United States Department of Agriculture

Research, Education, and Economics

Agricultural Research Service

Office of National Programs

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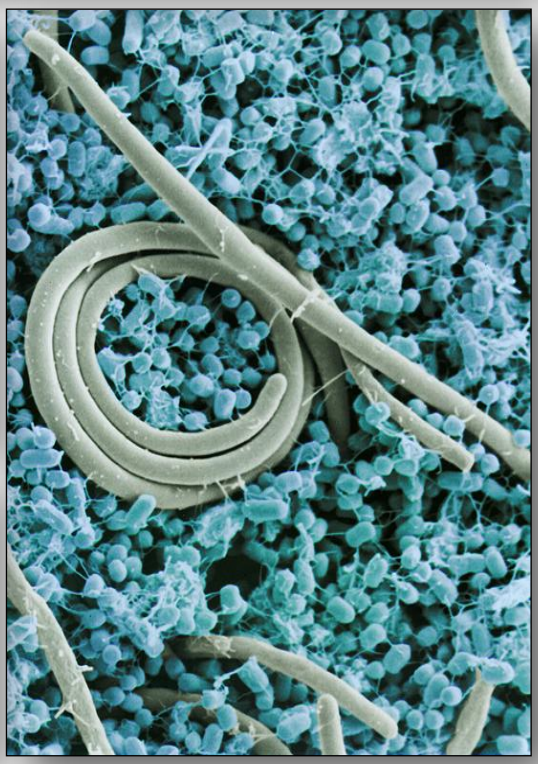
National Program 103

Animal Health

Accomplishment Report 2007-2011



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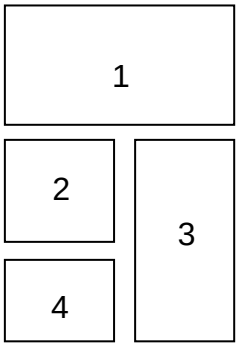


1. A sow and her piglets. Animals that have been weaned are particularly susceptible to bacterial infections and may benefit from nitro and chlorate treatments. *Photo by Keith Weller/ARS*

2. Food supplements, probiotics, and phytonutrients have been shown to help fight some poultry diseases. *Photo by Keith Weller/ARS*

3. Cells of *Salmonella enteritidis* change shape as they grow. This scanning electron micrograph shows a mixture of small cells with filaments and very large cells that lack filaments. Small cells arise only during certain growth stages and efficiently contaminate eggs when the time is right. *Photo by Jean Guard-Petter*

4. This U.S. cow and others like her are safe from mad cow disease (bovine spongiform encephalopathy) thanks in large part to ARS research on the disease and other transmissible spongiform encephalopathies. *Photo by Peggy Greb/ARS.*

National Program 103
Animal Health
ACCOMPLISHMENT REPORT 2007-2011

TABLE OF CONTENTS

APPENDIXES

United States Department of Agriculture
Research, Education, and Economics
AGRICULTURAL RESEARCH SERVICE

National Program 103
Animal Health

ACCOMPLISHMENT REPORT 2007-2011

Agricultural Research Service

The Agricultural Research Service (ARS) is the principal in-house research agency of the United States Department of Agriculture (USDA). ARS is one of four agencies in the Research, Education, and Economics (REE) mission and is charged with extending the Nation's scientific knowledge with research projects in agriculture, human nutrition, food safety, natural resources, and the environment. ARS supports more than 2,100 scientist years organized into approximately 1,050 permanent research projects at over 100 locations across the country and five overseas laboratories and more than 150 librarians, technical information specialists, and other library specialists.

Role

ARS conducts innovative research to find solutions to problems of high National priority that impact the American people on a daily basis. ARS often researches high-risk scientific endeavors to make significant breakthroughs in important problem areas. ARS research programs also complement the work of State Colleges and Universities, State Agricultural Experiment Stations, other Federal agencies, and the private sector. Mechanisms for addressing state and local issues are already in place; therefore, activities within ARS focus on issues having a regional or national scope and where there is a clear federal role. ARS also provides research support to USDA action and regulatory agencies and to a number of other Federal regulatory agencies, including the Departments of State and Defense and the Food and Drug Administration, and the Environmental Protection Agency.

Mission

The mission of the program is to deliver scientific information and tools to detect, control, and eradicate animal diseases of high national priority.

Office of National Programs
5601 Sunnyside Avenue ● George Washington Carver Center
Beltsville, Maryland 20705

Goal

The goal of National Program 103 (NP 103), Animal Health, is to protect and ensure the safety of the Nation's agriculture and food supply through improved disease detection, prevention, control, and treatment. Basic and applied research approaches are used to solve animal health problems of high national priority. Emphasis is given to methods and procedures to control animal diseases through the discovery and development of:

- Diagnostics
- Vaccines
- Biotherapeutics
- Animal genomics applications
- Disease management systems
- Animal disease models
- Farm Biosecurity measures

The vision for the program is to be recognized worldwide as a leader in animal health research that delivers effective solutions to prevent and control animal diseases that impact agriculture and public health.

The animal health national program has ten strategic objectives:

1. Establish ARS laboratories into a fluid, highly effective research network, to maximize use of core competencies and resources.
2. Ensure access to specialized high containment facilities to study zoonotic and emerging diseases.
3. Develop an integrated animal and microbial genomics research program.
4. Establish centers of excellence in animal immunology.
5. Launch a biotherapeutic discovery program providing alternatives to animal drugs.
6. Build a technology-driven vaccine and diagnostic discovery research program.
7. Develop core competencies in field epidemiology and predictive biology.
8. Develop internationally recognized World Organization for Animal Health (OIE) expert collaborative research laboratories.
9. Establish best-in-class training center for our nation's veterinarians and scientists.
10. Develop a model technology transfer program to achieve the full impact of our research discoveries.

Overall Program Impact

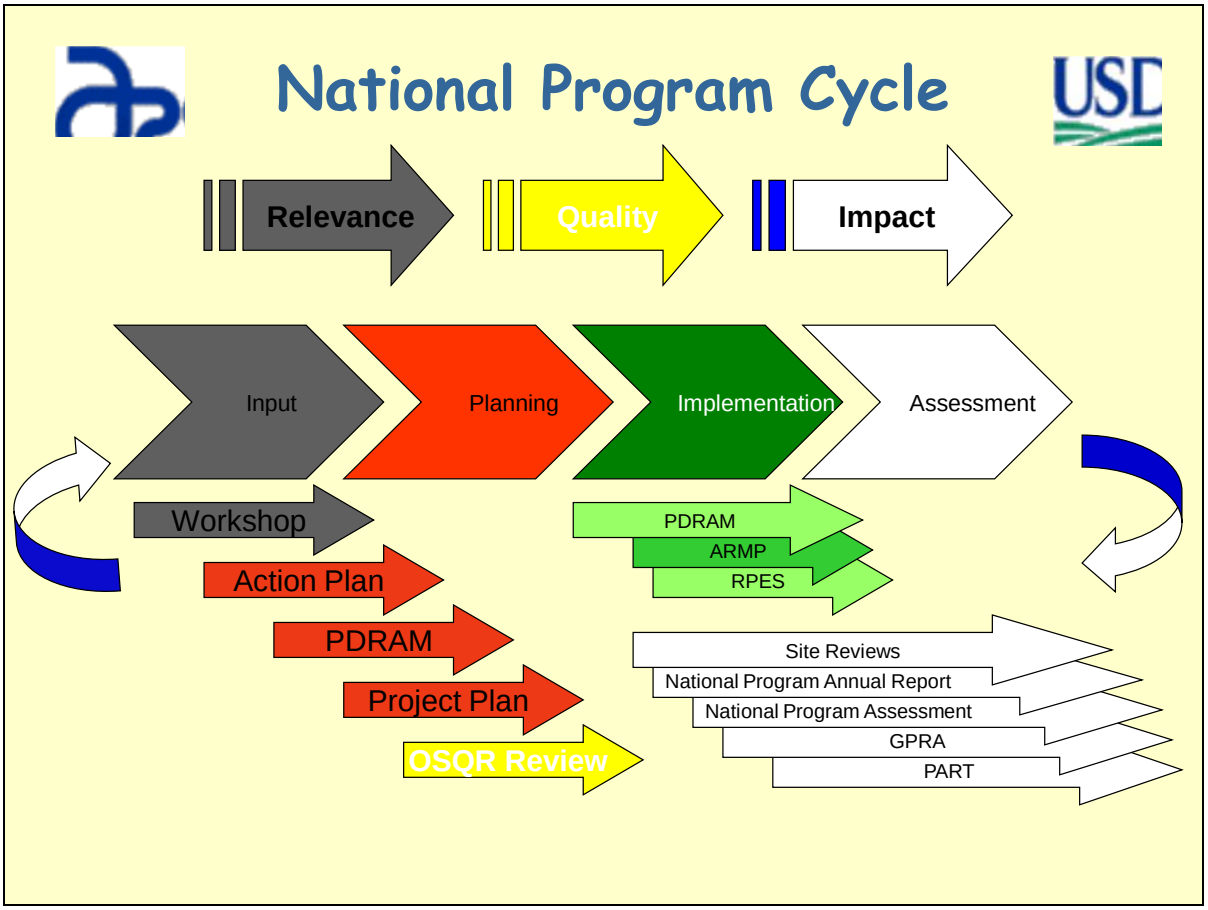
During the 5-year period covered by this report, ARS scientists have provided scientific information that has significantly enhanced our knowledge of endemic and foreign animal diseases, including new and emerging diseases such as pandemic H1N1. Scientific information for zoonotic pathogens has been used widely to establish the safety of our food products and support the export of agricultural products. Importantly, a number of tools for detecting and preventing animal disease outbreaks have been discovered and transferred to action and regulatory agencies and the private sector for full development. Examples include diagnostic

assays transferred to Animal and Plant Health Inspection Service (APHIS) to support surveillance programs, including the National Animal Health Laboratory Network. Although Cooperative Research and Development Agreements with the private sector are considered confidential, new vaccine technologies for priority diseases like foot-and-mouth disease (FMD) and Classical Swine Fever (CSF) have been transferred and are currently being developed by pharmaceutical companies with the support of ARS scientists. A recent example is the first molecular FMD vaccine, which was specifically designed for the U.S. National Veterinary Stockpile.

PLANNING AND COORDINATION FOR NP 103'S 5-YEAR CYCLE

National Program Cycle

The management and execution of all ARS research programs is organized around the five-year National Program Cycle, consisting of four sequential phases designed to ensure the relevance, quality, and impact of every National Program: 1) Input; 2) Planning; 3) Implementation; and 4) Assessment.



National Program Assessment

A National Program Assessment is conducted every five-years through the organization of one or more workshops. Workshops allow ARS to periodically update the vision and rationale of

each National Program and assess the relevancy, effectiveness, and responsiveness of ARS research. The Office of National Programs staff organizes National Program Workshops to facilitate the review and simultaneously provide an opportunity for customers, stakeholders, and partners to assess the progress made through the National Program and provide input for future modifications to the National Program or the National Program's research agenda.

Workshop

The workshop for NP 103 was held in Kansas City, Missouri, September 20-21, 2005, in cooperation with the external granting agency of USDA, Cooperative State Research, Education, and Extension Service (CSREES, now the National Institute of Food and Agriculture – NIFA). The purpose of the workshop was to receive input from the stakeholders, customers, and partners in planning the direction of the direction of the intramural (ARS) and extramural (CSREES/NIFA) national research programs. The outcomes of the workshop were used to identify the animal health needs of the livestock, equine, and poultry industries, prioritize research needs for the USDA's animal health research programs, support and strengthen the integration of USDA's research, technology transfer, and extension programs in animal health, and to encourage dialogue among USDA's partners, professional organizations, the livestock, equine, and poultry industries, other interested stakeholders and USDA national program leaders and scientists to help solve priority problems in American agriculture. Input from the workshop was used to formulate an Action Plan for Animal Health National Program, consisting of eight research components. This process provided a coordinated multi-location plan for research projects conducted by ARS scientists and cooperators that address regional and national priorities and result in fundamental advances in agricultural science. There were nine breakout groups that included: pork; beef; dairy/milk cattle; sheep/goats; wildlife; horses; poultry, divided into broiler/meat and layers/breeders; and the turkey industries.

