OFFLU STAR-IDAZ
Consultation on a
global animal influenza
research agenda

OFFLU Research Agenda and OFFLU-STAR-IDAZ survey

David E Swayne

OIE Collaborating Centre for Research On Emerging Avian Diseases

FAO Reference Centre for Avian Influenza

OFFLU Network Laboratory, and

SEPRL, ARS, USDA, Athens, Georgia, USA

1. First OFFLU Influenza Research Agenda: Objective

- **As a global animal influenza network, develop a animal influenza research priority list to:**
  - Provide OFFLU laboratories with guidance as to the long-term direction for animal influenza research
  - Assist laboratories in refocusing their existing resources on the most immediate and highest priority research needs in animal influenza
  - Assist government and non-government funding agencies in identifying the greatest research needs so these agencies can provide funding to the most critical research areas

Structure

- **Divided into four areas/group facilitator (Summer 2010):**
  - **Avian influenza: Wild birds and ecology/Ian Brown**
  - **Avian influenza: Poultry and agricultural systems/David Swayne**
  - **Equine influenza/Ann Cullinane**
  - **Swine influenza/Kristein van Reeth**
- **Pre-meeting Activities (OFFLU Meeting 11/2010):**
  - **Group facilitator developed a starting document**
  - **Circulated to experts in the area for input: OIE experts, FAO experts, university researchers, etc.**
  - **Modified the document by additions, deletions and corrections**
- **Contain common and specific research needs**
- **Posted to website January 2011:**

http://www.offlu.net/OFFLU%20Site/OFFLU%20Research%20Priorities.pdf

1. Influenza Research Agenda: Structure

Common research needs:

- **Determine the virus-specific, host specific and environmental factors including animal management/husbandry-specific factors associated with zoonotic transmission and infection of humans**
- **Develop quantitative tools for the evaluation of surveillance systems in both animal and human health**
- **Study the viral and host factors that contribute to the successful transmission of animal influenza viruses to other species, including identifying markers of animal influenza viruses with human pandemic potential**
- **Study the importance of vaccine strain (antigenic match) versus antigen dose and type of adjuvant for increasing efficacy of animal influenza vaccines**

1. Influenza Research Agenda: Structure

Common research needs:

- **Evaluate novel influenza vaccination strategies with the potential to induce a broader and more durable immune response, and to avoid interference from maternal and active immunity;**
- **Determine influenza virus survival characteristics, persistence and underlying factors in a range of settings relevant to animal production; and**
- **Develop immunological tools to study correlates of humoral, mucosal, cellular and innate immunity, and the relationship of such immunity assessment to protection of animals from influenza infections.**

2. Second OFFLU Influenza Research Agenda

- **Update and Prioritize OFFLU Research Agenda**
- **New Partnerships: STAR-IDAZ, and inputs from EU and USDA analyses for influenza research needs, others**
- **Before meeting: OFFLU-STAR-IDAZ survey (n=28)**
  - Equine Influenza: 2
  - Poultry Influenza: 15
  - Swine Influenza: 5
  - Wild Bird: 2
  - Zoonoses: 4

