvanted vaccines.

Projects

What activities are planned or underway?

Lead Summary 5

Title:	Development of a cross protective/multivalent DNA/RNA vaccine

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of a safe platform for production of a marker inactivated vaccine.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Improve efficacy.
Ensure cross protection (within and without serotype).
Improve duration of immunity.
Improve method of administration.
Generate the desired immune response.

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

Identity of protective antigens.
Availability of suitable molecular adjuvants
The availability of a standardised challenge model.

State of the Art

Existing knowledge including successes and failures

A double marker cDNA-derived Killed FMDV Vaccine Platform is being developed. This vaccine platform comprises a genetically engineered attenuated FMDV backbone, molecularly and antigenically marked by deletion of the Leader protein and conserved B cell immunodominant epitopes to allow serological differentiation of vaccinated from infected animals. Further modifications are the inclusion of unique restriction endonuclease sites for rapid replacement of capsid coding sequences. Although still at the Discovery phase, it seems to present several advantages as compared to conventional FMD vaccine platforms.

Projects

What activities are planned or underway?

Lead Summary 6

Title:	Development of a cross protective/multivalent species-specific subunit/peptide vaccine

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Virus-like particles (VLPs) are non-replicating, non-pathogenic particles that have structural characteristics and antigenicity similar to the parental virus. The structural components of some VLPs have also proven amenable to the insertion or fusion of foreign antigenic sequences, allowing the production of chimeric VLPs exposing the foreign antigen on their surface. The identification of suitable antigens and VLP expression system to develop a cross protective/multivalent species-specific subunit/peptide vaccine.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Address cellular toxicity of FMDV 3C protein, leading to low/variable yields of capsid (partially addressed already).
Manufacture mammalian cell culture systems.
Small size of vaccine antigens that can be incorporated into vaccine.
Define effects on non-humoral aspects of the immune response.
Reduce production costs.

Solution Routes

What approaches could/should be taken to address the research question?

Establishing that there isn't interference between the various antigens.
Monitoring the immune response following immunisation with the various combinations of candidate immunogens.
Challenge experiments with the various vaccine candidates.
If a multivalent vaccine isn't possible then strain specific vaccines based on recognised antigen combinations will be needed.
Use of a VLP expression system to develop a cross protective/multivalent species-specific subunit vaccine.
Production of virus-like particles containing all the desired surface proteins.

Dependencies

What else needs to be done before we can solve this need?

Identify a combination of antigens that would generate protective responses or a common single antigen to which immune responses are normally suppressed.
Identify the most suitable VLP expression system.
The availability of a standardised challenge model.

State of the Art

Existing knowledge including successes and failures

This platform is still in the Discovery phase. The majority of the VLP experimental FMD vaccines constructed to date have not been tested for efficacy in cattle or swine, and those that have been tested have shown only partial protection. Below some examples:

- Hepatitis B virus core particles, self-assemble into capsid particles and are extremely immunogenic, but formation of VLPs can be restricted by size and structure of heterologous antigens.
- Yeast-derived VLP experimental vaccines co-expressing either recombinant bovine IFN, IL-18 or HSP-70 and VLP P1 constructs has been shown to enhance SN and CMI responses in mice, but no livestock vaccine efficacy studies have been reported.
- Baculovirus- and *E. coli*-derived VLP experimental vaccines provide some protection against clinical disease in swine but fail to elicit strong protection against viral replication.
- The generation of VLP experimental vaccines using transgenic plants has shown some laboratory success but no vaccine candidate has been efficacy and safety tested in cattle or swine.

Projects

What activities are planned or underway?

Lead Summary 7

Title:	Development of cross-protective/multivalent species-specific vectored FMD Vaccines

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of a safe effective vaccine that gives broad cross-protection based on a recombinant replicating organism. A replicating organism presenting the protective antigens to cross-protect against a number of strains.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Prevent the development of immune responses to the vector.
Antigenic variation.
Ensure rapid onset of immunity.
Ensure safety in cattle and pigs.
Improve efficacy in cattle and pigs.
Improve potency standardisation.

Solution Routes

What approaches could/should be taken to address the research question?

Identifying the most appropriate vector.
Monitoring the immune response following immunisation with the various candidates involving single/combination of antigens.
Challenge experiments with the various vaccine candidates.
Development of vaccine platforms.
Identify most appropriate route of administration (parenteral/oral/nasal).

Dependencies

What else needs to be done before we can solve this need?

Identity of protective antigens.
Identity of virulence factors.
Identity of immunomodulators.

State of the Art

Existing knowledge including successes and failures

The Ad5-FMD vaccine platform is in the development phase represented by the lead vaccine candidate, Ad5-FMD subtype A24. The Ad5-FMD vaccine platform has several advantages over conventional FMD vaccine platforms. Similar to conventional FMD vaccines, the Ad5-FMD vaccine platform provides serotype-specific and subtype-specific protection against FMDV disease as early as 7 days post-vaccination. Purity, potency, safety, and efficacy testing are still underway.