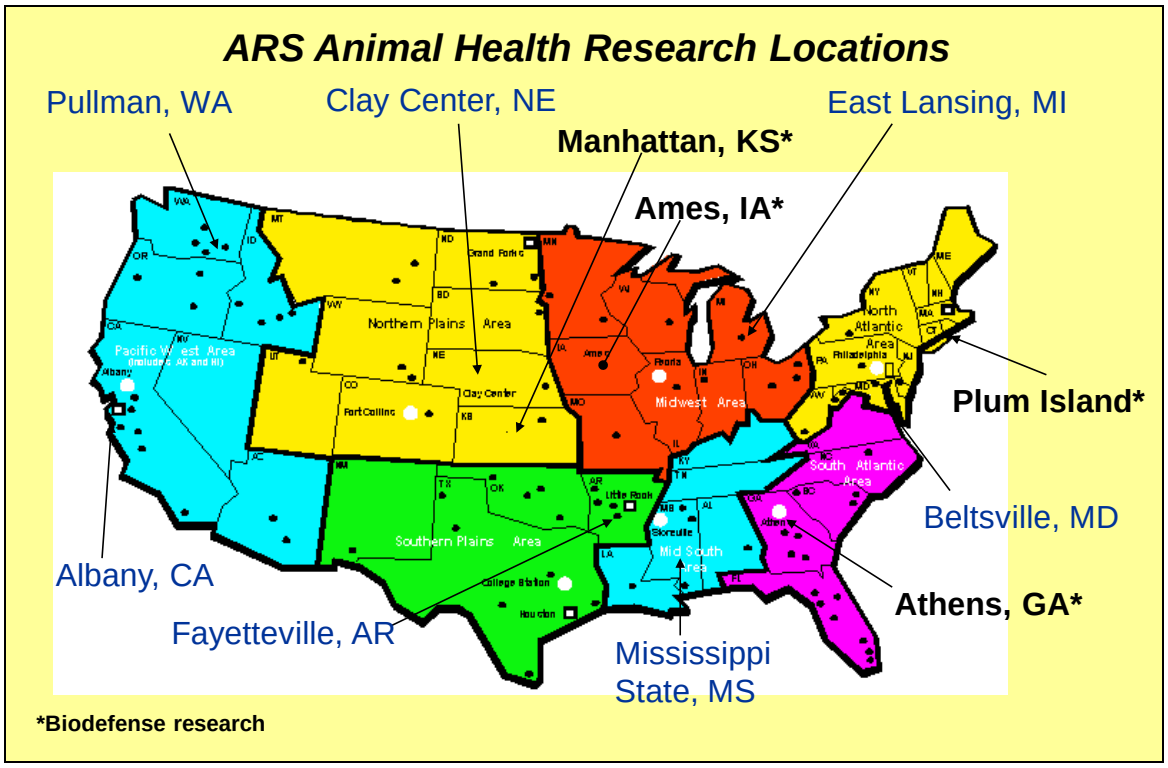


Figure 1: The scientists assigned to National Program 103, Animal Health, are conducting research in 11 different laboratory locations across the United States.

Animal Health National Program (NP 103)

The mission of the Animal Health Program is to conduct basic and applied research on selected diseases of economic importance to the United States livestock and poultry industries. The goals of the research mission are to produce knowledge and technology to reduce economic losses from infectious, genetic, and metabolic diseases of livestock and poultry. Dr. Cyril G. Gay, Senior National Program Leader, and Dr. Eileen Thacker, National Program Leader, lead this ARS animal health research program. Dr. Gay is lead on projects involving viruses and foreign animal diseases. Dr. Thacker oversees the projects on bacterial and parasitic pathogens. The Animal Health National Program currently includes approximately 48 core research projects supported by 124 scientists located at 11 research sites throughout the country. The ARS research budget for the Animal Health Program is approximately $63.6 million (NET).

Background

Providing useful information for problem-solving in veterinary medical research often demands an integrated approach where the experimental design may range from knowledge development at the molecular level to clinical trials that will lead to the development of countermeasures for preventing and controlling a disease outbreak in the field. NP 103 utilizes all of these measures to provide the means for the integration of research. For this purpose, select NP 103 projects will be aligned under "Major Initiatives." Each major initiative will be outlined as problem statements under the research components of the action plan. Major initiatives will draw upon relevant expertise within NP 103, coordinating and integrating that expertise to develop a

specific useful application of the knowledge. Major initiative projects may also attract federal, university, industry, and international partners. Objectives of major initiative projects will be consistent with those of their base projects. If successful, therefore, they enhance, rather than detract from, the impact of those base projects on their assigned topics. Because a significant number of projects in the animal health research portfolio focus on the discovery of novel technologies, intellectual property strategies are addressed in project plans to facilitate technology transfer and the investment by the private sector in the development of these technologies.

The anticipated products of the animal health program include:

- Finding new solutions to prevent economic losses from domestic and foreign animal diseases in agriculture species.
- Developing methods to help producers adjust to changing farming practices that will allow consumer driven issues to be accommodated without compromising financial viability.
- Providing information that will allow the establishment of on-farm practices to maximize biosecurity from naturally or intentionally introduced pathogens, thus increasing food security, farm productivity, and enhancing trade and exports.
- Establishing methods to detect, analyze, and respond to new and emerging agriculture pathogens.
- Finding solutions to maintain a barrier to pathogens at the domestic-wildlife interface.
- Establishing new detection technologies that will allow better tracking and control of animal pathogens.
- Building an integrated research program to discover genetic variations associated with disease susceptibility and resistance to increase productivity and competitiveness.
- Developing experimental animal disease models that will serve the animal and human health research communities to significantly shorten the timelines for developing breakthrough medicines and disease prevention tools and validate countermeasures.

STRUCTURE OF NP 103

Research Component Overview:
The eight research components of the program are:

Component 1: Biodefense Research

Component 2: Animal Genomics and Immunology

Component 3: Zoonotic Diseases

Component 4: Respiratory Diseases

Component 5: Reproductive and Neonatal Diseases

Component 6: Enteric Diseases

Component 7: Parasitic Diseases

Component 8: Transmissible Spongiform Encephalopathies

NP 103 RESEARCH CONTRIBUTES TO THE OVERALL ARS ANIMAL HEALTH RESEARCH EFFORT

Outputs of NP 103 research support the "Actionable Strategies" associated with the performance measures shown below from the *ARS Strategic Plan for 2003-2008.* Objective 3.2: *Develop and Deliver Science-Based Information and Technologies to Reduce the Number and Severity of Agricultural Pest, Insect, Weed, and Disease Outbreaks.*

Performance Measure 3.2.1: Provide scientific information to protect animals from pests, infectious diseases, and other disease-causing entities that affect animal and human health. **Target:** Increase the delivery of dependable high quality scientific information to customers, stakeholders, and partners. New discoveries and technologies are effectively communicated to improve the management of diseases that affect the livestock and poultry industries, and which may affect public health. Effective communication will also be achieved by publishing in highly regarded scientific journals and trade publications and on the internet and through presentations at industry meetings.

Performance Measure 3.2.2: Identify, develop, and release to the U.S. agricultural community genetic markers, genetic lines, breeds, or Germplasm that result in food animals with improved (either through traditional breeding or biotechnology) pest- and disease-resistance traits. **Target:** The release new and improved genetic lines, breeds, and/or Germplasm of food animals that will exhibit enhanced pest- and disease-resistance traits.

Performance Measure 3.2.3: Develop and transfer tools to the agricultural community, commercial partners, and Federal agencies to control or eradicate domestic and exotic diseases that affect animal and human health. **Target:** Develop diagnostic and preventative tools to control and/or eradicate domestic diseases that affect production, trade, and public health. Provide action agencies with data to support risk analyses to assess the impact of domestic and exotic diseases and develop control and eradication strategies.

HOW THIS REPORT WAS CONSTRUCTED AND WHAT IT REFLECTS

In this report, NP 103 achievements and their impacts are organized according to the eight Action Plan components. The report first outlines the rationale for the research, followed by the research needs anticipated products and impact for each of the components. Then, selected

accomplishments are listed as examples of contributions toward the high priority needs identified by customer/stakeholders and described in the NP 103 Action Plan.

For the most part, the content of this report is derived from the 2007-2011 annual reports from NP 103 research projects. This report does not include all accomplishments achieved by this national program rather, only selected accomplishments that illustrate and exemplify the total progress and achievements at the national level.

NP 103 currently encompasses approximately 48 core research projects supported by 124 scientists located at 11 research sites throughout the country. The ARS research budget for the Animal Health Program is approximately $63.6 million (NET). Research projects in NP 103 are listed in Appendix I; publications in peer-reviewed journals authored by NP 103 scientists are compiled in Appendix II; patents and technology transfer are listed in Appendix III; research collaborations are listed in Appendix IV; and the results of a stakeholder retrospective electronic survey conducted in 2011 to assess the impact of the Animal Health National Program is available in Appendix V.

This report was prepared for an external (to ARS) retrospective review of NP 103 to assess how well this national program attained its goals, as outlined in the FY 06-FY 11 Action Plan. Accordingly, the purpose of the retrospective review is not to judge the performance of individual research projects, but rather to gauge the overall impact of NP 103. Consequently, the report does not attempt to catalogue all the accomplishments of the constituent research projects of NP 103. Individual scientists or projects are not identified by name in the narrative text; their achievements are described in the context of contributions to the national program's commitments to U.S. agriculture.

This report provides extensive lists of animal health research priorities and anticipated products from the NP 103 Action Plan. Although these research priorities and anticipated products serve to help measure the national program's progress during the last five years, their primary purpose was to provide overarching targets for scientists working in the NP 103 National Program. Importantly, these extensive lists provided direction for acquiring additional resources (extramural funding and research collaborations) to build and expand research programs where needed during the course of the national program cycle. Based on the available funds and resources at the start of the national program cycle, ARS scientists were given specific research objectives to prepare their project plans, which were provided in Program Direction and Resource Allocation Memoranda.

Component 1: Biodefense Research

Rationale for the research:
The health of animals is continuously threatened by diseases naturally or deliberately introduced into a naïve healthy population of productive animals. These diseases vary in the degree of economic loss they cause, their potential to spread, ease of control and ability to eradicate. Many of these diseases are caused by high consequence animal pathogens that are not hindered by international borders and are thus labeled transboundary diseases by the Food and Agriculture Organization (FAO) of the United Nations. Since most of these diseases do not exist in the United States they are also referred to as foreign animal diseases. Of particular concern are emerging animal diseases that challenge our disease surveillance systems and our ability to prepare and respond to disease outbreaks. Introduction of these diseases in the United States could have devastating social and economic effects not only in the country's agricultural systems but also in a wide range of economic activities, such as the export and trade of agricultural products.

ARS biodefense research activities under Component 1 include research conducted on select agents identified under the Agricultural Bioterrorism Protection Act of 2002. Select agents pose a severe threat to animal health or animal products. Research on select agents is regulated by the Animal and Plant Health Inspection Service (APHIS) and/or the Center for Disease Control and Prevention (CDC) and requires high containment laboratories and animal facilities. Outputs under Component 1 are used by Federal and State regulatory agencies for surveillance and to mitigate accidental or potential intentional acts of agroterrorism.

The program direction provided to scientists assigned to biodefense research purposely target basic research aimed at increasing our understanding of how disease agents survive outside the host, move between susceptible hosts, infect animals, and how pathogens escape and shed from the host. To improve our response to disease incursions, the program also allocated significant resources towards the discovery of veterinary countermeasures for the U.S. National Veterinary Stockpile. The research program has successfully established strategic international research collaborations with scientists in countries where foreign animal diseases (many of which are select agents) are endemic. One notable accomplishment was the creation of the Global Foot-and-Mouth Disease Research Alliance (GFRA - http://www.ars.usda.gov/gfra/). Partnerships with researchers in other countries have contributed significantly to the program by providing access to critical samples, scientific information, resources, and the ability to test countermeasures in endemic settings.

Stakeholders at the September 2005 Animal Health Planning Workshop representing the beef industry ranked foreign animal diseases their 1st priority; the poultry layer industry their 1st priority; the poultry broiler industry their 2nd priority; the dairy industry their 5th priority; and the swine industry their 5th priority. Diseases in Component 1 include Foot-and-Mouth Disease, Avian Influenza, Rift Valley Fever, Classical Swine Fever, virulent Newcastle disease, Vesicular Stomatitis, and Exotic bluetongue virus. Additional diseases that can also impact our economy and trade are addressed under Component 7, Babesiosis, and Component 8, Bovine Spongiform Encephalopathy (BSE).

Research needs:
In order to control foreign animal diseases, a wide variety of agent detection platforms need to be developed and validated. Information for designing these platforms requires knowledge of pathogen genomics and proteomics and understanding the evolution and genetic variability of disease agents. There is a dearth of knowledge for many priority foreign animal diseases, such as understanding the host range of pathogens; their primary site of replication; tissue tropism; carrier state; duration and routes of shedding; transmission mechanisms (e.g. vectors, fomites, aerosols); ecology and epidemiology (e.g., wildlife reservoirs). If a disease outbreak should occur in the United States, effective veterinary countermeasures are needed to support suitable control strategies compatible with a short time to recovery to limit the economic impact. There is a need for developing vaccines and biotherapeutics suitable for the U.S. National Veterinary Stockpile. Importantly, integrated approaches for responding to foreign animal disease outbreaks are needed to enhance our capability to regain country disease-free status and retain economic sustainability.

