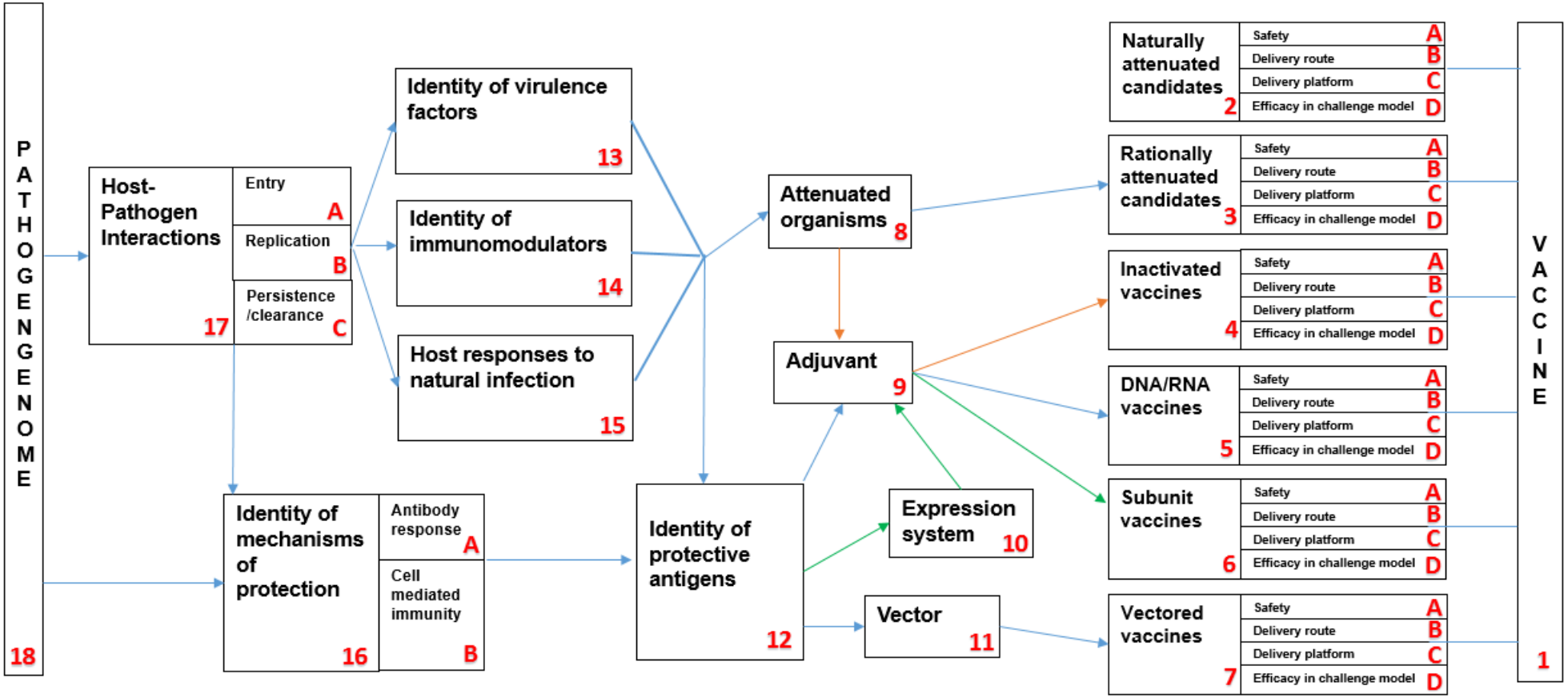
STAR-IDAZ
International Research
Consortium on Animal Health

Roadmaps for the development of candidate vaccines for Brucella, PRRSV and bTB

SIRCAH Deliverable 3.2

Version 1, 31/03/2018

The Secretariat for the STAR-IDAZ IRC (SIRCAH) is funded from the European Union's Horizon 2020 research and innovation programme under grant agreement No 727494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Roadmap for development of a candidate vaccine for Brucella

Version 1, 31/03/2018

Brucella Vaccine - Lead Summary 1

Title:	Brucella (*B. abortus*; *B. melitensis*; *B. suis*) vaccines

Research Question

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

The development of safe effective vaccines against *B. abortus*; *B. melitensis*; *B. suis*, allowing vaccinated to be differentiated from infected

B abortus and *B. melitensis* sometimes infect the same species so the development of a cross protective vaccine for cattle could be useful in some situations

The minimum requirement is that R_0 to <1 in vaccinated herds/flocks but ideally resulting in sterile immunity.

