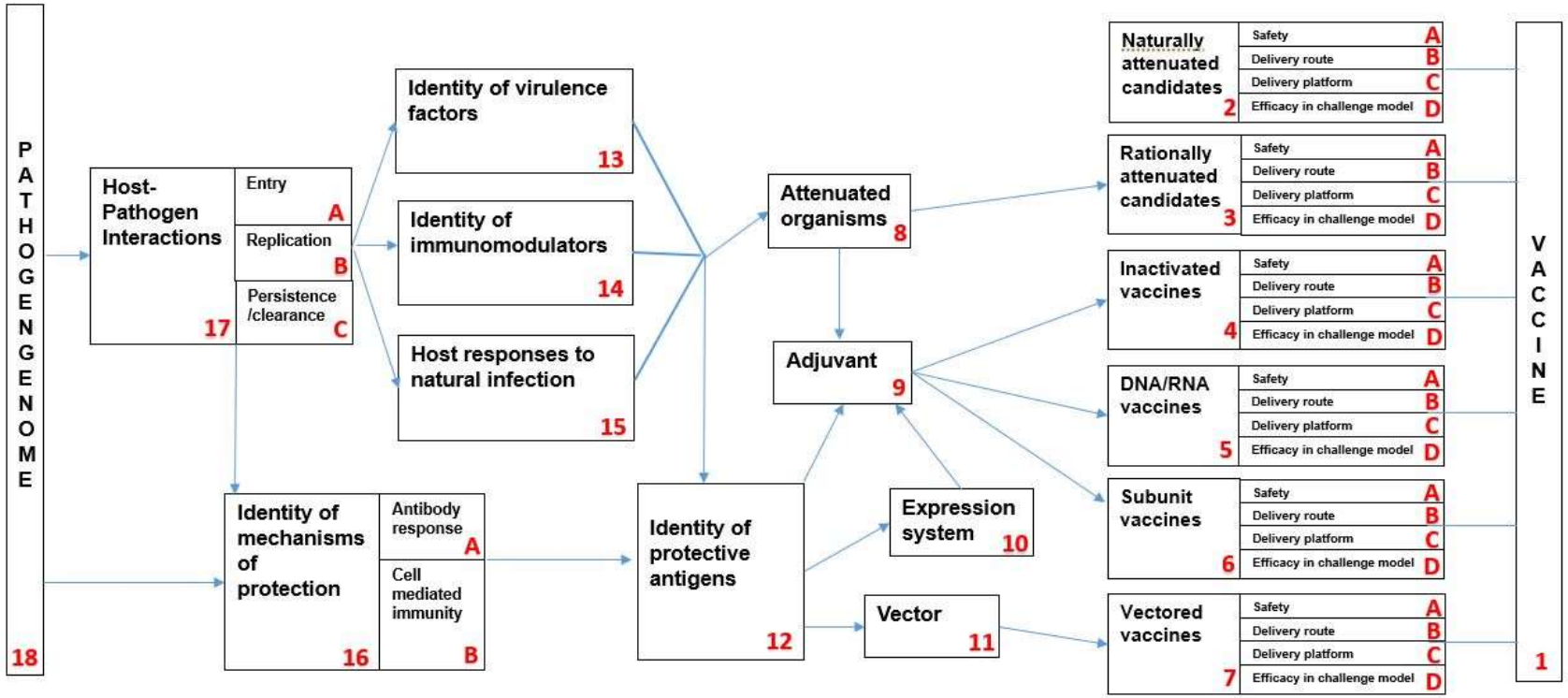
STAR-IDAZ
International Research
Consortium on Animal Health

Roadmap Lead Summaries

Disease/pathogen	Influenza					
Roadmap type	Vaccine Development					
Version: Date	Influenza V1	13/03/2023				

Roadmap for Vaccine Development



Lead Summary [1] - Vaccine

Research Question

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

Develop vaccines with DIVA tests that can be rapidly modified and suitable for mass - administration such as spray, feed or water or *in ovo* application

Mucosal vs systemic protection vaccine

Vaccine protection whole year or specific period of time or season.