Since no one can predict with certainty the cause of the next pandemic, there is a need to continuously isolate, identify, and characterize pathogen(s) associated with new disease complexes of unknown etiologies. The capabilities to rapidly detect, identify, and characterize new and emerging animal pathogens are paramount and a primary goal of the biodefense research program. Scientists need to conduct animal studies in the relevant host to fulfill Koch's postulate and determine the pathogenesis of monovalent and multivalent infections. Once a new agent is isolated there is a need to sequence partial or complete microbial genomes to identify unique sequences for diagnostic discovery and molecular epidemiology research. Research is needed to understand mechanisms of disease, disease transmission, and host range specificity to determine the prevalence and emerging potential of new diseases. Ultimately research is needed to identify predictors of disease emergence and disease outbreaks. Establishing strategic international research collaborations is critical to address many of these research needs.

The specific research priorities and anticipated products for Component 1 were derived from gaps analyses conducted by worldwide experts in the last five years. These gaps analyses were organized and led by ARS at the request of the interagency U.S. National Veterinary Stockpile Steering Committee. The results of these analyses are confidential due to recommendations made in the reports for stockpiling countermeasures. However, some reports have been amended for public distribution and can be made available upon request to the Director of the U.S. National Veterinary Stockpile, National Center for Animal Health Emergency Management, APHIS. The reports from these gap analyses provided the research priorities and anticipated products that are expected from the research and now serve to help measure the national program's progress during the last 5 years in meeting the needs of animal producers, researchers, and action and regulatory agencies. The following list of anticipated products from the Action Plan is followed by the expected impact of the research and a sampling of relevant accomplishments.

Anticipated Products from the Action Plan:
- Improved ability to predict or anticipate the emergence and introduction of foreign animal diseases.

- Capability to advise federal and state officials on scientific procedures for preventing the introduction of foreign animal diseases.
- Better capability to produce effective products to control and eliminate foreign animal diseases.
- Real-time detection of agents in a wide range of farm matrices.
- Searchable databases of genome and proteome information for major known foreign animal diseases agents.
- Discovery of effective candidate biotherapeutics.
- Discovery of effective candidate vaccines that allow differentiation of infected animals from vaccinated animals (DIVA).
- Viable integrated vector control strategies that minimize losses.
- Identification of new pathogens associated with emerging diseases.
- Establishment of methods to rapidly detect and characterize the etiology of new and emerging diseases.
- Development of predictors of new and emerging disease outbreaks.
- Tools and expertise to mitigate emerging diseases and rapidly implement countermeasures to respond to new disease outbreaks.

Impact:
The research provides improved methods for the prevention and control of select agents, which are considered high consequence pathogens. The research yields scientific information on disease transmission, pathogenesis, and intervention strategies to enable the detection, control and eradication of foreign animal diseases and/or new emerging diseases of humans and animals.

COMPONENT 1: SELECTED ACCOMPLISHMENTS

Glycosylation Sites of the Classical Swine Fever Virus are Determinants of Virulence.
Classical Swine Fever Virus (CSFV) is a highly infectious disease of pigs that results in high rates of mortality and morbidity and is a significant foreign animal disease threat to the U.S. national pork industry. Outbreaks in Western Europe have shown that there are critical gaps in the countermeasures available to control this disease. ARS scientists at the Plum Island Animal Disease Center, Greenpoint, New York, have shown that CSFV contains in its envelope three heavily glycosylated (sugar-coated) proteins (E0, E1 and E2), which play a critical role in virulence and immune responses. The role of the glycosylation of these proteins in virulence was established using reverse genetics techniques to alter, delete, and analyze CSFV glycosylation sites. The major accomplishment of this project is the discovery, mapping, and characterization of viral genetic determinants of virulence and their manipulation, which provide critical information to enable the development of next generation live attenuated vaccine strains.

Scientific Publication:
Sainz, I.F., Holinka, L.G., Lu, Z., Risatti, G.R., Borca, M.V. 2008. Removal of a N-linked glycosylation site of classical swine fever virus strain Brescia Erns glycoprotein affects virulence in swine. Virology. 2008 Jan 5; 370 (1):122-9. Epub 2007 Sep 29.

Novel Immunomodulatory Mechanism for Classical Swine Fever Virus.
ARS scientists at the Plum Island Animal Disease Center, Greenpoint, New York, conducted molecular virology studies aimed at understanding the mechanisms of Classical Swine Fever (CSF) viral pathogenesis, which is a critical step on the path to vaccine discovery. Protein domain analysis of the predicted amino acid sequence of the NS4B protein of highly pathogenic CSFV strain Brescia identified a putative Toll/interleukin-1 receptor (TIR)-like domain. This TIR-like motif harbors two conserved domains, box 1 and box 2, also observed in other members of the TIR superfamily, including Toll-like receptors. Changes within this receptor completely decreased the ability of CSFV to cause disease (virus attenuation), reducing viral replication in the oronasal cavity and limiting spread from the inoculation site to secondary target organs.

Scientific Publication:
Fernandez-Sainz I., Gladue D.P., Holinka L.G., O'Donnell V., Gudmundsdottir I., Prarat M.V., Patch J.R., Golde W.T., Lu Z., Zhu J., Carrillo C., Risatti G.R., Borca M.V. 2010. Mutations in NS4B of Classical Swine Fever Virus affect virulence in swine. J Virol. 2010 Feb; 84(3): 1536-49. Epub 2009 Nov 18.

New discovery has Important Implication in Future Classical Swine Fever Vaccines.
Previous studies demonstrated that removal of specific glycosylation sites yielded attenuated and immunogenic CSFV mutants vaccine strains. ARS scientists in Greenpoint, New York, in collaboration with scientists at the University of Connecticut analyzed the effects of removing the glycosylation sites of the Erns, E1, and E2 proteins on immunogenicity. Interestingly, Erns, E1, and E2 proteins lacking glycosylation failed to induce a detectable virus neutralizing antibody response and protection against CSFV. Similarly, no neutralizing antibody or protection was observed in pigs immunized with E1 glycoprotein. Analysis of Erns and E2 proteins with single site glycosylation mutations revealed that detectable antibody responses, but not protection against lethal CSFV challenge is affected by removal of specific glycosylation sites. In addition, it was observed that single administration of purified Erns glycoprotein induced an effective protection against CSFV infection. This discovery had important implications for the manufacturing and future development of CSF vaccines, demonstrating that complete deglycosylation of E2 and Erns erase completely their immunogenicity in swine. Additionally, this is the first report indicating that Erns can be immunogenic and induce protection by itself. The glycosylation patterns of CSFV structural proteins E0 and E2 have been determined along with their role in virus replication *in vitro* and *in vivo* in pigs. Manipulation of the E2 glycosylation site allowed the development of an experiment vaccine strain that has been shown to induce protection as early as 3-days post vaccination. The manipulation of the glycosylation sites also presents opportunities for developing negative marker attenuated vaccines able to induce early protection. These technologies have been transferred to a multinational biopharmaceutical company that is investing in the development of a new CSF vaccine designed for the control and eradication of CSF.

Scientific Publication:
Gavrilov B.K., Rogers K., Fernandez-Sainz I.J., Holinka L.G., Borca M.V., Risatti G.R. (2011). Effects of glycosylation on antigenicity and immunogenicity of classical swine fever virus envelope proteins. Virology 420: 135–145.

Primary Sites of Foot-and-Mouth Disease Virus Replication in Cattle.
It is well established that the respiratory tract is the most important route of infection of foot-and-mouth disease virus (FMDV) in cattle. However, conflicting data from different research groups have implicated regions of either upper respiratory tract (nasopharynx) or lower respiratory tract (lungs) as the primary sites of infection. ARS scientists at the Plum Island Animal Disease Center, Greenpoint, New York, have demonstrated that after aerosol exposure to the virus the early pathogenesis events involve: 1) primary replication in epithelial cells of the pharyngeal mucosa-associated lymphoid tissue crypts and 2) subsequent widespread replication in pneumocytes in the lungs, which coincides with 3) the establishment of sustained viremia. This infection model demonstrated that massive viral amplification occurs in the lungs (with associated shedding to the environment) prior to appearance of the first vesicle. Viremia is established coincidently with further viral amplification in the lungs and at lesion (vesicle) predilection sites. This scientific information is critical to the development of foot-and-mouth disease (FMD) countermeasures as it is critical that prophylactic products target these previremic events in the pharynx and lungs. Based on this information, it is speculated that enhancement of mucosal immunity has a high probability of improving protection. Once viremia is established, on an individual animal basis, the battle has already been lost. Continued efforts to improve the understanding of virus host interactions during early phases of infection will greatly contribute to the development of effective tools to block viral infection.

Scientific Publications:
Arzt, J., Gregg, D.A., Clavijo, A., and Rodriguez, L.L. 2009. Optimization of immunohistochemical and fluorescent antibody techniques for localization of Foot-and-mouth disease virus in animal tissues. J Vet Diagn. Invest 21, 779-792.

Arzt, J., J. M. Pacheco, and Rodriguez, L.L., 2010: The Early Pathogenesis of Foot-and-Mouth Disease in Cattle After Aerosol Inoculation: Identification of the Nasopharynx as the Primary Site of Infection. Vet Pathol. 47(6):1048-63. Epub 2010 Jun 29.

Induction of the Cellular Immune Response to Foot-and-Mouth Disease Virus by Unique Vaccine Targeting.
The host response to FMDV infection has historically been focused on neutralizing (virus blocking) antibody responses. However, the cellular immune response has been much more difficult to assess. ARS scientists at the Plum Island Animal Disease Center, Greenpoint, New York, discovered vaccination strategies to induce the humoral or cellular response separately so it could be determined what the contribution of these different responses were in protecting animals from infection. The experimental FMDV vaccine, vectored by human replication defective adenovirus 5, induces strong humoral immune responses but no cellular immunity. An altered Ad5-FMDV construct induces cellular immune responses and poor humoral immunity. The research showed for the first time that the cellular response to FMDV, in the absence of significant humoral immunity, reduces clinical disease, most notably by blocking virus spread via blood in animals challenged with live virus. This approach reveals the effect of cellular immunity alone and indicates that adding vaccination for cellular immune responses has the potential to improve the performance of the Ad5-FMDV vectored vaccine.

Scientific Publication:
Patch J.R., Pedersen L.E., Toka F.N., Moraes M., Grubman M.J., Nielsen M., Jungersen G., Buus S., Golde W.T. 2011. Induction of foot-and-mouth disease virus-specific cytotoxic T cell killing by vaccination. Clin Vaccine Immunol. 2011 Feb; 18(2): 280-8. Epub 2010 Dec 22.

Increased Efficacy of an Adenovirus-vectored Foot-and-Mouth Disease Virus Vaccine Expressing Nonstructural Protein 2B.
ARS scientists at the Plum Island Animal Disease Center, Greenpoint, New York, previously demonstrated that an adenovirus-vectored FMDV serotype A24 vaccine, Ad5-A24, expressed under the control of a cytomegalovirus promoter (CMV) can protect swine and bovines against homologous challenge, but swine vaccinated with an Ad5-vectored FMDV O1 Campos vaccine are only partially protected when challenged 21 days post-vaccination. ARS scientists have now demonstrated that inclusion of the complete coding region of nonstructural protein 2B in the Ad5-A24 vector resulted in improved immune responses in pigs. Interestingly, although a significant antigen specific-CD8+ T cell response was also detected in all vaccinated groups, it was higher in the group receiving the Ad5-vectored FMDV O1 Campos vaccine with the complete 2B coding region. These results indicate that a vector containing 2B improves the efficacy of Ad5 vaccines.

Scientific Publication:
Moraes M.P., Segundo F.D., Dias C.C., Pena L., Grubman M.J. 2011. Increased efficacy of an adenovirus-vectored foot-and-mouth disease capsid subunit vaccine expressing nonstructural protein 2B is associated with a specific T cell response. Vaccine. 2011 Nov 28; 29(51): 9431-40. Epub 2011 Oct 24.

Competence of U.S. Arthropods for Rift Valley Fever Virus.
Rift Valley fever virus (RVFV), a zoonotic insect transmitted virus endemic to Africa and the Arabian Peninsula, causes abortions and high mortality in newborn ruminants. The potential of RVFV as a bioterrorism agent and/or being accidentally introduced into North America is widely recognized. To determine which arthropods should be targeted for control should RVFV be detected in North America, ARS scientists in Manhattan, Kansas, in collaboration with U.S. Army scientists at Fort Detrick, Maryland, evaluated mosquito species from the western, midwestern, and southern United States for their ability to transmit the virus. *Culex tarsalis* mosquitoes transmitted Rift Valley fever virus most efficiently, whereas none of the other *Culex* species tested transmitted the virus as well. Although *Aedes vexans* mosquitoes from Florida and Louisiana were relatively efficient vectors of Rift Valley fever virus, specimens of this species captured in Colorado or California were virtually incompetent, illustrating the need to evaluate local populations for the ability to transmit a pathogen. This was the first comprehensive vector competence study of U.S. mosquitoes for Rift Valley fever virus and provides key targets for vector control should an outbreak of Rift Valley fever virus ever occur in the United States.