Equine Influenza

Disease characteristics	Understand the mechanism and assessing the likelihood of interspecies transmission EIV
	Identification of reservoirs for EIV
	Impact of varied equestrian activities on virus transmission and disease expression
	Effects of transport and the synergism of bacterial pathogens and EIV
	Assessment of the contribution of the immune response to pathogenesis
	Identify host and vaccine determinants that influence virus shedding
	The development of challenge models in the natural host and in laboratory animals
Vaccines and antivirals	Assess different vaccination regimes to identify the regime which minimises the windows of susceptibility (randomised blinded comparative vaccination regime studies, and collection and statistical analysis of field data).
	Efficacious regimes need to be developed that protect horses without resorting to over vaccination - elucidation of the nature of immunological response to multiple vaccinations with both the same vaccine and different vaccines.
	Understand why a significant number of horses respond poorly to vaccination - identify factors (genetic, immunological, environmental etc.)that affect the response to vaccination with different types of vaccines
	Independent comparative vaccine studies for harmonisation of protocols, registration of new vaccines and update of existing vaccines.
	Characterisation of the nature and kinetics of the immunological response to vaccination and to natural infection with a view to elucidating why vaccinated horses become infected and shed virus
	The development of mathematical models to predict when problems could arise with existing vaccines
	Studies that integrate genetic and phenotypic variation with protection studies to demonstrate the need to update vaccine strains in a timely manner
Surveillance, risk analysis, control	Active surveillance for equine influenza in other species for elucidation of extent of interspecies transmission
	Evaluate different management and treatment regimes in the field (cohort studies).
	Evaluate the therapeutic effect of antiviral drugs in controlled trials and apply cost-benefit analyses periodically.
	Identification of high risk populations/situations
	Coupling surveillance / viral epidemiology with host population structure using approaches such as mathematical / contact network modelling for understanding what factors influence the rate of evolution / enable co-circulation of lineages
Virology	Identification of virus determinants that influence virus transmissibility and disease severity
	The development of a comprehensive range of specific antisera (ferret, horse and other species as appropriate) for antigenic characterization of viruses
Diagnostics	Standard procedures for investigation of outbreaks and recording of vaccination breakdown
	Validation of a real time RT-PCR assay that accurately predicts the infection status of a horse with a predetermined degree of statistical certainty
	Antigenic cartography and other tools to interpret different data relating to antigenic and genetic characterisation
	Sensitive, cheap and easy to perform stall-side diagnostic assays for detection of infected horses
	Assays to reliably measure virus-neutralising antibodies and cell-mediated immune responses
	Rapid whole EIV genome sequencing

Poultry

Disease characteristics	Knowledge on gain of virulence and AIV transmission
	Host genetic factors for pathogenicity
	Host genetic/molecular factors for infection and transmission of AIVs
	Uniqueness of mucosal immunity in chickens and other avian species
	Viral molecular determinants of virulence in ducks (reverse genetics)
	Host adaptation of AIVs to new species that increase viral replication & transmission, especially adaptation of AIVs that have been circulating in wild birds
	Measurement of cell mediated immunity through experimental studies
	Effect of population changes on infectivity and transmission dynamics of H5N1 in duck flocks and at population levels
	Multiple passages of specific common lineages of LPAI in domestic poultry to evaluate the potential to convert to HPAI & the time for the conversion to occur
Vaccines and antivirals	Novel vaccine vector that is tolerable under immunity against currently used against avian diseases other than AI
	Effective vaccines for younger birds – develop new or modify current vector vaccines
	Development and licensing of Duck Enteritis-AI vector vaccine for ducks at day of age lay
	Vaccines that overcome maternal antibody suppression
	Practical mass application AI vaccines (field use and in hatcheries)
	Universal vaccine independent of HA variability
	Compare different vaccination strategies using modelling approaches
	Investigate level of vaccination coverage against genetic mutation rate (modelling approach)
	Vaccines with different protective epitope for breeders and meat birds
	Determine shortest and longest duration of protection from vaccines (titres from existing data and new studies)
	Single or combination (with rNewcastle disease virus, rFowl pox virus, rHerpes virus) of existing vaccine technologies to improve protective immunity (broader and longer lasting)
	Mucosal adjuvants for avian sp.
	Antigenic cartography to assist vaccine seed strain selection
Surveillance, risk analysis, control	Factors leading to country endemicity (e.g. local poultry trade, poultry production systems, value chain)
	Surveillance strategies to address evolving epidemiological patterns of AIV over time and place
	Socio-economic drivers of disease reporting behaviour
	Interventions aimed at behaviour change amongst actors in poultry value chain
	Risk factors involved in farm-to-farm transmission to proritize mitigation strategies to enable effective control in low resource settings
	Quantitative risk for individual biosecurity practices supported with laboratory data
	Determinants of live bird market's role in the spread/maintenance of AIV
	Diagnostic algorithms for pre- and post- vaccination monitoring
Virology	Viral persistence in different substrates (e.g. manure)
	Virus survival under different environmental conditions
	Validation of diagnostic tools for environment and climate samples
Diagnostics	Highly specific and sensitive haemagglutinin antibody tests – standardised reagents or new tests
	New test to identify neuraminindase protein
	Pen side differential tests for Newcastle disease virus and AIV
	Pen side tests to identify H5 and H7 respectively
	Multiplex tests for poultry samples for rapid differential diagnosis
	Validate existing DIVA strategies
	Rapid diagnostic tests for identification of conserved antigenic epitope among H5 HAs or among H7 HAs
	Enzyme linked lectin assays as an alternative to microneutralisation assays
	Primers/probes that can bind all H7 influenza viral genomes
	Primers/probes that can bind one gene of all type A influenza for development of a common A influenza screening assay
	Improved method of library preparation for whole genome sequencing
	An assay that can detect all subtypes (H and N) A influenza for viral isolates (for antibody and for antigen)
	Strategies such as muliplex technology for rapid differential diagnosis
	Testing and validating sample pooling methods for influenza surveillance
	Development of animal experimental models for humans other that ferret