Develop potent vaccines for less immunogenic influenza subtypes (e.g. H9, H7)

Development of protective vaccines to prevent outbreaks of influenza in poultry, horses and swine

Challenge(s)

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

Develop and transfer a process to select and update antigenic epitopes in vaccines based on regional circulating influenza viruses

Develop and validate DIVA tests for specific vaccine technologies

Develop and validate multi - species vaccine platforms that are broadly cross-protective: a universal flu vaccine

Detection systems for vaccine failure

Understanding the role of vaccines in driving escape mutations, and how to prevent them

How to evaluate levels of residual virus in vaccinated animals (Vaccination may not result in sterile immunity)?

Quick development and scale-up of vaccines

Correlates of protection: what are the minimum levels of HA antigen-specific antibodies (Hi, ELISA/or VN) of each of the different formulations of unconventional vaccines e.g. (vectored/ subunit) that could induce complete protection from clinical diseases as well as hidden impacts such as reduction in egg production or compromised resistance from other respiratory infections?

How to evaluate levels of residual virus in vaccinated animals (ie is lack of sterilizing immunity is a concern)

Develop appropriate vaccine protocols (How many doses of each vaccine H5, H7 or H9 or H6?Single or multivalent vaccine?)

Is there a practical way to vaccine wild birds?

Vaccination should be acceptable for international trade

What is the underlying driver for increased breadth of cross-protection?

Solution Routes

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

Testing of nucleic acid-based, vectored, inactivated or subunit vaccine candidates

Assessment of novel vaccines according to their ability to prevent infection and transmission for prolonged periods post-immunization

Vaccine performance under field conditions/studies that validate laboratory models of vaccination by comparison to field conditions
Novel antigen / vaccine designs in industry
Vaccine platforms that express different multiple antigens(multivalence constructs)
Ability to compare recently developed vaccine constructs head-to-head in sufficiently sized studies to quickly reach conclusions on usefulness of novel concepts using established criteria (mRNA vaccines, ORF vectored IAV, bivalent LAIV with elastase dependence strains, computationally, optimized HA antigens in various vectors, chimeric bat NS1-truncated, MLVs, etc.)
Develop alternative to eggs culture for vaccine production – i.e. development of tissue culture system
Research on the various combinations included in the definition of "heterologous prime/boost"

Dependencies

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

Critical to develop an "adequate surveillance program" that can be implemented with any vaccination strategy to meet trade requirements (IABS meeting 2022) (see disease control roadmap)
Design vaccination strategies that fit species, age, production type and maternal antibody status including priming and boosting with various technologies to optimize protection and duration of immunity (see disease control roadmap)
Develop serological or other in vitro correlates / tests for assessing vaccine protection

Development of nucleic acid-based, vectored, inactivated or subunit vaccines
Diagnostic kits for DIVA compatible vaccines – need to get industrial partners involved
Quick development of vaccine (also not DIVA) to respond rapidly to disease outbreak management during emergency (pandemic/epidemic emergency)
Correlates/tests for vaccine protection in avian species and swine
Knowledge on vaccine effectiveness in different ages

State of the Art

Existing knowledge including successes and failures

Many DIVA compatible vaccines developed without associated diagnostic kits.
More Difficult DIVA when more than one AIV coinfecting viruses and multiple subtypes of vaccines are used such as H5, H7 and H9.
The minimum requirement of HI titers in field vaccinated birds, there is a description in OIE terrestrial Manual 2012 Chapter 3.3.4, C Requirements for vaccine 2.3.2. It says, 1/32 to protect from mortality or greater than 1/128 to provide reduction in challenge virus replication and shedding.

Projects

What activities are planned or underway?

Lead Summary [2] - Naturally attenuated candidates

Research Question

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

Develop safe live virus Influenza vaccines - without risk of reassortment.
Amenable for mass vaccination – control

Challenge(s)

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

Develop vaccines easy to administer that induce strong mucosal immunity able to block shedding, and prevent infection and transmission of LPAIV and HPAIV
Regulatory issues regarding attenuated vaccine usage due to safety for public health (possible reversion of virulence)
Risk of reversion to virulence and/or recombination
Application may depend on target species swine, equine versus avian species
Cost of vaccine for each species

Solution Routes

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

Solution for blocking reversion of virulence and reassortment

Dependencies

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

State of the Art

Existing knowledge including successes and failures

No incentive for industry to invest in research on Al attenuated vaccines as current regulation do not allow its use

Projects

What activities are planned or underway?