Scientific Publication:
Turell, M., Bennett, K.E. and Wilson, W.C. 2010. Potential for North American mosquitoes to transmit Rift Valley fever virus. J. Med. Ent. 47: 884-889.

Developing Diagnostics to Detect Rift Valley Fever Virus in North America.
Currently, regional veterinary biosafety level 2 (BSL-2) diagnostic laboratories lack safe, modern, validated diagnostic tests to detect RVFV. For RVFV antigen detection, reagents are typically produced at BSL-3Ag or BSL-4 conditions and require inactivation and safety testing for use outside of containment. ARS scientists in Manhattan, Kansas, modified an existing one-step, real-time RT-PCR (rRT-PCR) assay for quick virus inactivation for use in BSL-2 laboratories. The researchers produced an antiserum against recombinant RVFV-nucleocapsid (N) to develop an immunohistochemical (IHC) assay that was subsequently evaluated on formalin fixed lamb and calf tissues at BSL-2 laboratory conditions. Once validated and approved by national regulatory agencies, these assays can be safely produced and distributed to regional diagnostic laboratories, providing capacity for early detection of RVFV in suspected ruminant samples.

Scientific Publication:
Drolet, B.S., Weingartl, H.M., Jiang, J., Neufeld, J. Marszal, P., Lindsay, R., Miller, M.M., Czub, M., Wilson, W.C. 2011. Development and evaluation of one-step rRT-PCR and immunohistochemical methods for detection of Rift Valley fever virus in North American biosafety level 2 diagnostic laboratories. J. Virol. Meth. 179: 373-382.

Reducing the Dose of Avian Influenza Vaccines Is Not a Good Idea.
Vaccination is an emergency tool that can be used to confront outbreaks of H5N1 high pathogenicity avian influenza (HPAI), but the number of vaccine doses in the U.S. National Veterinary Stockpile is limited. To determine if the available vaccine doses could be stretched by using reduced vaccine dose, while maintaining adequate efficacy, ARS scientists in Athens, Georgia, conducted a vaccination-challenge study in chickens using full, half, one-fourth, and one-tenth vaccine doses. The researchers found that all avian influenza (AI) vaccinated chickens were protected from disease and death. However, they found that using less vaccine than the full dose had some negative effects, including reduced serological titers, more chickens excreting challenge virus, and higher quantities of challenge virus growth and excretion from intestines and respiratory system. These studies emphasize the importance of following label directions and administering the full vaccine dose. This is especially important when considering that commercial chickens under field condition are typically less responsive to AI vaccination than the specific pathogen free chickens used in vaccine trials.

Scientific Publication:
Goetz, S., Spackman, E., Hayhow, C., Swayne, D.E. 2008. Assessment of reduced vaccine dose on efficacy of an inactivated avian influenza vaccine against an H5N1 high pathogenicity avian influenza virus. Journal of Applied Poultry Research. 17:145-150.

Wood Ducks are Highly Sensitive to Avian Influenza.
Since 2002, H5N1 HPAI viruses have caused mortality in numerous species of wild aquatic birds in Asia and Europe. Some HPAI viruses cause severe disease in several species of wild ducks in experimental infections. In collaboration with the Southeastern Cooperative Wildlife Disease Center at the University of Georgia, ARS scientists in Athens, Georgia, evaluated five species of wild ducks intranasally inoculated with an Asian strain of H5N1 HPAI virus. The wood duck was two to four times more susceptible to infection than were chickens, the latter being highly

susceptible to the virus. Mallards (*Anas platyrhynchos*), northern pintails (*Anas acuta*), blue-wing teals (*Anas crecca*), and redheads (*Aythya americana*) were less sensitive to infection, produced virus in low concentrations for short periods of time, and did not exhibit clinical signs. These data suggest that the wood duck would represent a sensitive indicator species for H5N1 HPAI should it enter North America.

Scientific Publication:
Brown, J.D., Stallknecht, D.E., Beck, J.R., Suarez, D.L., Swayne, D.E. 2006. Susceptibility of North American ducks and gulls to H5N1 highly pathogenic avian influenza viruses. Emerging Infectious Diseases. 12(11):1663-1670.

Cooking Poultry Meat Inactivates Avian Influenza Virus.
HPAI viruses can be present in the meat of infected poultry and pose a potential health risk. ARS researchers in Athens, Georgia, showed that cooking was effective in killing an H5N1 HPAI virus. Two additional HPAI viruses (H5N2 Pennsylvania/83 and H5N2 Texas/04) were tested for thermal inactivation in naturally or artificially infected meat, and researchers found that cooking the meat to an internal temperature 165 degrees Fahrenheit was effective at killing the viruses in less than one minute. This study demonstrated that proper cooking of poultry using the USDA Food Safety Inspection Service's Salmonella standards would be effective at killing HPAI viruses.

Scientific Publication:
Thomas, C., Swayne, D.E. 2007. Thermal inactivation of H5N1 high pathogenicity avian influenza virus in naturally infected chicken meat. Journal of Food Protection. 70(3):674-680.

2009 Pandemic H1N1 Influenza A Virus.
Soon after the emergence of the pandemic H1N1 Influenza A virus in April 2009, ARS scientists at the National Animal Disease Center, Ames, Iowa, began research using virus samples provided by the CDC. The first step was to address the safety of pork. Thirty-five-week-old cross-bred pigs from a herd free of swine influenza virus were inoculated to determine the susceptibility of swine to the human virus and also address whether meat, blood, and tissue from pigs infected with the pandemic 2009 A/H1N1 influenza virus are free of the infectious virus. The pigs were observed daily for clinical signs of disease, and nasal swabs and fresh samples from lung, tonsil, inguinal lymph node, liver, spleen, kidney, skeletal muscle (ham), and colon contents were tested by the most sensitive virus detection assays at three, five, and seven days post-infection. Live 2009 A/H1N1 influenza virus was detected only in the respiratory tract of infected pigs, and the virus did not appear to spread and replicate in other tissues. This information was used by the pork industry during the pandemic H1N1 outbreak to communicate to consumers that pork was safe to eat.

Scientific Publications:
Vincent A.L., Lager K.M., Harland M., Lorusso A., Zanella E., Ciacci-Zanella J.R., Kehrli M.E., Jr., Klimov A. (2009) Absence of 2009 pandemic H1N1 influenza A virus in fresh pork. PLoS ONE. 2009 Dec 18;4(12):e8367.

Vincent AL, Lager K.M., Faaberg K.S., Harland M., Ciacci-Zanella JR, Kehrli M.E., Jr., Janke B.H., Klimov A. (2009). Experimental inoculation of pigs with pandemic H1N1 2009 virus and HI cross-reactivity with contemporary swine influenza virus antisera. Influenza Other Respi Viruses. 2010 Mar; 4(2):53-60.

Efficacy of Swine Influenza Vaccines against Pandemic H1N1.

The gene constellation of the 2009 pandemic A/H1N1 virus is a unique combination from swine influenza A viruses of North American and Eurasian lineages, but prior to April 2009 this new and emerging virus had never before been identified in swine or other species. Although its hemagglutinin gene is related to North American H1 swine influenza A virus, it is unknown if vaccines currently used in U.S. swine would cross-protect against infection with the pandemic A/H1N1. ARS scientists in Ames, Iowa, evaluated the efficacy of inactivated vaccines prepared with North American swine influenza viruses as well as an experimental homologous A/H1N1 vaccine to prevent infection and disease from the 2009 pandemic A/H1N1. All vaccines tested provided partial protection ranging from reduction of pneumonia lesions to significant reduction in virus replication in the lung and nose. The multivalent vaccines demonstrated partial protection. However, none were able to prevent all nasal shedding or clinical disease. An experimental homologous 2009 A/H1N1 monovalent vaccine provided optimal protection with no virus detected from nose or lung at any time point. Based on cross protection demonstrated with the vaccines evaluated in this study, the U.S. swine herd likely has significant immunity to the 2009 A/H1N1 from prior vaccination or natural exposure. However, consideration should be given for development of monovalent homologous vaccines to best protect the swine population, thus limiting shedding and the potential transmission of 2009 A/H1N1 from pigs to people.

Scientific Publication:

Vincent, A.L., Ciacci-Zanella, J.R., Lorusso, A., Gauger, P.C., Zanella, E.L., Kehrli Jr, M.E., Janke, B.H., Lager, K.M. 2010. Efficacy of Inactivated Swine Influenza Virus Vaccines Against the 2009 A/H1N1 Influenza Virus in Pigs. Vaccine 28(15):2782-2787.

A Genetically-Engineered Swine Influenza Vaccine Confers Cross-Protection against Emerging Variant Virus Strains.

It is widely recognized that the diversity of swine influenza virus (SIV) strains impedes the effective immunization of swine herds. This is of great concern as emerging variant swine influenza viruses could emerge into the human population. New variant viruses may also have significant negative economic impact on the swine industry. Therefore, the evaluation of modern vaccine technologies for SIV in the swine host is important for achieving greater control of emerging variant virus strains in swine populations and limiting the risk of transmission to humans. Live virus vaccines are considered to be more effective than inactivated or non-replicating virus vaccines as inducers of cellular immunity, but all licensed SIV vaccines in the United States are based on inactivated virus antigens. ARS scientists at the National Animal Disease Center, Ames, Iowa, used molecular approaches to construct mutated H3N2 SIV genomes that result in attenuated replication properties. Truncation of a key viral protein (NS1) used by influenza virus to evade the host immune system produced a mutant virus with restricted replication in the swine respiratory tract but strong immunogenic properties. Intranasal inoculation of pigs with this virus resulted in robust protection against homologous challenge

and significantly reduced viral replication and clinical signs upon challenge with a heterologous H1N1 SIV strain.

Scientific Publication:
Kappes M.A., Sandbulte M.R., Platt R., Wang C., Lager K.M., Henningson J.N., Lorusso A., Vincent A.L., Loving C.L., Roth J.A., Kehrli M.E. (2011). Vaccination with NS1-truncated H3N2 swine influenza virus primes T cells and confers cross-protection against an H1N1 heterosubtypic challenge in pigs. Vaccine. 2012 Jan 5;30(2):280-8. Epub 2011 Nov 7.

The Risk of Low-pathogenic Avian Influenza Viral Strains Becoming Virulent.
The use of reverse genetics to make avian influenza viruses with a specific sequence has proven to be a valuable tool in examining how these viruses cause disease in poultry. From 1994 to 2006 low-pathogenic H7N2 avian influenza viruses circulated in the live bird markets of northeastern United States. There has been considerable concern that these viruses might change or mutate to the virulent form of the virus. Using reverse genetics techniques, ARS scientists in Athens, Georgia, selected a representative H7N2 virus and genetically changed the virus to try and understand the minimum number of nucleotide changes needed for the virus to become virulent. The results of this study showed that the virus needed insertions of amino acids at a key site in the virus, the cleavage site, to become virulent, and simple mutations at the cleavage site by themselves would not make the virus virulent. This study improved understanding of how avian influenza viruses become virulent and will help to understand risks of low-pathogenic viruses changing to the highly pathogenic form in the future.

Scientific Publication:
Lee, C., Lee, Y., Senne, D.A., Suarez, D.L. 2006. Pathogenic potential of North American H7N2 avian influenza virus: A mutagenesis study using reverse genetics. Virology. 353:388-395.

Epidemiology and Evolution of Virulent Newcastle Disease.
Newcastle disease (ND) is an infection of birds caused by a virulent Newcastle disease virus (vNDV) and is a worldwide problem for poultry production. The virulent form of the disease, called exotic ND (END) in the United States, has been eradicated from U.S. poultry. Recent analysis of genomic sequences has revealed the existence of two distinct clades: class I and II. Class I isolates have been recovered primarily from waterfowl and are generally attenuated in poultry. The class II NDV comprise the vast majority of vNDV and include isolates recovered from poultry, pet, and wild bird viruses. Current weaknesses in the USDA standard real time (r) reverse transcriptase polymerase chain reaction (RT-PCR) assay to detect class I viruses suggests that viral transmission could occur unnoticed among wild birds and poultry. Although it is impossible to predict which genotypes represent the most significant threat to the U.S. poultry industry, the geographic proximity of vNDV and the large volume of commerce and travel with Mexico and countries of Southeast Asia suggest that further evaluation of the efficacy of current U.S. vaccines and diagnostic assays on emerging viruses are needed. ARS scientists in Athens, Georgia, have developed an alternative rRT-PCR test that can detect a majority of class I isolates from the United States. This test will enable the surveillance of class I viruses and help identify the genotypes of viruses with the potential to acquire virulence upon replication in poultry, an important step in improving the capacity to prevent future outbreaks.