Challenge(s)

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

The development of a better vaccine based on the rational attenuation of the organism or on purified immunogens delivered by various mechanisms.

Vaccines can sensitise animals to current diagnostic tests resulting in false positives.

Solution Routes

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

Establish safety and protection levels with various candidate vaccine options, **including priming with one vaccine and boosting with a different vaccine**.

Modelling level of vaccine coverage required to get R_0 <1

Establishing the impact of vaccination in carrier/persistently infected animals

Dependencies

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

Development of a novel attenuated vaccine that isn't excreted

Development of an inactivated vaccine

Development of a subunit vaccine

Development of a DNA vaccine

Development of a vectored vaccine

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 3

Title:	Development of a novel Brucellosis attenuated vaccine allowing DIVA

Research Question

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

The development of a novel attenuated vaccine that gives better protection and/or improved safety than current vaccines and allows differentiation of infected and vaccinated animals

Challenge(s)

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

Which strain of the various Brucella species to start with

Solution Routes

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

Establishing the immune responses to genetically modified Brucella organisms
Challenge experiments involving animals vaccinated with candidate organisms.

Dependencies

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

The generation of GM organisms where the genes for selected virulence factors have been removed.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 4

Title:	Development of a killed/inactivated Brucella vaccine

Research Question

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

The development of an effective killed vaccine that can be used in pregnant animals.

Challenge(s)

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

Having the protective response involving both Abs and CTC

Solution Routes

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

Generation of a range of recombinant organisms expressing protective Antigens from a range of Brucella species.
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 a combination of antigens for expression by a GM strain of Brucella
The availability of suitable adjuvants to stimulate strong CTC and Ab responses.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 5

Title:	Development of a DNA vaccine for Brucellosis

Research Question

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

The development of an effective DNA vaccine for use on its own or in combination with other Brucella vaccines in a prime-boost combination.

Challenge(s)

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

Solution Routes

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

Establishing the immune responses following immunisation with DNA coding for various protective antigens.
Challenge experiments involving animals vaccinated with DNA fragments identified from experiments looking at the immune responses.

Dependencies

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

Identifying a combination of protective antigens the genes for which could form part of a DNA vaccine
Identifying suitable molecular adjuvants to stimulate strong cell-mediated immune responses

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 6

Title:	Development of a Brucella subunit vaccine

Research Question

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

The development of an effective subunit vaccine for use on its own or in combination with other Brucella vaccines in a prime-boost combination.

Dependencies

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

The availability of suitable adjuvants to stimulate strong cell-mediated immune responses
Identifying expression systems that give correct Antigen conformation

Challenge(s)

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

State of the Art

Existing knowledge including successes and failures

Solution Routes

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

Establishing the immune responses to the various subunits
Challenge experiments involving animals vaccinated with subunit candidate vaccines that resulted in interesting immune responses.
Establishing that there isn't interference between the various antigens

Projects

What activities are planned or underway?

Lead Summary 7

Title:	Development of a vectored Brucella vaccine

Research Question

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

The development of an effective novel vaccine. A replicating organism expressing the correct combination of Ags is more likely to generate the required type of immune response but as it would have a restricted combination of Brucella antigens it is unlikely to give false positive test results in the standard skin test

Challenge(s)

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

Generating a strong protective immune response
Preventing the development of immune responses to the vector

Solution Routes

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

Establishing the immune responses to Brucella antigens following vaccination with the vectored vaccine.
Establishing the immune responses to the vector
Challenge experiments involving animals vaccinated with candidate organisms.

Dependencies

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

Identifying a combination of antigens for expression by a vector or a common single Ag to which immune responses are normally suppressed
Identifying a suitable vector

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 8

Title:	Rationally attenuated genetically modified Brucella organisms

Research Question

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

Rational attenuation of Brucella by removing virulence genes so that it protects against infection but doesn't cause disease.