Lead Summary [3] - Rationally attenuated candidates

Research Question

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

Develop safe live rationally attenuated vaccine candidate

Challenge(s)

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

Safety for VPH- vaccines without risk of reassortment
Regulatory issues regarding vaccine usage
No incentive for industry to invest in AI vaccines that can't be used

Solution Routes

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

Mechanisms to reduce shedding (route, type of immune response)
Cold-adapted LAIVs vaccines?

Dependencies

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

State of the Art

Existing knowledge including successes and failures

US Patent No. 11,214,799 B2 (Jan 4th 2022) entitled 'HA-specific influenza virus attenuated vaccine comprising mutations in segment 7 and uses therefor'; D.R. Kapczynski, , P. Digard, L. Vervelde and D. Suarez.

Projects

What activities are planned or underway?

Lead Summary [4] - Inactivated vaccines

Research Question

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

Fast production of highly immunogenic inactivated vaccines for novel strains

Challenge(s)

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

Low immune response
Low speed of production for novel strains
Rapid production of vaccine due to the limitation of virus growth on eggs
Inactivated vaccines do not allow for mass application and need to match the circulating strain to confer reasonable protection

Solution Routes

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

Development of a suitable tissue culture system for production
Strategies to increase mucosal immune responses after inactivated vaccines
Novel/improved adjuvants
Ability to overcome Maternally Derived Antibodies (MDA) interference. Build on improvement in humans research

Dependencies

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

Identification of best vaccination strategies (Mucosal vs systemic protection vaccine?
vaccine protection whole year or specific period of time or season?)

State of the Art

Existing knowledge including successes and failures

Mostly egg based inactivated vaccines. Egg manufacturing platform is costly, and supply is limited.
Currently the inactivated vaccine provides suboptimal immunity in birds with Maternally derived antibodies (MDA), but birds are vaccinated in ovo and day old in the hatchery.

Projects

What activities are planned or underway?

Lead Summary [5] - DNA/RNA vaccines

Research Question

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

Efficacious and safe nucleic acid-based vaccines

Challenge(s)

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

Durable protection
Identification of the most suitable antigens and its genetic code.
Adjuvants for DNA/RNA vaccines
Storage and delivery of vaccine
Cost-effectiveness

Solution Routes

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

Enhanced immunogenicity using molecular adjuvants
Production and trial (in-ovo trials) of the most suitable antigens

Dependencies

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

Develop adjuvants that can increase immunogenicity

State of the Art

Existing knowledge including successes and failures

There are mRNA candidate vaccines currently under clinical trials. DNA vaccine licensed in US but not currently in use. RNA vaccine have limited use in LMIC due to storage issues

Projects

What activities are planned or underway?

Lead Summary [6] - Subunit vaccines

Research Question

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

Immunogenic subunit vaccines and optimal expression systems

Challenge(s)

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

Low immunogenicity
Can be developed as multivalent with several mixture of antigens.
Cost effective
Still fairly empirical with respect to success ~~of~~ in the antigenic/stability properties of the antigens
Adjuvants in general (killed vaccines and other vaccine platforms) need further research

Solution Routes

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

Use of adjuvants that could increase immunogenicity
Production and trial of the most suitable antigens.

Dependencies

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

Develop adjuvants that could increase immunogenicity
For Commercialization, adjuvant withdrawal time is a major hurdle depending on species and use

State of the Art

Existing knowledge including successes and failures

Baculous virus

Projects

What activities are planned or underway?