Scientific Publications:

Kim, L.M., Afonso, C.L., Suarez, D.L. 2006. Effect of probe-site mismatches on detection of virulent Newcastle disease viruses using a fusion-gene real-time reverse transcription polymerase chain reaction test. Journal of Veterinary Diagnostic Investigation. 18:519-528.

Kim, L.M., King, D.J., Suarez, D.L., Wong, C.W., Afonso, C.L. 2007. Characterization of Class I Newcastle disease virus isolates from Hong Kong bird markets and detection using real-time reverse transcription PCR. Journal of Clinical Microbiology. 45:1310-1314.

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Component 2: Animal Genomics and Immunology

Rationale for the research:
The last fifty years in animal agriculture has seen tremendous improvements in animal breeds based on quantitative genetics and the selective breeding of farm animals. Most of these successes have been achieved through selection using traditional quantitative genetics tools, but the recent access to animal genomes and genome-enabled tools is having a significant impact on selection programs to improve production traits. However, a key challenge remains the selection of animals with improved health traits. For instance, the genetic control of complex traits like disease resistance has been unreliable when applied to outbred populations under field conditions. The number of genes, the extent of their effect on disease susceptibility, and the interactions between them remain unknown. There are also significant gaps in our understanding of animal immunology, contributed in large part by the dearth of available immunological reagents. Notwithstanding, significant advances made in mouse and human immunology, including innate defense mechanisms, are contributing significantly to our understanding of animal immunology. Continued efforts to develop immunological reagents along with genome-enabled tools are having a major impact on our understanding of functional-genomics and host-pathogen interactions. We now have molecular tools that are propelling animal health research towards new fields of investigation in transcriptomics, proteomics, and metabolomics. The application of animal genomics research has the potential to revolutionize the speed and scope of problem-solving in animal health.

Because the anticipated products that were put forth five years ago for research in animal genomics and immunology are very broad in scope and remain largely inspirational, the ARS animal health national program focused available resources in three strategic areas: 1) identify genetic and biological determinants of disease susceptibility; 2) understand host-pathogen interactions, including mechanisms of pathogen immune evasion and host protective immunity; and 3) the development of genomics-based diagnostics, vaccines, and biotherapeutics to prevent and control priority diseases in target farm animal populations.

Stakeholders at the September 2005 Animal Health Planning Workshop ranked cross-cutting issues such as animal genomics and immunology to improve animal health as their 2nd priority. The research in Component 2 focuses on understanding the functional genomics of host-pathogen interactions in livestock and poultry, providing important scientific information that cross-cut the other seven Research Components of the NP 103 National Program.

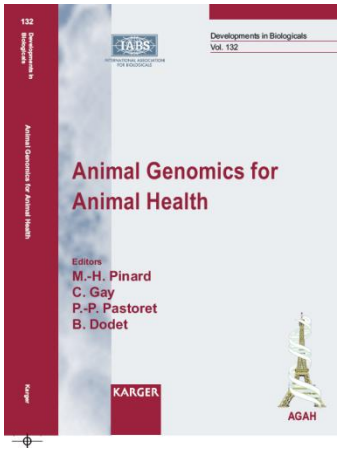
Research Needs:
The significant advances made in the last decade in human biomedical research can be attributed in large part to new breakthroughs in genomics and immunology, including an expanded understanding of the complexities of innate defense mechanisms. However, animal genomics and immunology continues to lag behind its human counterparts. Although the “genomics” revolution is expending the opportunities for understanding host-pathogen interactions and providing new strategies for developing countermeasures to prevent and treat human diseases, the application of these tools in animal health research is still at the infancy stage.

Research in animal genomics and immunology is needed to understand gene interactions involved in immune cell activation, migration, and host responses. This knowledge will be applied towards the discovery of effective biotherapeutics and vaccines. An important area of research is the discovery and development of alternatives to antibiotics. A genomics approach will be used to discover naturally expressed antimicrobials. New tools based on protective host proteins will also be developed to modulate innate immune responses to treat infections and/or increase host clearance of pathogens.

The specific research priorities and anticipated products for Component 2 were derived in large part from the outcomes of two international symposiums on "Animal Genomics for Animal Health" organized by ARS in 2007 and 2010. The first symposium was organized in 2007 in collaboration with the World Organization for Animal Health (OIE) and the European Animal Disease Genomics Network of Excellence for Animal Health and Food Safety (EADGENE). One of the major outcomes was the publication of a report capturing the outcomes of the symposium expert panel discussion which included key recommendations and next steps for advancing the integration of genome-enabled technologies in animal health research (Archibald, A., Audonnet, J.C., Babiuk, L., Bishop, S.C., Gay, C.G., McKay, J., Mallard, B., Plastow, G., Pinard van der Laan, MH., Torremorell, M. 2008. Animal genomics for animal health report: critical needs, problems to be solved, potential solutions, and a roadmap for moving forward. *Dev Biol (Basel)*, 132:407-24).

The second symposium was organized in 2010 as a follow up to the first international symposium on animal genomics for animal health https://colloque.inra.fr/agah2010. A major outcome was again the publication of a report capturing the outcomes of the symposium expert panel discussion, which identified gaps that hinder the application of genomics in animal health research and specific recommendations for moving the field forward in the next five years (Bishop SC, Lunney JK, Pinard-van der Laan MH, Gay CG. 2011. Report from the second international symposium on animal genomics for animal health: critical needs, challenges and potential solutions. BMC Proc. 2011 Jun 3; 5 Suppl 4:S1).

These two symposiums and the ensuing published reports and recommendations provided research direction, opportunities for research collaborations at the national and international levels, and support from funding agencies such as the European Commission, USDA-NIFA, and the National Pork Board. The reports from these symposiums provided research priorities and anticipated products that were expected from the research and that now serve to help measure the National Program's progress during the last five years in advancing the field of science and the needs of animal producers. The following list of anticipated products is followed by the expected impact of the research and a sampling of relevant accomplishments.



Anticipated Products In Action Plan:

- Identify genetic variations associated with difference in immune cell activation, migration, and host responses to pathogens.
- New methods for preventing and controlling mastitis.
- New biotherapeutic platforms based on protective host proteins to induce the cow's innate immune response.
- Therapeutics to reduce cell damage during mastitis.
- Markers for mammary stem cells and methods for their regulation.
- New biotherapeutic platforms based on targeted expression of host-derived inflammatory products with receptor antagonists and/or siRNA molecules.
- Innovative approaches using naturally expressed host antimicrobial peptides to increase resistance to prevalent pathogens.
- Basic research information to understand how genetic variations influence the immune response to Marek's disease infection.
- Basic research information to understand how the interplay between specific host and Marek's disease viral genes, and the variation within these genes, leads to disease susceptibility or resistance.
- Simple molecular tests to pathotype field strains of Marek's disease virus.
- Identification of viral genes responsible for pathogenesis and identification of predictors of virulence shifts.
- Elucidation of viral genes associated with immune evasion mechanisms.
- Characterization of biological pathways that lead to the development of disease.
- Characterization of vaccine-induced determinants of protective immunity.
- A safe and highly effective vaccine with mass vaccination capability that conveys protection against emerging Marek's disease viral strains in defined host animal genotypes.
- Discovery of genes that confer susceptibility to mucosal diseases of cattle, pigs, and poultry.
- Identification of genomic regions or specific structural variations associated with differences in disease-resistance traits.
- Improved methods of predicting genetic merit based on dense SNP-based marker data.
- Development of enabling tools (immunological reagents, SNP markers and SNP Haplotypes) to propel our understanding of host responses to diseases.
- Identification of the genes mediating resistance from previously determined quantitative trait loci (QTL) associated with susceptibility to diseases of livestock and poultry
- Differences in host immunological and physiological responses to mucosal diseases will be associated with genetic markers and then fine-mapped to specific genes.
- Gene expression and genetic variations associated with protective immune responses.
- Biological determinants of innate and adaptive protective immunity will be identified and characterized.
- Comparative genetic maps to identify areas of similarity (synteny) between the bovine, swine, avian, humans, and mice genome.
- Identification of markers for the detection of underlying disease infections.
- Highly effective diagnostics, vaccines, and biotherapeutics designed to prevent and control mucosal diseases in targeted animal populations.

Impact:
The development of new genomics and immune-based research approaches provide new synergistic approaches for understanding and mitigating animal diseases that will benefit the animal agriculture industry with the design of effective disease control programs.

COMPONENT 2: SELECTED ACCOMPLISHMENTS

A Novel Haplotype Networking Approach Reveals a Bovine Prion Gene Haplotype Association with Atypical BSE.

Three distinct transmissible spongiform encephalopathies have been identified in cattle: classical bovine spongiform encephalopathy (BSE), atypical High-type BSE, and atypical Low-type BSE (See Component 8). Atypical BSEs have only recently been recognized as distinct, relatively rare cattle prion diseases; approximately 51 cases have been identified worldwide. To test bovine prion gene (*PRNP*) variation for associations with either classical or atypical BSE, a 25.2-kb segment of *PRNP* was recently sequenced in 192 U.S. cattle representing 21 beef or dairy breeds. Analysis of 388 polymorphisms found in these cattle revealed that the gene is composed of two distinct regions of high and low linkage disequilibrium (LD). Accordingly, haplotype diversity at the *PRNP* locus was characterized with independent Median-Joining networks for the two (high and low) LD regions in these cattle as well as additional samples from atypical BSE-affected animals. A haplotype from one of these networks showed strong association with atypical BSE, as it was significantly more prevalent in affected animals than in the overall population. The haplotype spans a portion of *PRNP* that includes part of intron 2, the entire coding region of exon 3 and part of the three prime untranslated region of exon 3 (13 kb), and has been indentified in H- and L-type atypical BSE cases from Canada, France, and the United States.

Scientific Publication:
Clawson M.L., Richt J.A., Baron T., Biacabe A.G., Czub S., Heaton M.P., Smith T.P., Laegreid W.W. 2008. Association of a bovine prion gene haplotype with atypical BSE. PLoS One. 2008 Mar 19;3(3):e1830.

Identification of a Heritable Polymorphism in the Bovine Prion Gene Associated with Genetic Transmissible Spongiform Encephalopathy.

Classical BSE is associated with ingestion of BSE-contaminated feedstuffs while H- and L-type BSE, collectively known as atypical BSE, differ from classical BSE by displaying a different disease phenotype and they have not been linked to the consumption of contaminated feed (See Component 8). Interestingly, the 2006 U.S. H-type atypical BSE animal had a polymorphism at codon 211 of the bovine prion gene resulting in a glutamic acid to lysine substitution (E211K). This substitution is analogous to a human polymorphism associated with the most prevalent form of heritable transmissible spongiform encephalopathy (TSE) in humans, and it is considered to have caused BSE in the 2006 U.S. atypical BSE animal. In order to determine if this amino acid change is a heritable trait in cattle, ARS scientists in Ames, Iowa, sequenced the prion alleles of the only known offspring of this animal, a 2-year-old heifer. It was discovered that both the dam and the offspring carry the E211K polymorphism, indicating that the allele is heritable and may persist within the cattle population. This is the first evidence that the E211K polymorphism is a germline polymorphism, not a somatic mutation, suggesting BSE may be transmitted genetically

in cattle. In the event that E211K proves to result in a genetic form of BSE, this would be the first indication that all 3 etiologic forms of TSEs (spontaneous, hereditary, and infectious) are present in a non-human species. Atypical BSE arising as both genetic and spontaneous disease, in the context of reports that at least some forms of atypical BSE can convert to classical BSE in mice, suggests a cattle origin for classical BSE.

Scientific Publication:
Nicholson E.M., Brunelle B.W., Richt J.A., Kehrli M.E. Jr/, Greenlee J/J. Identification of a heritable polymorphism in bovine PRNP associated with genetic transmissible spongiform encephalopathy: evidence of heritable BSE. PLoS One. 2008 Aug 13;3(8):e2912.

Prevalence of the Prion Protein Gene E211K Variant in U.S. Cattle.
The finding of the bovine E211K mutation is important because it is analogous to the most common pathogenic mutation in humans (E200K), which causes hereditary Creutzfeldt-Jakob disease, an autosomal dominant form of prion disease. ARS scientists in Clay Center, Nebraska, in collaboration with scientists in Beltsville, Maryland, used a high-throughput matrix-associated laser desorption/ionization-time-of-flight mass spectrometry assay for scoring the prion gene E211K variant and determine an upper limit for the E211K allele frequency in U.S. cattle. The scientists found that the E211K allele was not detected in 6062 cattle, including those from five commercial beef processing plants (3892 carcasses) and 2170 registered cattle from 42 breeds. Based on these results, the upper bounds for prevalence of the E211K variant was estimated to be extremely low, less than 1 in 2000 cattle. No groups or breeds of U.S. cattle are presently known to harbor the prion gene E211K allele. Because a carrier was not detected, the number of additional atypical BSE cases with E211K is expected to be low.