Challenge(s)

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

That the GM bacterium is stable and can be grown in culture

Solution Routes

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

Removal of one or more virulence genes and establishing viability and virulence/safety and immunogenicity of the resulting organism

Dependencies

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

Identity of virulence factors
Identity of immunomodulatory factors in the bacterium

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 9

Title:	Identifying suitable delivery systems for subunit vaccine candidates, killed bacteria and DNA vaccine candidates

Research Question

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

Generation of an optimal immune response to the various sub-unit candidates, killed bacteria and DNA candidates

Challenge(s)

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

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
Molecular adjuvants for DNA candidates

Dependencies

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

Identity of protective mechanism and antigens

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 11

Title:	Identifying suitable vector for the expression/delivery of Brucella protective Antigens

Research Question

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

Generation of a protective responses without the presence of possible virulence. Replicating organisms are likely to give the best immune response but attenuated organisms may have excessive virulence causing safety concerns.

Challenge(s)

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

That the Brucella antigens are presented by a replicating organism in a manner that will generate protective immunity

Solution Routes

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

Generation of genetically modifies organisms (viruses or bacteria) expressing possible protective antigens of Brucella. Preparation of bacterial spores with the possible protective antigens of Brucella adhered to the surface.

Dependencies

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

Identity of the protective antigens

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 12

Title:	Establishing the identity of protective antigens of the various Brucella species

Research Question

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

The identity the Brucella components that the host needs to respond to to **prevent** and **contain** infection

Challenge(s)

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

Differentiating protective antigens from other antigens that the host is responding to which may be assisting the bacterium evade the hosts' responses at a particular stage of infection.
Identifying common antigens across the various Brucella species
Immunogenicity vs virulence

Solution Routes

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

To identify the antigens that are responsible for protective cellular responses.
The identity of the antigens that the host is generating Abs to and their role in protection (preventing and clearing infection).
Identifying possible protective antigens in the Brucella genome, their expression and trial in challenge experiments

Dependencies

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

Identity of protective mechanisms operating in immune hosts – the role of cell-mediated immune responses and Abs.
The genome sequence of various virus isolates

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 13

Title:	Identification of the Brucella virulence factors 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

Challenge(s)

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

Immunogenicity may be linked to virulence

Solution Routes

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

Generation of a range of knock-out bacteria where putative virulence factors have been removed and their use in experimental infections

Dependencies

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

Improved understanding of Brucella - macrophage interaction – Brucella and macrophage gene expression in different in vivo environments (macrophages from naïve, immune and carrier hosts)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 14

Title:	To establish the identity of the immunomodulatory factors and stealth mechanisms operating in Brucella infections

Research Question

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

Pathogens manipulate the immune responses of the host in an attempt to survive. Establishing how the various Brucella species manipulate the host's immune response will allow these factors to be removed and thus allow the hosts immune system to react to the organism in a different way, possibly enhancing protection

Challenge(s)

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

Identifying deleterious immunomodulatory factors from ones that may be beneficial.

Solution Routes

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

Generation of a range of knock-out Brucella organisms 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?

Improved understanding of Brucella-macrophage interaction – Brucella and macrophage gene expression in different in vivo environments (macrophages from naïve, immune and carrier hosts)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 16

Title:	To identify protective mechanisms in Brucella-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 Abs and CMI in **preventing** and **containing** infection.

Challenge(s)

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

Solution Routes

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

Characterising the innate immune responses of infected animals.
To identify the role of CMI and Ab in providing protection against infection – passive transfer experiments; identity of cell types responding in recall responses.
To establish the role of the various cell types and cytokine responses in preventing/clearing infection
To characterise the cytokine and cellular responses in latency and carrier states.
Identify biomarkers of immunity

Dependencies

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

An improved understanding of host pathogen interaction at the level of the infected cells.
The genome sequence of the various Brucella species, including s19, Rev 1 and RB51.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 17

Title:	Host Pathogen interaction in Brucellosis 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 Brucella species **enter**, **replicate** and **survive** in and are **released** from infected cells

Challenge(s)

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

Brucella species infect macrophages which are an important contributor to the immune response so establishing how the bacterium interacts with macrophages is central to identifying the protective mechanisms and how the virus evades them.

Solution Routes

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

Brucella species and macrophage gene expression(transcriptome/RNA sequence data) in different in vivo environments (macrophages from naïve and immune hosts and in carrier animals)
Compare response where macrophages are infected with different Brucella species and strains, including s19, Rev 1 and RB51 looking at gene responses of the macrophage and the bacterium.
Comparison of the macrophage-bacteria response following clearance, in latency/carrier states and in active infections.
Identify disease stage biomarkers

Dependencies

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

The genome sequence of the various Brucella species, including s19, Rev 1 and RB51.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?