Swine Influenza

Disease characteristics	**Determinants for interspecies transmission (pigs, birds (turkeys), humans)**
	Viral genetic markers for virulence
	Viral genetic markers for transmission (intra and interspecies)
	Viral genetic markers for host specificity
	Adaptation of avian and human influenza viruses to pig populations
	Cross protection in pigs between different subtypes
	Effect of production system type on SIV evolution
	Effect of host immune status on SIV evolution
	Effects of swine population immunity on emergence of novel viruses
	Role of host immune status on pathology
	Effects of SIV co-infections with other viruses (other influenza viruses, PCV-2 and/or PRRS)
	Protection from maternal (passive) immunity
Vaccines and antivirals	**Effective antigenic matching with field strains and timely vaccine updates**
	Effect of maternal (passive) immunity on vaccination
	Improved vaccine delivery platforms / routes of delivery
	Heterologous/universal/ broad spectrum vaccines
	Cost benefit analysis of vaccination
	Measurable correlates of vaccine protection
	Overcoming interference from maternal derived immunity
	Vaccine enhanced pathology
	Impacts of vaccination vs. non-vaccination policies
	Development of cell culture and subunit vaccines (cf. whole organism)
	Broader repository of vaccine candidate viruses
Surveillance, risk analysis, control	**Determinants of SIV persistence and reoccurrence on farms**
	Determinants for seasonal patterns of SIV
	Risk factors for disease spread between epidemiological groups (and transmission routes)
	SIV elimination from farms
	Most effective herd sampling strategies (age group etc.)
	Effect of interspecies transmission (humans and pigs, turkeys and pigs) on SIV epidemiology and viral evolution
	Economic impact of SIV
	Biosecurity and biosafety compliance – risk communication (farms, markets, slaughterhouses)
	Addressing gaps in global SIV surveillance data
	Virus isolation from oral fluid samples
Virology	**Correlation between genetic and antigenic diversity**
	Database with emerging and endemic AIV in swine
	Adaptation of swine adapted influenza viruses to humans
	Correlation between geographic area and antigenic profile
Diagnostics	**Access to sensitive relevant diagnostic reagents (including culture material)**
	Rapid tests for antigenic and genetic characterisation
	Pen-side tests
Human animal interface	**Comparative public health/pandemic risk from swine and avian viruses**
	Role of humans in SIV epidemiology
	Cross immune reactivity between human adapted and swine adapted influenza viruses
	Occupational health risks
	Cross protection between influenza in swine, and between those circulating in humans and swine