Scientific Publication:
Heaton M.P, Keele J.W., Harhay G.P., Richt J.A., Koohmaraie M., Wheeler T.L., Shackelford S.D., Casas E., King D.A., Sonstegard T.S., Van Tassell C.P., Neibergs H.L., Chase C.C. Jr., Kalbfleisch T.S., Smith T.P., Clawson M.L., Laegreid W.W. Prevalence of the prion protein gene E211K variant in U.S. cattle. BMC Vet Res. 2008 Jul 14; 4:25.

Ovine Progressive Pneumonia Virus.
Research on Ovine Progressive Pneumonia Virus (OPPV) advanced our understanding of the genetic basis for susceptibility to OPPV. It was demonstrated that OPPV peripheral provirus concentration is predictive of lesion severity, and showed breed differences in peripheral proviral concentrations. Together, these results suggested a genetic basis for control of OPPV severity, in addition to previously known differences in OPPV prevalence by breed. Quality ruminant sequence of the most polymorphic genes in the MHC Class IIa region (DRB1, DQA1, DQA2, DQB1, DQB2) along with expression data for all five loci were used to assess hereditablity. Also, an association between specific alleles of both DRB1 and CCR5 and proviral concentration in one flock was demonstrated. These allelic associations provided 1) indications of genes involved in differential control of OPPV severity and 2) a basis for additional experiments to validate genetic markers to enable selection of animals better able to control OPPV lesion severity. Finally, it was demonstrated that non-maternal transmission was the major mode of transmission in one large range flock. This demonstrated that maternal transmission is not always the major mode of transmission as previously reported for OPPV and caprine arthritis-

encephalitis virus (CAEV) and highlight the importance of intervention strategies like genetic selection that do not depend solely on interrupting maternal transmission.

Scientific Publication:
Herrmann-Hoesing L.M., White S.N., Mousel M.R., Lewis G.S., Knowles D.P. 2008. Ovine progressive pneumonia provirus levels associate with breed and Ovar-DRB1.Immunogenetics. 2008 Dec; 60(12):749-58. Epub 2008 Sep 17.

The PRRS Host Genetics Consortium (PHGC).
Understanding the role of host genetics in resistance to porcine reproductive and respiratory syndrome virus (PRRSV) infection, and the effects of porcine reproductive and respiratory syndrome (PRRS) on pig health and related growth, are goals of the PRRS Host Genetics Consortium (PHGC). The project uses a nursery pig model to assess pig resistance/susceptibility to primary PRRSV infection. Six groups of 200 crossbred pigs from high health farms were donated by commercial sources. After acclimation, the pigs were infected with PRRSV in a biosecure facility and followed for 42 days post infection (dpi). Blood samples were collected at 0, 4, 7, 10, 14, 21, 28, 35 and 42 dpi for serum and whole blood RNA gene expression analyses; weekly weights were recorded for growth traits. All data have been entered into the PHGC relational database. Genomic DNAs from all PHGC1-6 pigs were prepared and genotyped with the Porcine SNP60 SNPchip. Results have affirmed that all challenged pigs become PRRSV infected with peak viremia being observed between 4-21 dpi. Multivariate statistical analyses of viral load and weight data have identified PHGC pigs in different virus/weight categories. Sera were compared for factors involved in recovery from infection, including speed of response and levels of immune cytokines. Genome-wide association studies (GWAS) were used to identify genes and chromosomal locations that identify PRRS resistant/susceptible pigs and pigs able to maintain growth while infected with PRRSV. Overall, the PHGC project will enable researchers to discover and verify important genotypes and phenotypes that predict resistance/susceptibility to PRRSV infection. The availability of PHGC samples provides a unique opportunity to continue to develop deeper phenotypes on every PRRSV infected pig.

Scientific Publication:
Lunney J.K., Steibel J.P., Reecy J.M., Fritz E., Rothschild M.F., Kerrigan M., Trible B., Rowland R.R. 2011. Probing genetic control of swine responses to PRRSV infection: current progress of the PRRS host genetics consortium. BMC Proc. 2011 Jun 3;5 Suppl 4:S30.

Next Generation Recombinant Marek's Disease Virus Vaccine Lacking Meq Oncogene.
Marek's disease virus (MDV) oncogene meq has been identified as the gene involved in tumorigenesis in chickens. ARS scientists in East Lansing, Michigan, have recently developed a Meq-deleted virus, designated rMd5 Delta Meq, in which the oncogene meq was deleted. Vaccine efficacy experiments with rMd5 Delta Meq virus or a conventional Marek’s disease vaccine indicated that rMd5 Delta Meq provided superior protection when challenged with a very virulent plus MDV. ARS scientists also investigated the vaccine efficacy of rMd5 Delta Meq in the field compared to several commercial preparations of Marek’s disease vaccines. Three large-scale field experiments, in which seeder chickens were inoculated with a very virulent plus strain of MDV. Experimental results showed that rMd5 Delta Meq was a better or

equal vaccine compared to any of the commercial vaccines tested under field conditions. This next generation vaccine may become an important tool against the continuously evolving MDV.

Scientific Publication:
Lee L.F., Kreager K.S., Arango J., Paraguassu A., Beckman B., Zhang H., Fadly A., Lupiani B., Reddy S.M. 2010. Comparative evaluation of vaccine efficacy of recombinant Marek's disease virus vaccine lacking Meq oncogene in commercial chickens. Vaccine. 2010 Feb 3;28(5):1294-9. Epub 2009 Nov 24.

The U.S. Veterinary Immune Reagent Network.
The U.S. Veterinary Immune Reagent Network http://www.umass.edu/vetimm/ is one of the key outcomes of a seminal immunology workshop organized by ARS in 2003. The workshop proceedings and recommendations from this workshop (http://www.ars.usda.gov/SP2UserFiles/Program/103/ARS2003ImmunologyResearchWorkshop.pdf) have served as a roadmap for funding research priorities in veterinary immunology at ARS. The participants of the workshop, representing many of the opinion leaders conducting research in animal immunology, identified the lack of immunological reagents for veterinary research as a major gap hindering significant advancements in animal immunology. The lack of tools for basic veterinary research was also identified as key priorities at the 2007 and 2010 International Symposiums on Animal Genomics for Animal Health. The creation of the U.S. Veterinary Immune Reagent Network exemplifies the team approach taken by ARS and NIFA in solving problems of national priority. NIFA provided the initial $2.3 million seed funds to develop priority reagents to advance veterinary immunology and the development of countermeasures to control diseases of ruminants, swine, poultry, equine, and aquaculture species. ARS has led the development of poultry and swine immunological reagents. A significant accomplishment in 2010 included a grant from the Department of Homeland Security to produce immune reagents to support the development of countermeasures for the U.S. National Veterinary Stockpile. To date, ARS scientists have developed, characterized, and transferred to the commercial sector over 20 avian recombinant cytokines, chemokines, and interferons, including 14 hybridomas providing monoclonal antibodies to study host immune responses in chickens. These monoclonal antibodies can now be used to assess the immune status of chickens vaccinated with different infectious agents. These monoclonal antibodies are also useful in the identification of lymphocyte subpopulations and macrophages in the tissues and the peripheral blood from chickens infected with microbial agents or vaccinated with the vaccines. A total of 22 swine recombinant cytokines, chemokines, and interferons, including five hybridomas have been developed, characterized, and transferred to the commercial sector for distribution to the animal health research community. These swine immune reagents can now be used to assess swine immune responses to infectious diseases and vaccines. Products from this research enhances an expanding base of scientific knowledge on host innate and adaptive immune responses, and can be applied to support the discovery and development of vaccines and biotherapeutics for priority diseases of poultry and swine.

Scientific Publications:
Scott T.R., Lillehoj H.S. 2007. Monoclonal antibodies against chicken interleukin-6. Vet. Immunol. Immunopathol.114:173-177.

Yoo J.M., Chang H.H., Bae Y.H., Seoung C.N., Lillehoj H.S., Min W.G. 2008. Monoclonal antibodies reactive with chicken IL-17A. Vet. Immunol. Immunopathol. 121: 359-363.

Yoo J.M., Jang S.I., Kim S., Cho J.H., Lee H.J., Rhee M.H., Lillehoj H.S., Min W.G. 2009. Molecular cloning and characterization of duck interleukin-17. Vet. Immunol. Immunopathol. 132:318-322.

Hong Y.H., Lillehoj H.S., Lee S.H., Park M.S., Min W., Labresh J., Tompkins D., Baldwin C. 2010. Development and characterization of mouse monoclonal antibodies specific for chicken interleukin 18. Vet. Immunol. Immunopathol.138:144-148.

Li G., Zeng Y., Lillehoj H.S., Ren X. 2010. Cloning, prokaryotic expression and biological analysis of recombinant chicken IFN-γ. Hybridoma 29:1-6.

Lee S.H., Lillehoj H.S., Jang S.I., Baldwin C., Tompkins D., Wagner B., Parcells M., Del Cacho E., Hong Y.H., Min W., Lillehoj E.P. 2011. Development and characterization of mouse monoclonal antibodies reactive with chicken interleukin-2 receptor α chain (CD25). Vet. Immunol. Immunopathol. 144:396-404.

Lee S.H., Lillehoj H.S., Park M.S., Baldwin C., Tompkins D., Wagner B., Del Cacho E., Babu U., Min W. 2011. Development and characterization of mouse monoclonal antibodies reactive with chicken CD80. Comp, Immunol, Microbiol.34:273-279.

Jeong J., Lee C., Yoo J., Koh P.O., Kim Y.H., Chang H.H., Choe N.H., Lillehoj H.S., Min W. 2011. Molecular identification of duck and quail common cytokine receptor γ chain genes. Vet. Immunol. Immunopathol.140:159-65.

Entrican G., Lunney J.K., Rutten V..P, Baldwin C.L.. 2009. A Current Perspective on Availability of Tools, Resources and Networks for Veterinary Immunology. Vet. Immunol. Immunopathol. 128: 24-29.

Boyd P., Hudgens E., Loftus J.P., Tompkins D., Wysocki M., Kakach L., LaBresh J., Baldwin C.L., Lunney J.K. 2010. Expressed gene sequence and bioactivity of the IFNγ-response chemokine CXCL11 of swine and cattle. Vet. Immunol. Immunopathol. 136: 170-175.

Lawson S., Lunney J.K., Zuckermann F., Osorio F., Nelson E.A., Welbon C., Clement T., Fang Y., Wong S., Kulas, K., Christopher-Hennings J. 2010. Development of an 8-plex Luminex assay to detect swine cytokines for vaccine development: Assessment of immunity after porcine reproductive and respiratory syndrome virus (PRRSV). Vaccine. 32: 5383-5391.

Hudgens E., Tompkins D., Boyd P., Lunney J.K., Horohov D., Baldwin C.L. 2011. Expressed gene sequence and bioactivity of the IFNγ-response chemokine CXCL9 of cattle, horses and swine. Vet. Immunol. Immunopathol. 141: 317-321.

Alternatives to Antibiotics.
Probiotics or direct-fed microbials (DFM) are live microorganisms that provide alternatives to antibiotics. They are also known to confer health benefits on the host by influencing the host immune system via increased antibody production, up-regulation of cell-mediated immunity, and augmentation of innate defense mechanisms. ARS scientists in Beltsville, Maryland, examined the role of *Bacillus subtilis*-based DFMs on macrophage functions such as nitric oxide production and phagocytosis, the two most important innate immune functions of macrophages. In controlled studies, the scientists demonstrated that certain strains of *Bacillus subtilis* increase macrophage function in broiler chickens. These studies provide the scientific basis for future studies to investigate DFMs as immunopotentiating agents to enhance host protective immunity against enteric pathogens in broilers chickens.

Scientific Publication:
Lee, K.W., Lee, S.H., Lillehoj, H.S., Li, G.X., Jang, S.I., Park, M.S., Kim, D.K., Lillehoj, E.P., Neumann, A.P., Rehberger, T.G., Siragusa, G.R., Babu, U.S. 2010. Effects of Direct-Fed Microbials on Growth Performance, Gut Morphometry, and Immune Characteristics in Broiler Chickens. Poultry Science. 89:203-216.