Projects

What activities are planned or underway?

Lead Summary 8

Title:	The generation of rationally attenuated genetically modified FMD virus

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To generate organisms that are less virulent in terms of pathological changes that they cause and/or their ability to modulate the host's immune responses – rationally attenuated vaccine.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Ensure that the organisms are stable and can be produced in cell culture.
Ensure generation of a protective response.

Solution Routes

What approaches could/should be taken to address the research question?

Generation of infectious cDNA clones.
Generation and characterisation of a range of rationally attenuated organisms (using codon pair deoptimisation).
Immune response to the attenuated organisms.

Dependencies

What else needs to be done before we can solve this need?

Identity of virulence factors and their genes.
Identity of immunomodulators.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 9

Title:	Identifying suitable and physiologically relevant adjuvants to improve the efficacy and safety of current inactivated FMD vaccines

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The discovery of new adjuvants to improve the efficacy and safety of current inactivated FMD vaccines.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Identify physiologically relevant adjuvants generating both a strong VN Ab and a CTC response.
Investigate the relation of adjuvants with the speed and robustness of response, and longevity of protection from challenge.
Investigate if adjuvants could improve vaccine efficacy in pigs.
Technological transfer pipelines between research and industry.
Investigate mode of action of adjuvants.

Solution Routes

What approaches could/should be taken to address the research question?

Immune response to antigens delivered on Nanoparticles.
Immune response following inclusion of various adjuvants with the candidate vaccines including molecular adjuvants for DNA/RNA vaccines.

Dependencies

What else needs to be done before we can solve this need?

Identity of protective antigens.
Identity of mechanism of protection.

State of the Art

Existing knowledge including successes and failures

FMD vaccines formulated with aluminum hydroxide provide satisfactory results in European cattle, but are less effective in pigs. Oil adjuvants were developed to increase the potency of FMD vaccines in pigs. Not much progress has been done in terms of new adjuvants and formulations in the past few years.

Projects

What activities are planned or underway?

Lead Summary 10

Title:	Identifying suitable expression systems for the production of FMD subunit/peptide vaccines.

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The empty capsid, or virus-like particle (VLP), strategy can also be using a viral vector to generate empty capsids *in vitro* to be used as a vaccine antigen. The development of suitable expression systems for the production of FMD subunit/peptide vaccines should be implemented.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Ensure quality of produced peptides.
Reduce cellular toxicity.

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Several VLP systems have been already tested, with promising results:

- Hepatitis B virus core particles, self-assemble into capsid particles
- Yeast-derived VLP.
- *E. coli*-derived VLP.
- Stabilised empty FMDV capsids have been successfully produced in vitro in a baculovirus expression system.
- The generation of VLP experimental vaccines using transgenic plants has shown some laboratory success but no vaccine candidate has been efficacy and safety tested in cattle or swine.

Projects

What activities are planned or underway?

Lead Summary 11

Title:	Identifying suitable vector for the expression/delivery of protective FMDV antigens

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of safe vectors to be used for producing safe, effective, cross-reacting DIVA vaccines for FMD.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Prevent the development of immune responses to the vector.
Ensure the expression of the protective antigens by a replicating organism with the development of VN-Abs and CTC responses.
Create stable genetically modified organisms expressing the desired FMD antigens.
Identify the Ag combination to give widest protection against the various field isolates.

Solution Routes

What approaches could/should be taken to address the research question?

Generation of genetically modifies organisms (viruses or bacteria) expressing the protective antigens of different FMDV strains.
Incorporation of molecular adjuvants.

Dependencies

What else needs to be done before we can solve this need?

Identity of protective antigens.

State of the Art

Existing knowledge including successes and failures

Replication-defective human adenovirus type 5 (Ad5) vectors that contain the capsid-encoding regions of FMD virus (FMDV) are currently used and are promising in terms of efficacy, cross reaction and safety.

Projects

What activities are planned or underway?

Lead Summary 12

Title:	Identifying protective antigens of FMD virus

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The identity of the virus components (epitopes) that the host needs to respond to prevent and clear infection.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Determine what factors define broad protection and broad coverage, through identifying cross-protecting antigens/epitopes.

Enhance antigen production systems that preserve the integrity of the capsid and tertiary protein structures.

Validate statistical tools for the identification of protective epitopes.

Antigen drift within serotypes.

Solution Routes

What approaches could/should be taken to address the research question?

The identity of the antigens that the host is generating Abs to and their role in protection (preventing and clearing infection).

To identify the antigens that are responsible for protective cellular responses.