Lead Summary [7] - Vectored vaccines

Research Question

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

Safe vectored vaccines

Challenge(s)

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

Issues with environmental release and GMO
Identity of suitable vector
Anti-vector responses if reused
Current vaccines are mostly directed to a single antigen (HA)
Lack of streamlined regulations for live vectored vaccines proven safe (e.g HVT, FPV)
Increased cost to license is limiting the updates of vaccines
Potential spill over into non-targeted species
Mass administration (some practical, some are not)

Solution Routes

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

Intensify research focused on novel viral vectors that provide robust immune response, drastic reduction of shedding and can be mass administered in the field
Flexibility on vector choice to avoid anti-vector responses if reused: for instance, one for prime, a different one for boost
New technologies and improvement of current vectored vaccines

Dependencies

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

Identity of protective antigens and their genetic code – multiple antigens needed
Identity of suitable vectors
Safety for live vectored vaccines platforms
Better understanding of balanced immune responses would lead to vaccines with additional viral antigen components

State of the Art

Existing knowledge including successes and failures

Mixture of two or more separate rHVT as mixture expressing different antigens do not equally work together

Projects

What activities are planned or underway?

Lead Summary [8] - Attenuated organisms

Research Question

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

Efficient methods for obtaining attenuated organisms

Challenge(s)

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

Egg manufacturing platform is costly, and supply is limited.

Solution Routes

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

Alternative methods to egg manufacturing for vaccines e.g. cell culture

Dependencies

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

Identity of virulence factors

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [9] - Adjuvant

Research Question

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

New adjuvant stimulating durable immune response and no adverse reaction for the animal

Challenge(s)

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

Promote an appropriate immune response with reduced amount of antigen
Withdrawal time of adjuvant in livestock production systems
Adjuvants to improve/broad responses using vectors or attenuated organisms
Stability, safety and immunogenicity at a feasible cost
Adjuvants are primarily targeted to antibody response: harder to measure mucosal or cellular response and this limits field of application

Solution Routes

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

Better understanding of the mechanisms and immune - system - wide effects of new and existing adjuvants to enable rational design of improved vaccines with rapid onset of broadly - protective humoral, cellular and innate immunity
Development of vaccines/adjuvants to induce broad/universal clinical cross-protection
Mucosal adjuvants for IN application in swine/equine? and spray in poultry
Studies to establish the most suitable molecular adjuvants for nucleic acid-based vaccines that could be used in food producing species

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 [10] - Expression system

Research Question

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

Fast and cost feasible protein expression systems

Challenge(s)

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

Other antigens/factors than HA that can improve vaccine effectiveness
HA are not all created equal, some are poor immunogens
Speed of expression system
Cost
Scale up-capacity

Solution Routes

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

Re-engineering of existing systems
Multi-omics or a system-based biological approach may improve the quality of the expressed protein, such as creating a molecule with a better glycosylation profile
Identification of novel expression system

Dependencies

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

State of the Art

Existing knowledge including successes and failures

Current expression systems are mostly focussed on HA

Projects

What activities are planned or underway?

Lead Summary [11] - Vector

Research Question

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

Selection of appropriate safe vector with no possibility of prior immunity in the targeted animals

Challenge(s)

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

Selection of safe vectors
Accelerate process for rapid update of antigens in vectored vaccines

Solution Routes

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

Engage regulatory groups on developing an accelerated process for rapid update of antigenic cassettes in live vectored vaccines

Development of a safe, persistent vector for swine

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 [12] - Identity of protective antigens

Research Question

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

To identify the viral antigens that give strongest protection

Challenge(s)

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

Is it a humoral or cell mediated immune response that is required or both
Select best antigen based on age / type of animal

Solution Routes

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

Generation of a range of viral antigens and use them to study response to natural and experimental infections
Antigenic analysis of H5 and H7 viruses to ensure good (neutralizing) matching with potential vaccines.