Type I Interferon Rapidly Protects Swine against Challenge with Foot-and-Mouth Disease Virus.
Foot-and-mouth disease virus (FMDV) vaccines require approximately seven days to induce protection, but prior to this time vaccinated animals are still susceptible to the disease. Type I interferon (IFN-alpha/beta) is the first line of host defense against viral infection and upon its induction results in the upregulation of hundreds of IFN-stimulated genes and their products. ARS scientists at the Plum Island Animal Disease Center, Greenpoint, New York, previously demonstrated that intramuscular (IM) inoculation, at one site in the right hind limb, of a replication-defective human adenovirus type 5 (Ad5) vector containing the porcine IFN-alpha gene (Ad5-pIFNalpha) can sterilely protect swine challenged one day later by direct intradermal (ID) needle infection with FMDV serotypes A O1 Campos, Asia-1, as well as A24 Cruzeiro and against A24 Cruzeiro in a direct contact challenge model. To attempt to reduce the protective dose of Ad5-pIFNalpha, ARS scientists inoculated animals IM at four sites in the neck with a lower dose. Eighty percent of animals were sterilely protected as compared to only 33 percent of animals inoculated IM at one site in the right hind limb. These proof-of-concept studies demonstrate the utility of Ad5 delivered type I IFN as a means to rapidly protect swine against FMDV and suggest that various modifications of this approach may enable this strategy to be successfully used, on a practical scale, to treat other FMDV susceptible species.

Scientific Publication:
Dias C.C., Moraes M.P., Segundo F.D., de los Santos T., Grubman M.J. 2011. Porcine type I interferon rapidly protects swine against challenge with multiple serotypes of foot-and-mouth disease virus. J Interferon Cytokine Res. 2011 Feb; 31(2): 227-36. Epub 2010 Sep 28.

Alternative Strategies for Treating Mastitis in Dairy Cattle.
Mastitis is both the most prevalent infectious disease in dairy herds and the most costly disease for dairy producers. Antibiotics are the mainstay for mastitis treatment and control. Dairy cattle with mastitis receive more antibiotic therapy for its prevention and treatment than for all other

dairy cattle diseases combined. Valid concerns by consumers regarding antibiotic usage need to be addressed by research on non-antibiotic alternatives. In preliminary proof-of-concept studies, ARS scientists in Ames, Iowa, showed that vitamin D may be an effective non-antibiotic option for treatment of mastitis. When injected into infected mammary quarters of dairy cows, there was a reduction of mastitis severity. Vitamin D is a simple and natural immune stimulator which, when used in combination with current antibiotics, could become an effective therapy for mastitis. With vitamin D's ability to stimulate the immune system, the time and amount of antibiotics needed to treat mastitis could be reduced. This combination therapy also may be an infective treatment for mastitis infections that are currently resistant to antibiotic treatment alone. The benefits of this therapy could be a reduction in antibiotic residues that may get into the food supply, reduced potential of antibiotic resistance, and an increase in consumer confidence and international trading opportunities.

Scientific Publications:

Lippolis, J.D., Bayles, D.O., Reinhardt, T.A. 2009. Proteomic changes in Escherichia coli when grown in fresh milk versus laboratory media. Journal of Proteome Research. 8(1):149-158.

Lippolis, J.D., Reinhardt, T.A., Sacco, R.E., Nonnecke, B.J., Nelson, C.D. 2011. Treatment of an intramammary bacterial infection with 25-hydroxyvitamin D3. PLoS One. 6(10):e25479.

Nelson, C.D., Reinhardt, T.A., Beitz, D.C., Lippolis, J.D. 2010. In vivo activation of the intracrine vitamin D pathway in innate immune cells and mammary tissue during a bacterial infection. PLoS One. 5(11):e15469.

Reinhardt, T.A., Lippolis, J.D., Nonnecke, B.J., Sacco, R.E. 2012. Bovine milk exosome proteome. Journal of Proteomics. 75(5):1486-1492.

Identifying Potentially New Means to Fight Mastitis in Dairy Cows.

Novel means to fight mastitis (infections of the mammary gland) in dairy cattle are needed by dairy producers to improve animal health and profitability of milk production. Scientists from the Bovine Functional Genomics Laboratory in Beltsville, Maryland, studied changes in gene expression over time and among different regions of bacterial-infected mammary glands. Their data provided strong support for an important immune surveillance role played by the teat and the first documentation of an immune response by the teat to bacterial infection. These results provide a basis for future research to enhance the cow's response to mastitis pathogens and suggest that the teat may provide a site for immunization against bacterial infections.

Scientific Publication:

Rinaldi, M., Li, R.W., Capuco, A. 2010. Mastitis associated with transcriptomic disruptions in cattle. Vet. Immunol. Immunopath. 138:267-279.

Understanding Avian Influenza Virus and the Host Immune Response.

Highly pathogenic avian influenza (HPAI) can result in up to 90 percent mortality in infected flocks and affect international trade by inhibiting exports from an infected country. HPAI is also a potential zoonotic agent. As a result of continued reports of H5N1 infections in humans in Asia, the public health community is concerned that a worldwide pandemic is impending. The

most effective way of controlling many zoonotic diseases is at the source, thus, expending resources to control and eradicate an outbreak at this level is the best strategy for safeguarding public health and preventing a potential pandemic. ARS scientists in Athens, Georgia, have been conducting studies in chickens to understand the mechanisms the virus uses to escape the immune protective responses of the host. Understanding the immune response of chickens to avian influenza virus is important to help us better target vaccines for control of the disease. The interferon response in chickens plays an important role in the control of avian influenza virus. Two variants of the avian influenza virus, one that had a full length NS1 protein and the other with only a partial length NS1 protein, were compared and it was demonstrated that the virus with a short NS1 protein induced higher levels of interferon that resulted in poor growth of the virus in chickens. The NS1 protein had previously been shown to be an important interferon blocker in mammals, but this study showed it has the same role in chickens and has expanded our understanding of the pathogenesis of the virus.

Scientific Publication:
Cauthen, A.N., Swayne, D.E., Sekellick, M.J., Marcus, P.I., Suarez, D.L. 2007. Amelioration of influenza pathogenesis in chickens attributed to the enhanced interferon-inducing capacity of a virus with a truncated NS1 gene. Journal of Virology. 81(4):1838-1847.

Comparison of the Innate Immune Response to Avian Influenza in Chickens and Ducks.
Wild birds, especially ducks and shorebirds, are reservoirs of avian influenza viruses. Excrement and respiratory fluids from infected birds are the most important source of the virus. Virus shedding can be detected as early as one day post infection in poultry and may continue for up to four weeks in a population of birds. Comparison of the innate immune response in chickens and ducks to H5N1 avian influenza show a markedly different response between species. The innate immune response is responsible for detecting invading microorganisms during the initial stages of infection, which is a crucial determinant of disease resistance or susceptibility. ARS scientists in Athens, Georgia, found differential cytokine expression between chickens and ducks following exposure with H5N1 viruses recovered from Southeast Asia. Ducks generally displayed increased cytokine expression and resistance to challenge, whereas chickens exhibit decreased cytokine expression. These studies emphasize the importance of innate immunity in birds and correlate increased pathogenicity of recent H5N1 viruses for wild waterfowl with an enhanced suppression of the host immune response.

Scientific Publication:
Pantin Jackwood, M.J., Swayne, D.E. 2007. Pathobiology of Asian highly pathogenic avian influenza H5N1 virus infection in ducks. Avian Diseases. 51:250-259.

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Component 3: Zoonotic Diseases

Rationale for the research:
Zoonotic diseases represent one of the leading causes of illness and death in people. By definition, zoonotic diseases encompass all infectious diseases that are transmitted from animals to man. Zoonotic diseases have a negative impact on commerce, travel, and economies worldwide. In developing countries, zoonotic diseases stand out as the most prevalent and important threat to public health. In industrialized nations, zoonotic diseases remain a concern for human health, but are of particular concern to the agricultural sector as eradication attempts are made. Priority diseases include those that are especially difficult to diagnose and cause substantial morbidity and mortality, resulting in significant economic costs to producers when they persist or reemerge. Because many determinants of zoonotic diseases lie outside the purview of the health sector, agriculture and the animal health community play an important role in controlling these diseases in domestic animals, starting with surveillance systems. Over the years, the USDA has invested significant resources in attempts to eradicate a number of important endemic zoonotic diseases from livestock populations (e.g., brucellosis and tuberculosis). However, their persistence in wildlife reservoirs continues to pose challenges to the eradication process. Moreover, some zoonotic agents have been identified as having the potential to be used for bioterrorism. Effective countermeasures are needed to eliminate zoonotic agents at the source and protect our Nation from these important public health threats.

The ARS zoonotic disease research program focuses on brucellosis, leptospirosis, and tuberculosis (TB) with the strategic goal of developing countermeasures to prevent disease transmission in domestic livestock and wildlife reservoir hosts. Zoonotic diseases that pose a significant threat to the Nation (e.g., avian influenza, Rift Valley fever) and are exotic to the United States are addressed under Component 1: Biodefense Research. Additional zoonotic diseases are also addressed under Component 7 (Babesiosis) and Component 8 (Bovine spongiform encephalopathy).

Stakeholders at the September 2005 Animal Health Program Planning Workshop representing the swine and the wildlife industries ranked zoonoses as their 2nd priority; the dairy industry as their 3rd priority; and the beef industry their 4th priority.

Research needs:
Some of the most important gaps in our knowledge about *Brucella* include the need to analyze the genome to identify unique sequences that can be used for vaccine or diagnostic assay development. This research will help in developing new generation vaccines for control infections in domestic animals thereby, lowering the incidence of disease and protecting the public and farm workers from *Brucella*-associated zoonoses. One area that is most important in controlling and potentially eradicating brucellosis is through the identification and characterization of the immune responses in wildlife and domestic livestock to both wild type *Brucella* species and to the current and new experimental vaccines. Diagnostic and vaccine countermeasures specifically designed for the control and eradication of brucellosis in wildlife needs to be investigated and understood in order to protect domestic livestock.

Leptospirosis remains a serious threat to human and animal health and has become more common as the interface between wildlife, domestic animals, and humans increases due to urban sprawl. Research is needed to characterize spirochete strains associated with field outbreaks, determine how these bacteria interact and elicit host responses during infection, and identify the mechanisms of protective immunity in incidental versus maintenance host infections. Recent progress in genome sequencing of *Leptospira borgpetersenii* serovar *hardjo* (the most prevalent serovar of cattle) needs to be extended to other *Leptospira* species for comparative microbial genomics studies that will help continue to lead to the identification of unique sequences to support diagnostic and vaccine discovery research programs. Diagnostic tools to support molecular epidemiology studies are also needed to understand the ecology of *Leptospira* species and serovars.

Bovine tuberculosis eradication efforts were initiated in the United States in 1917. The crux of the eradication program has historically been based on abattoir inspections, testing, and depopulation of infected herds. These efforts have been largely successful. The reactor rate in cattle has been reduced from about 5 percent to currently less than 0.02 percent. Consequently, the incidence of human tuberculosis caused by *Mycobacterium bovis* has also decreased significantly. However, as the incidence of tuberculosis in the United States declines, Federal and State control programs are facing new challenges. First, there has been a resurgence of bovine tuberculosis in recent years, both in domestic cattle herds and wildlife. This resurgence is due to several factors: the importation of *Mycobacterium bovis* infected cattle from Mexico; infections in captive deer and elk herds; the presence of tuberculosis in zoo and wildlife species maintained for exhibition; and most recently, the emergence of TB in the first free-ranging wildlife reservoir (i.e., white-tailed deer) in the United States. The detection of tuberculous cattle and wildlife has serious economic consequences, primarily due to restrictions imposed by regulatory officials on the interstate and international shipment of livestock. As a result, USDA/APHIS requested that ARS redirect its tuberculosis research efforts to examine alternatives to abattoir inspections, and test and slaughter campaigns. Specific needs identified include rapid, specific, and accurate diagnostic tests for cattle and wildlife, and the discovery of highly efficacious vaccines directed at cattle and wildlife to mitigate the transmission of *Mycobacterium bovis* in infected herds.

Anticipated Products In Action Plan:

- Comparative genomic analyses of *Brucella* species to identify unique sequences associated with phenotypic variations in virulence, host range, and persistent infections, and to support diagnostic and vaccine discovery research initiatives.
- Scientific information to increase our understanding of immunologic responses in bison, elk, and feral swine to *Brucella* species, including mechanisms of persistent infections, host tolerance, and protective immunity.
- The development of a safe and efficacious brucellosis vaccine for bison that can be remotely delivered.
- New vaccine platforms designed to control and eradicate brucellosis in elk.
- New vaccine platforms designed to control and eradicate brucellosis in feral swine.
- New diagnostic platforms with improved sensitivity and specificity profiles to facilitate the diagnosis and epidemiologic trace back of *Brucella* strains in field outbreaks.