Identifying possible protective antigens in the virus genome, their expression and trial in challenge experiments.

Dependencies

What else needs to be done before we can solve this need?

The genome sequence of various virus isolates.

Availability of genetic database and epidemiological information for knowing what strains the highest risks to a given country are in order to select a vaccine antigen.

Identity of virulence factors.

Identity of protective mechanisms operating in immune hosts – the role of neutralising Abs and CTCs.

Need to understand persistent infection and carriers, and their role in transmission.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 13

Title:	Establishing the identity of the virulence factors in FMDV that contribute to disease pathology

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Identifying and removal of the factors contributing to pathological changes are essential for generating rationally attenuated vaccines Identify determinants of viral virulence for different serotypes of FMDV in cattle, sheep, and swine.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Identify genetic determinants of virulence.
Study of virulence determinants observed in the field.
Assess role of subclinical infection.

Solution Routes

What approaches could/should be taken to address the research question?

Generation of a range of knock-out viruses and their use in experimental infections to establish the impact of the changes on virulence.

Dependencies

What else needs to be done before we can solve this need?

Host-pathogen interaction.

State of the Art

Existing knowledge including successes and failures

New molecules involved in the FMDV life cycle have been identified, some may have a role in virulence such as: RHA, Sam68, JMJD6, Gemin5, Beclin 1, Vimentin, DCTN3 and LYPLA/ATP1. However, it is still not clear which host factors are critical for virulence.

Projects

What activities are planned or underway?

Lead Summary 14

Title:	Establishing the identity of the immunomodulatory factors/evasion mechanisms of FMDV

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Identify the immunomodulatory factors/evasion mechanisms of FMDV.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Determine FMDV immune evasion mechanisms: is diversity a virulence factor?
Identify the mechanisms of immunomodulation and the virus proteins responsible.

Solution Routes

What approaches could/should be taken to address the research question?

Studying the biological significance of the antagonistic events under physiological conditions of FMDV infection, preferably in primary cells from relevant target tissues of natural host species.
Generation of a range of knock-out viruses where the genes for various immunomodulatory factors or other stealth mechanisms have been removed and their use in experimental infections.

Dependencies

What else needs to be done before we can solve this need?

Host pathogen interaction.

State of the Art

Existing knowledge including successes and failures

FMDV can evade innate immune responses through its ability to shut down cellular protein synthesis, including IFN type I, in susceptible epithelial cells. While earlier work identified roles for FMDV L(pro) and 3C(pro) in inhibiting the production of type I IFN, new data show that 3C(pro) can also impede signalling downstream of the type I IFN receptor. Recent research also identified distinct roles for the two forms of L(pro) that arise during viral replication, Lab(pro) and Lb(pro), with implications for our understanding of this protein as a molecular virulence factor.

Projects

What activities are planned or underway?

Lead Summary 15

Title:	Characterising host responses to natural infection

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Characterising the host's responses to natural infection to help define how the pathogen evades or suppresses the protective responses.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Identify the mechanisms responsible for animal survival following infection, including the mechanisms involved in the natural response to infection (innate immunity).

Solution Routes

What approaches could/should be taken to address the research question?

Perform studies in the different hosts.
Perform studies on natural survivors.
Investigate the role of persistent infection and carriers in FMD perpetuation in natural environments.

Dependencies

What else needs to be done before we can solve this need?

Improve understanding of the host pathogen interaction including persistence versus clearance.

State of the Art

Existing knowledge including successes and failures

Natural infections in the field are always very different than experimental results obtained in controlled environment with clone-derived viruses from the laboratory. Host response to natural infection should be further investigated.

Projects

What activities are planned or underway?

Lead Summary 16

Title:	Identifying protective mechanisms in FMDV infected animals

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Identify the mechanisms operating in immune animals, establishing the role of antibodies and cell mediate immunity in preventing and clearing FMDV infection.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Identify mechanisms of virus neutralisation, epitope mapping, and protein structural constrains governing immunological recognition.
Establish consistent ways to measure and evaluate protection.
Discover the mechanisms that lead to the establishment and longevity of memory responses.
Characterise mucosal immune system of FMDV-susceptible species.
Understand how mucosal and systemic immunity combine to provide effective protection following vaccination or during infection.

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

Improve understanding of host virus interaction at the level of the infected cells.
Genome sequence of various FMDV isolates.

State of the Art

Existing knowledge including successes and failures

Recent studies have shed light on the mechanisms underlying formation of the bovine B- and T-cell response; there is also a greater understanding of the significance of non-neutralising antibodies during FMDV infection and the interactions of antibody-bound virus with immune cells.

Projects

What activities are planned or underway?