Neuraminidase can be important, but harder to measure and harder to get high enough immune response
Knock out viruses

Dependencies

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

Immune response to natural/experimental infections

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [13] - Identity of virulence factors

Research Question

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

Molecular determinants of virulence and immune evasion in target species

Challenge(s)

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

Increase knowledge on virulence factors

Solution Routes

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

Identify determinants of virulence, particularly in waterfowl, other than HA cleavage site
Animals model to determine virulence markers
Test in the model system not just rodent
Study the role of internal genes in virulence in different species

Dependencies

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

Identify high-reassortment strains could improve pandemic preparedness or reveal new treatments (see disease control roadmap)
Viral, host and environment factors that influence the risk of acquiring an HA multibasic cleavage site
Virus determinants (other than MBCS) of local replication and potential systemic spread in target species

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [14] - Identity of immunomodulators

Research Question

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

Identity of main immunomodulators

Challenge(s)

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

Lack of knowledge of main roles of virus immunomodulators

Solution Routes

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

Standardized protocols for a set of cytokines to go with regular qPCR/Titration assays

Dependencies

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

Better understanding of innate immunity in birds, swine, equine, canine
Role of prior exposure to other pathogens that might limit the host response to vaccination(e.g. Virus combinations)
Correlates of protection and effects of immunomodulators (some use just classical assays ie. HI)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [15] - Host response to natural infection

Research Question

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

Better understanding of host response so that vaccines can be designed to address the challenges for multiple target species

Challenge(s)

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

Role of prior infections to aid innate immune response or affect vaccines response e.g. subsequent vaccine uptake
Effect of co - infection with different viruses and bacteria on AIV transmission and pathogenesis
Role of pre - exposure to AIV on subsequent AIV infections
Impact of NDV infection on AIV replication
Knowledge on the duration of immunity of LP and HP in wild birds
Some vaccines don't produce measurable correlates of protection
Identify what is the main immune responses generated and against what
Inhibition of immunity by other co- vaccines or co- infection (e.g. role of immunosuppressive diseases)
What determines antigenic drift?

Solution Routes

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

Immune response to IAV vaccine in young pigs co-infected with immunosuppressive viruses (PCV2 and/or PRRSV)
lack of knowledge in horses too
Characterisation of the post-infectious adaptive immune response that determines protection from reinfection with homologous or heterologous strains
Vaccine matching / role of intermediary immunity in protection and virus mutation
Role of prior infections to aid innate immune response
Dysregulation of the innate responses (or the lack of it) in target species?
Investigate immune mechanisms that impact the immunopathology

Dependencies

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

Strategies to improve vaccine responses in ovo or in young animals, especially in the presence of maternal antibody (issue in both poultry and swine) (see control strategies roadmap)
Develop strategies or technologies to induce earlier vaccine protection in ovo and in young poultry , e.g. rHVT (see control strategies roadmap)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [16] - Identity of mechanisms of protection

Research Question

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

Understand host susceptible and immune response in inter-and intra-host transmission

Challenge(s)

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

Increase knowledge on host factors in natural host associated with resistance or susceptibility to influenza infection and several hosts (e.g. cell receptors, intracellular enzymes, innate immunity, etc.)
Identify the contribution of the various arms of the immune response to protection – correlates of protection particularly in wild bird.
Knowledge on immunity levels required for re-infection of same or variants

Solution Routes

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

Identification of B and T cell epitopes that provide best protection from inactivated and vectored vaccines
Better understanding of response to attenuated pathogens - very limited our knowledge in avian species
Identification of conserved B- and T- cell epitopes within and between virus subtypes for targeting by vaccines
Role of unregulated cytokine expression in production of vaccine-associated enhanced respiratory disease of swine
Immune correlates of vaccine-induced protection
More reliable in vitro assays that can measure correlate of protection

Dependencies

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

Development of rapid or reliable in vitro assays superior to HI / VN that also account for cellular and mucosal immune response and correlate with protection

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [16a] - Antibody Response

Research Question

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

Identification of antibody that elicit protection to influenza infections – establish the contribution of the antibody response to protection

Challenge(s)

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

Identify immune correlates of protection in different breeds and ages
How long antibody last?
Ability to detect antibodies, lack of sensitivity (e.g. capacity of antibodies to limit virus entry in the cell sometimes last longer than our capacity to detect it by HAI essays)

Solution Routes

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

Studies to understand why the presence of antibody titers is not a necessary prediction of protection against infection/mortality/shedding.
Passive transfer studies to establish the role of antibodies in protection

Identification of antibody epitopes important for antigenic drift in swine and avian species
Development of models to predict epitopes based on HA sequence evolution
Evolutionary models that can predict direction of epitope changes
Recommendations of when vaccines need to be updated based on antigenic drift

Dependencies

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

State of the Art

Existing knowledge including successes and failures

Study on antigenic drift has been done in human studies but not in animal species

Projects

What activities are planned or underway?