Wild Birds

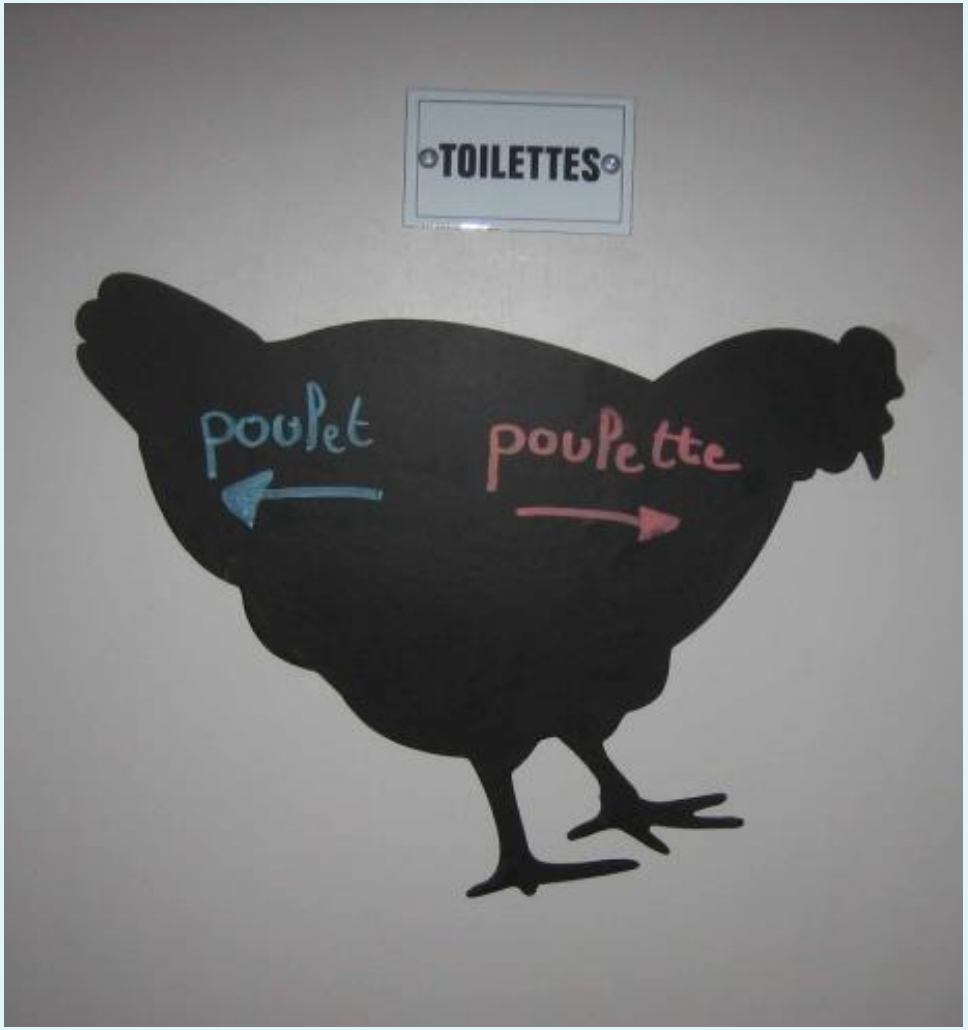
Disease characteristics	**Host factors determining resistance to clinical disease (pathogen interactions, genomics, modelling)**
	Host factors for pathogenicity of AI (pathogen interactions, genomics, modelling)
	Immunology dynamics and differences between orders and/or species of wild bird
	Interaction between virus and hosts in differents orders of wild birds
	Experimental infection of poultry with influenza viruses from wild birds
	Behaviour of different strains of AIV in different wild bird species
Surveillance, risk analysis, control	**Targeted detection/surveillance for AIV of concern or interest by nationwide wild bird surveillance – early warning e.g. HPAI H5N1 and H7N9**
	Surveillance and strain identification outside of country based on availability of national virology research funding by host pathogen interactions, virology, diagnostics, genomics
	Serological surveillance in wild birds
	Standardised approaches to wild bird surveillance for better comparison of results
	Increased wild bird sampling in neglected geographic areas
	Modelling AIV spread between wild birds and wild bird populations for risk analysis
	Demonstrate the importance of wild bird AIV reservoirs – potential for migratory birds to spread AIV when returning from north hemisphere
	Sampling native (non-migratory) wild birds sharing the same environment with migratory wild birds
	Risk factors for poultry infection from wild birds
	Study of implementation of better measures of biosecurity in farms to prevent AIV introduction to poultry
	Ecology of AIV in selected geographic locations targeting waterfowl and shorebirds by surveillance, virus identification, epidemiology
	To study the diversity of influenza genotypes circulating in wild birds by targeted, collaborative surveillance at key sites and with key taxonomic groups at a global scale, genetic sequencing and sharing of samples and results, modelling
Diagnostics	**Pen-side tests to enable easy field surveillance**
	Quantitative diagnostic tests to demonstrate concentration of AIV in cloacal/faecal swabs
	Tests for checking viability of AIV in different kind of conditions (temperature, humidity, pH, sunlight) in faecal samples
Virology	**Role of non-water birds in AIV ecology by surveillance, host – pathogen interactions, modelling**
	Sequencing data to compare different clusters of AIV from wild birds
	Differences between cell receptors in wild and domestic birds
	International network experts share non published information about new isolates and their