Lead Summary 16A

Title:	Defining the key aspects of antibodies in protection to FMDV

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To define the role of antibodies in FMD protection.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Develop vaccine that could override maternally derived antibody upon the neonate's ability to respond to FMD vaccination.
Define the roles of non-neutralising antibody-bound virus complexes with immune cells in vivo in target species.
Determine how to achieve optimal IgG class ratios and other determinants protective capacity.
Setup test to differentiate between Ig isotypes.

Solution Routes

What approaches could/should be taken to address the research question?

Passive transfer experiments and challenges.

Dependencies

What else needs to be done before we can solve this need?

Details of host-pathogen interaction.

State of the Art

Existing knowledge including successes and failures

Protection can be achieved with low Ab titres (memory cells), is the quality of the antibodies what determine cross-reactive responses (avidity), and other cytokines (IFN, IL-12, IL-15).

Projects

What activities are planned or underway?

Lead Summary 16B

Title:	Defining the role of cell-mediated immune responses in protection to FMDV

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Establish and define the importance of cell-mediated immune response to FMDV.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Define immunological parameters involved in protection against homologous and heterologous infection, besides antibody titres.
Investigate the importance of T-cell responses to optimise vaccine-induced immunity.
Explore potential of CD8 T-cell stimulation, especially in ruminants.
Investigate the role of mucosal immunity.

Solution Routes

What approaches could/should be taken to address the research question?

Transfer experiments

Dependencies

What else needs to be done before we can solve this need?

Details of host-pathogen interactions.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 17

Title:	Characterising Host Pathogen interaction in FMD infection

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To gain an improved understanding of how FMDV **enters**, **replicates** and **survives** in and is **released** from infected cells.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Provide a holistic model for challenge model that helps to define tropism.
Explain the mechanisms that govern permissiveness to infection of distinct species- breeds, and how do these factors apply to variability of virulence across cattle breeds.
Determine the mechanisms of emergence of viruses (why some and not others?).

Solution Routes

What approaches could/should be taken to address the research question?

Exploitation of precise, quantitative, high-throughput molecular techniques to study FMDV for advancing understanding of pathogenesis at the cellular level.

Dependencies

What else needs to be done before we can solve this need?

Genome sequence of various FMDV isolates.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 17A

Title:	Defining entry mechanisms of FMDV into host cells

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Establishing how the virus enters host cells would indicate a possible route that could be blocked by targeted specific immune responses.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Identify virus components that interact with cell surface receptors.

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

There has been recognition of the importance of autophagosomes for FMDV entry into the cytoplasm following cell surface receptor binding, and that distinct internal cellular membranes are exploited for viral replication and immune evasion.

Projects

What activities are planned or underway?

Lead Summary 17B

Title:	Establishing how FMDV replicates in the cell

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To generate knowledge on virus replication.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Investigate virus replication at the point of entrance in animals (how to prevent replication at the primary sites). Investigate the mechanisms that lead to the formation of vesicles and how the infection carries on.

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 17C

Title:	Establishing the mechanisms of virus persistence/clearance from infected cells

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To establish how FMDV result in persistent infection and investigate persistent infection and carriers, and their role in disease transmission.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Define immune mechanisms related to persistence and innate immunity activation.
Define sites of persistence.
Demonstrate if persistence is a dead-end infection or find definitive evidence of the role of persistent infection and carriers in FMD perpetuation in natural environments.

Solution Routes

What approaches could/should be taken to address the research question?

Proteomic approaches in persistent /not persistent cells would allow to detect specific markers of persistence

Dependencies

What else needs to be done before we can solve this need?

Understand the mechanisms of persistence.
The pathogen and host factors that contribute to FMDV persistence are currently not understood.

State of the Art

Existing knowledge including successes and failures

Some mechanisms of persistence at the cellular level (in the soft palate) begin to be understood.

Projects

What activities are planned or underway?

Lead Summary 18

Title:	Better define FMD challenge models for the different species

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To refine and better standardise reproducible FMD challenge model in the different species (especially in pigs).

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Define in vitro homologous and heterologous correlates of protection.
In vitro quality control methods (reduce animal use, at least to reduce number of batches tested, also including ruminants).
Improve reproducibility in pigs' study (*e.g.* point of inoculation, need of trained personnel).
Define dose.
Determine a unique point of inoculation for challenge.
Develop methods for measure the viral clearance during challenge.

Solution Routes

What approaches could/should be taken to address the research question?

Shall not look at individual responses while using grouped animals.
Use of big data, using already available data.

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Many challenge models exist, used for various purposes.

Projects

What activities are planned or underway?

Lead Summary 19

Title:	Gene sequence of FMD strains

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

There are a range of viruses' strains which differ in terms of virulence. Having virus genome sequences is essential for identifying the host pathogen interactions and how this can be manipulated. Establishing the genomic differences of the various strains will assist in the identification of virulence mechanisms.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Understand the bases for functional genomic and predictive genomics.

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?