Lead Summary [16b] - Cell Mediated Immunity

Research Question

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

Identify the role of Cellular immune response to protect from infection

Challenge(s)

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

Understand the role (and duration) of the cellular immune response in protection and in the pathogenesis of different influenza strains
Understanding of the cellular immune response of chickens to HPAI and its significance during infection

Solution Routes

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

Role of cell mediated immunity in protection following infection in wild birds versus poultry, and in particular its role in determining transmission
Characterization of the post-vaccination adaptive cellular immune response in swine
Passive transfer studies

Study on LPAI capacity to replicate within birds in extra respiratory and extra GI sites and the relative alteration of immunity response
Improved diagnostic tools to measure the cellular immune response that allows us to predict protection
Interferon type I and type II needs to be measure
Which phenotype of immune cells respond to infection of vaccines

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 [17] - Host-pathogen interaction

Research Question

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

Understanding host-pathogen interaction relevant for virulence and immune response
Host-virus protein interactions
Functions of viral proteins
Molecular determinants of virulence

Challenge(s)

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

Identify changes in the viral genome/proteins affecting virulence/immune response (e.g. HA and NA and what impact this has on transmission)
Determine influence of virus on host cell molecular biology
Molecular changes required for virulence
Limitation to conduct long-term studies
Viral, host and environment factors that influence the risk of acquiring an HA multibasic cleavage site
Virus determinants (other than MBCS) of local replication and potential systemic spread in target species

Solution Routes

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

Gene expression in infected cells
Understand the significance in changes of EIV NA (drift and shift)
Identify mutations in the HA and non-HA genes that enhance transmission, shedding, and replication in different species
Infectivity, pathogenicity, and transmission studies with emerging viruses in different domestic and wild bird species
Long term pathogenesis studies to better characterize the dynamics of virus transmission in flocks
Effect of multiple IAV strain infections in pig host
Pathogenesis studies of new AIV subtypes to identify molecular mechanisms of adaptation/zoonotic risk
Mechanisms behind increased pathology and transmission observed with some H9N2 and H5N2 LPAI strains – also strains like H3N1
Better understanding of the increase in host range and virulence observed with H5Nx clade 2.3.4.4b viruses
Better understanding of how genetic reassortment in swine happened, causing circulation of multiple types
Better understanding of the propensity of this virus to reassort

Dependencies

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

Effect of environmental factors (stress , ammonia , temperature , etc.) on AIV transmission and pathogenesis (critical particularly for H9N2)
Knowledge on mechanisms of transmission and environmental persistence of the virus (see control strategies roadmap)
Effect of age, breed and physiological state (e.g. LPAI affects ability for egg production)
Understanding the role of microbiome and co-infections in virus pathogenicity expressions and vaccine efficacy

Understanding the role of factors such as pregnancy
and obesity on the susceptibility of breeding sows to SIV infection

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [17a] - Entry

Research Question

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

Understanding the mechanism of virus entry

Challenge(s)

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

Lack of knowledge on cleavage sites for HPAI and LPAI

Solution Routes

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

Basic research on pathogenesis – how -
Knowledge on multi-basic cleavage site of haemagglutinin of H5 and H7 subtypes of AIV
Develop approaches to correlate expression of sialic acid (SA) receptor in different tissues with adaptation or restriction to AIV subtypes infection and shedding pattern in different species
Identify other factors for host adaptations

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 [17b] - Replication

Research Question

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

Knowledge on mechanisms that increase fitness/adaptability in different host range

Challenge(s)

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

Limited knowledge on the functions of each gene segment in terms of virus-host interactions aiding in the replication and/or increase in virulence.
Limited knowledge on virus replication markers (e.g. antibodies to NS proteins or other)