OIE FAO network of expertise on animal influenza

Zoonotic influenza

Disease characteristics	Determinants of airborne transmission by understanding aerobiology and pathogenesis of infection and shedding
	Determinants of host range and interspecies transmission by understanding pathogenesis at the molecular level
	Larger cohort studies and access to infected humans is required to study impact of human host genetics on susceptibility
	Research into novel immunologic assays and model development
	Field studies and development of better transmission models to understand how zoonotic strains are transmitted to humans most efficiently, i.e, fomite, airborne etc
	Factors defining increased host resistance
Vaccines and antivirals	To develop universal vaccines that are effective, safe, and inexpensive for poultry and swine byunderstanding mechanism of protective immunity conserved across subtypes
	Develop vaccines that meet the needs for eradication as part of a comprehensive control plan
	Development of assays to predict and measure antigenicity for seed strain selection
	Human and animal studies addressing the impact of priming antigen on response to subsequent vaccinations
	Research into how humans respond to vaccination with vaccines derived from zoonotic strains.
	Development and deployment of vaccines for zoonotic influenza viruses
	Tools to allow decisions: Blanket vs. targeted (autogenous) vs. no vaccination
	Vaccine efficacy: Protection at least within subtype level
	Vaccine delivery: Develop systems that are "needle-independent" and can be used in all poultry sectors
Surveillance, risk analysis, control	Larger studies needed to identify risk factors to acquire knowledge on factors that influence risk for zoonotic infection
	Matching assays for serological and/or genetic DIVA
	Defining standards of biosecurity for poultry holdings
	Develop criteria to decide between need to cull vs. allowance to slaughter
	Internationally co-ordinated in depth and focussed surveillance programs in swine
	Holostic multidisciplinary and public/private research to match novel detection and characterization technologies with epidemiologically sound surveillance approaches that will be economically efficient and acceptible to farming interests as enhancing busines continuity
	Combination engagement among regulators, animal production interests, economists and social scientists with expertise in behavioural norms along the "value chain" including consumer behaviours
Virology	Identify factors that influence/drive mutation of an LP H5/H7 virus to HP phenotype
	Dissecting factors that define the "elusive" genome constellation (characterize pleiotropic effects)
	Define/recognize factors that characterize frequently reassorting "mobile" genome segments
	Tools to assess antigenic drift
Diagnostics	Develop diagnostic tests that meet the needs to support control plans
	Develop and validate new serologic DIVA tests for use in appropriate target
	Develop and validate new practical serological tests that provide subtype and strain exposure history information
	Develop and validate new diagnostic technologies for increase sensitivity, specificity, throughput and reduce test time holding costs down
	Develop approaches to stabilize the molecular targets of detection
	Develop stabilizing solutions to preserve infectivity of virions at ambient temperatures in tropical climates
	Optimized and sensitive methods to sequence full genomes from swab/sample material
	Reproducible methods to purify individual viruses from mixed infections
	Develop HI-independent subtype-specific antibody assays for distinction of subtypes

Merci Beaucoup!



Animal Influenza Meetings: 12-17 April 2015

9th International Symposium on Avian Influenza

- **12-15 April, 2015**
- **University of Georgia, Athens, Georgia, USA**
- **Co-chairs: David Swayne, Ian Brown, David Stallknecht**
- **Questions: David.Swayne@ars.usda.gov**

- **OFFLU Meeting, 15 April 2015, secretariat@offlu.net**

- **3rd International Neglected Influenza Viruses meeting, 16-17 April 2015**
- **Chair: Stacey Schultz-Cherry; stacey.schultz-cherry@stjude.org**