Solution Routes

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

Identification of viral gene segments or specific amino acid residues that are critical in altering the phenotype of each AIV subtype (replication fitness and virulence)
Identify virulence determinants other than the cleavage site of HA both for LPAI and also for HPAI viruses capable of promoting replication in specific organic districts.
Mechanisms behind increased pathology observed with some H9Nx and H5N2 LPAI strains
'Cost' effective studies related to virus and host fitness

Dependencies

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

State of the Art

Existing knowledge including successes and failures

In avian Influenza, the hemagglutinin proteolytic cleavage site is known to be the major determinant of virulence of Influenza for gallinaceous birds, however, there is variation among HPAI viruses in the severity of the disease. The viral mechanisms for these differences are unknown.

Projects

What activities are planned or underway?

Lead Summary [17c] - Persistence/clearance

Research Question

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

Identify the factors that influences susceptibility/resistance to infection

Challenge(s)

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

Lack of knowledge on genetic determinants/mechanisms of resistance to influenza
Understand how stress influences virus susceptibility
Improved understanding of the mechanisms of resistance of some species of fowl and endemic situation in swine
Levels of immune expression in different species due to virus infection

Solution Routes

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

Study the mechanisms of resistance of duck to HPAIV infection compared to other birds
Identify the host factors that influences high susceptibility of turkeys to HPAIV
Genetic determinants of resistance to HPAI strains in known reservoir species (e.g. ducks)
Mechanism of action of duck RIG-I in conferring AI resistance, and whether there are homologues in other avian species
Information on a possible carrier state in some species or immune-suppressed individuals
Understand how some LPAIV subtypes can affect the immune response and subsequent susceptibility/restriction to further infection
Identification of carrier bird species
Research on memory T cell immunity against AI, because is present for short period of time (months).

Dependencies

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

Existence of carrier state in some species (pheasants) or immunocompromised animals
Understanding the routes of transmission in different species
Breeding conditions are extremely important for successful vaccination

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [18] - Challenge models

Research Question

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

Need standardised challenge models to compare different vaccines and approaches to vaccination (including chicken, ducks and turkeys)
Assess vaccine performance under field conditions to validate laboratory models of vaccination

Challenge(s)

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

Reproducibility of studies of virulence, transmission, innate and adaptive immune responses - Credibility of research enterprise
Equine model is expensive
Identification of factors that can affect the effectiveness of AIV vaccination
Different breeds of chickens (Broilers Vs Layers and breeder respond differently.

Solution Routes

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

Conduct comparative vaccine efficacy studies in avian species other than egg - type chickens, including turkeys, broilers and domestic ducks
New models for equine flu
Data algorithm for vaccine implementation in swine
In vitro, ex vivo and different animal challenge models
Development of standardized challenge models relating to challenge dose and route of administration for different species

Dependencies

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

Establish parameters that suggest vaccine success
Understanding host-pathogen interactions in these systems is very important
Understand changes in genome that can effect virus
Integrative studies that involve surveillance, molecular epidemiology, animal studies and reverse genetics (DURC study - how do we make it happen?) (see disease control roadmap)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [19] - Pathogen genome

Research Question

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

Knowledge of pathogen genome

Challenge(s)

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

Genome sequencing time and cost Bioinformatic analysis
Ability to fully interpret virus sequences– and understand epistatic interactions between virulence markers on different segments

Solution Routes

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

Increase the full genome sequencing of recent circulating influenza strains from different species
Evaluation of whole genome sequencing platforms
Rapid whole genome sequencing and automated analysis pipelines
Improve sensitivity and purification methods for whole-genome sequencing
Need to identify molecular marker promoting high spread in poultry due to an excellent adaptation to domestic birds (Galliformes in particular)
Studies to understand the emergence of LPAIV to HPAIV
AI/machine learning/modelling approaches to understand whole genome effects
Include omics on virus cell interaction

Dependencies

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

Increase bioinformatic capacity
Identification of segments with increased pathogenic risk for veterinary public health and monitoring of those (see disease control strategy roadmap)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

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