- *In vitro* disease models for Leptospirosis consisting of host cell cultures leading to molecular characterization of host-bacterial interactions, variations in gene expression, and associated pathogenic mechanisms.
- Characterization of protective immune responses to spirochete antigens in large and small animal disease models.
- Large-scale sequence analysis to characterize the genome of selected spirochetes and identify strain specific regions in various *Leptospira* strains.
- Genetically altered *Leptospira* bacteria using *in vitro* and *in vivo* studies to establish key links between specific genes and phenotype.
- Discovery of efficacious molecular vaccines to prevent the spread of Leptospirosis in domestic animals and wildlife.
- Identification of microbial immunogens critical for development of protective immunity against TB.
- Scientific information to increase our understanding of the molecular pathogenesis of *Mycobacterium bovis* infections.
- Comparative analyses to understand the variations of host immune responses to natural infections by *Mycobacterium bovis* versus vaccination as well as neonatal versus adult cattle responses and differentiate infected versus vaccinated animals.
- Discover improved sensitive and specific diagnostic platforms amenable to the rapid screening of large cattle herds for *Mycobacterium bovis*.
- Discover diagnostic platforms to differentiate *Mycobacterium bovis* infected versus vaccinated animals.
- Discover effective vaccine platforms to prevent and control *Mycobacterium bovis* in cattle and relevant wildlife reservoir hosts.

Impact:
The discovery of new countermeasures specifically designed to prevent and control brucellosis in wildlife has assisted in identifying new sources of infections and in developing new intervention strategies for controlling brucellosis in wildlife. Control of brucellosis in wildlife reduces transmission and safeguards our domestic livestock against infection. Scientists in Ames, Iowa, have been successful in developing assays that enable improved fingerprinting of bacteria and allowing bacterial genotyping. In addition, they have developed new diagnostic assays that better allow rapid diagnosis of infected animals. The scientists have also developed safe and effective vaccination strategies for bison for *Brucella abortus*. Scientists at Ames, Iowa, have determined that elk do not appear to respond to the current vaccines immunologically. This is an important finding as elk are an important reservoir for *Brucella abortus* in the Greater Yellowstone region.

Leptospirosis is a challenging bacterium to culture. The scientists in Ames, Iowa, have developed several small animal models which will enable them to begin understanding the virulence factors as well as test efficacy of developed vaccines. The functional genomic analysis of *Leptospira* strains has enabled the identification of virulence determinants, vaccine discovery research, and new diagnostic platforms for classification of field strains. This research will help in developing new generation vaccines that will help control of maintenance and accidental host infections in domestic animals thereby, lowering the incidence of disease and protecting farm workers from spirochete-associated zoonoses. Additionally, scientists in Ames, Iowa, have been

able to identify new wildlife reservoirs. This knowledge will be used to help educate the public to provide protection against inadvertent transmission from wildlife and the resulting disease.

Research on *Mycobacterium bovis* in Ames, Iowa, has resulted in improved diagnostic capabilities. Because of the difficulty and inconsistency of the caudal tail fold assay, development of a serological assay was considered important. ARS scientists have worked with industry partners to develop several serological assays that have the potential to improve the accuracy and speed of diagnosing TB in cattle. In addition, efforts have concentrated on diagnostics and vaccination strategies for control of *Mycobacterium bovis* in white-tailed deer, an important reservoir for the disease in parts of the country.

COMPONENT 3: SELECTED ACCOMPLISHMENTS

Brucella suis infection in cattle.

The elimination of *Brucella abortus* from cattle in the United States was the result of a national eradication program that began in 1934 with the total cost exceeding 10 million dollars. Although several wildlife reservoirs remain a threat for reintroduction, ongoing monitoring activities are designed to detect any transmission events to domestic cattle. Although *B. abortus* has been largely eliminated from domestic cattle, the prevalence of *Brucella suis* in feral swine has emerged as a significant problem for domestic cattle. *B. abortus* infection of cattle is a regulatory issue and can lead to the loss of a State's brucellosis-free status and economic costs to producers and State regulatory agencies. Feral swine populations continue to increase in the United States and illegal transportation continues to expand their range into new States or regions. Contact with infected feral swine has led to *B. suis* infections in cattle, particularly in the south and southeastern United States. Cattle infected with *B. suis* test seropositive (indicating previous exposure) on brucellosis surveillance tests and antibody responses cannot be readily differentiated between infections with *B. suis* and those due to infection with *B. abortus*. At this time, data is lacking on the time course for the development of antibodies to *B. suis* in the serologic responses of cattle after acute infection. In many states, vaccination for *B. abortus* using the vaccine RB51 is still utilized in domestic cattle. In a study conducted in Ames, Iowa, the serologic responses of cattle to *B. suis* infection and lesions and tissue localization of *B. suis* in pregnant RB51-vaccinated and control cattle after experimental challenge was assessed. It was found that there was variation in the ability of various brucellosis screening or confirmatory tests in detecting infection of cattle with *B. suis.* Although experimental challenge with *B. suis* did not cause abortions in cattle, there was an increased incidence of retained placentas. In addition, cattle vaccinated with RB51 were not protected against *B. suis* infection. There was a significant increase of frequency and level *B. suis* isolated in the mammary gland with shedding in milk increasing the potential of transmission to humans. Research is ongoing to further develop vaccines strategies against *B. suis* in swine and cattle.

Scientific Publication:

Olsen, S.C. and Hennager, S.G. 2010. Immune Responses and Protection against Experimental *Brucella suis* biovar 1 Challenge in non-vaccinated or RB51-Vaccinated Cattle. Clin Vaccine Immunol. 2010 Dec;17(12):1891-5. Epub 2010 Oct 13.

Genetic Characterization and Diagnosis of Brucella species

During the past five years, the *Brucella* research project has built on previous molecular work which had included sequencing *B. abortus* and the development of rapid PCR-based assays. Historically, the only method for subtyping *Brucella* strains for epidemiological use was a complicated biotyping strategy that only provided a limited number of subtypes (1 to 7) per *Brucella* species. In 2006, we reported a new method for genotyping of *Brucella*, which we called "HOOF-Prints", which is based on variable numbered tandem repeats (VNTRs) at multiple loci (MLVA). As the genus *Brucella* is very homologous with high degree of genetic similarity between strains, this method was important as it allowed a rapid, scientific based method for typing *Brucella* isolates, and was the first molecular test that could provide scientific data regarding the degree of genetic relationship between strains. This assay has continued to be refined and expanded in many laboratories worldwide. A couple of new assay strategies have been developed elsewhere with the addition of more loci, but they are still based on the loci and foundation of the original HOOF-Print assay. This method is now applied routinely to *Brucella* isolated in diagnostic labs here in the United States (APHIS) and in other countries. The HOOF-PRINT assay has been used to confirm that elk were the source of cattle infections in the Greater Yellowstone Area. The project also determined the DNA genomic sequences of the strain 19 and RB51 vaccine strains of *B. abortus*. In addition to providing basic knowledge on genetic differences between virulent *Brucella* strains and attenuated vaccine strains, these sequences provided new molecular markers for a *Brucella* SNP typing assay.

Scientific Publications:

Almendra C., Silva T.L., Beja-Pereira A., Ferreira A.C., Ferrão-Beck L., de Sá MI,Bricker B.J., Luikart G. 2009. "HOOF-Print" genotyping and haplotype inference discriminates among *Brucella* spp.isolates from a small spatial scale. Infect Genet Evol 9:104-7.

Beja-Pereira A., Bricker B., Chen S., Almendra C., White PJ, Luikart G.. 2009. DNA genotyping suggests that recent brucellosis outbreaks in the GreaterYellowstone Area originated from elk. J Wildl Dis 45:1174-7.

Bricker B.J., Ewalt D.R.. 2006. HOOF prints: *Brucella* strain typing by PCR amplification of multilocus tandem-repeat polymorphisms. Methods Mol Biol 345:141-73.

Crasta O.R., Folkerts O., Fei Z., Mane S.P., Evans C., Martino-Catt S., Bricker B., Yu G., Du L., Sobral B.W. 2008. Genome sequence of *Brucella abortus* vaccine strain S19 compared to virulent strains yields candidate virulence genes. PLoS One 2008 May 14;3(5):e2193.

Gopaul K.K., Sells J., Bricker B.J., Crasta O.R., Whatmore A.M.. 2010. Rapid and reliable single nucleotide polymorphism-based differentiation of *Brucella* live vaccine strains from field strains. J Clin Microbiol 48: 1461-4.

Development of a hamster model for infection with Leptospira borgpererseniі serovar Hardjo.

The golden Syrian hamster (*Mesocricetus auratus*) is frequently used as a model to study virulence for several *Leptospira* species. Onset of an acute lethal infection following inoculation with several pathogenic *Leptospira* species has been widely adopted for pathogenesis studies. An important exception is the outcome following inoculation of hamsters with live *L. borgpetersenii*

serovar *Hardjo,* the primary cause of bovine leptospirosis and a cause of human infections. Typically, inoculation of hamsters with *L. borgpetersenii* serovar *Hardjo* fails to induce clinical signs of infection. In this study, the authors assessed infection with 2 strains of *L. borgpetersenii* serovar *Hardjo*: JB197 and 203. Both strains infected hamsters with ID(50) values of approximately 1.5 × 10(2) bacteria yet differed in tissue invasion and interaction with leukocytes, resulting in widely divergent clinical outcomes. Hamsters infected with strain 203 established renal colonization within 4 days postinfection and remained asymptomatic with chronic renal infections similar to cattle. In contrast, hamsters infected with strain JB197 developed a rapidly debilitating disease typical of acute leptospirosis common in accidental hosts (eg, humans). Evidence that strain JB197 resides in both extracellular and intracellular environments during hamster infection was obtained. Development of models that result in chronic and acute forms of leptospirosis provides a platform to study *L. borgpetersenii* pathogenesis and to test vaccines for the prevention of leptospirosis.

Scientific Publication:
Zuerner R.L., Alt D.P., Palmer M.V. 2012. Development of chronic and acute golden Syrian hamster infection models with Leptospira borgpetersenii serovar Hardjo.Vet Pathol. Mar;49(2):403-11. Epub 2011 Jun 13.

Documentation and Diagnosis of a Unique Leptospira interogans serovar Pomona in California Sea Lions.
Leptospirosis is a bacterial disease that can be spread from infected animals to humans via urine. A new species of *Leptospira* organisms was recently isolated from sea lions in California. Sea lions infected with *Leptospira* are a potential public health hazard due to the possibility of spread from infected animals to humans. Infection with *Leptospira interogans* serovar *Pomona* causes the sea lions to beach themselves increasing the opportunities for exposure of humans to the bacteria as they interact with the sick sea lions. Currently, the diagnostic tools for detecting Leptospira in sea lions are slow and lack the ability to confirm infection in all animals. ARS scientists at the National Animal Disease Center, Ames, Iowa, are developing an improved diagnostic assay to detect the presence of *Leptospira* in infected sea lions. The more rapid and accurate diagnostic assay for leptospirosis infection in the sea lions will reduce exposure time of humans to the infected animals by facilitating the rapid treatment, isolation, and quarantine of infected animals.

Scientific Publication:
Cameron, C.E., Zuerner, R.L., Raverty, S., Colegrove, K.M., Norman, S., Lambourn, D.M., Jeffries, S.J., Gulland, F.M. 2008. Detection of Pathogenic Leptospira Bacteria in Pinniped Populations via PCR and Identification of a Source of Transmission for Zoonotic Leptospirosis in the Marine Environment. Journal of Clinical Microbiology. 46(5):1728-1733.

Bovine tuberculosis.
The mainstay of the bovine tuberculosis (TB) eradication program has been the tuberculin skin test, combined with slaughter of both infected and exposed animals (whole herd depopulation), and with indemnity payments to producers paid by both USDA and state authorities. Although this traditional test and slaughter policy has been effective in lowering the prevalence of disease, eradication of bovine TB in the United States has not been achieved in spite of almost 93 years

of concerted effort. Additionally, new obstacles have emerged with changes in the livestock industry, trade policies, and the increasing popularity of the captive cervid industry. In particular, the current obstacles are: importation of infected cattle from Mexico; a reservoir of infection found in free-ranging white-tailed deer in Michigan; continued detection of TB in captive cervids with transmission to cattle; and persistence of infection in large dairy herds. Farmed deer represent a significant alternative livestock industry, with numbers exceeding 2 million in New Zealand, 1 million in China, 500,000 in the United States, 400,000 in Russia, and 100,000 in Canada. Farmed deer are exposed to various other livestock and to free-ranging wildlife, and are moved between herds and across borders. Thus, there is an increased risk of disease infection among and between farmed deer, traditional livestock, and free-ranging wildlife. The only approved test for TB in use in deer and elk has been the tuberculin skin test. Skin test procedures are problematic in captive cervid species because of the variable accuracy of the test, and injury risks due to handling of the animals (i.e., skin test requires two handling events) and impossible in wild cervids. Each of these obstacles demonstrates the diversity of issues relating to bovine TB control in the United States. The research results highlighted below has had a positive benefit for livestock and captive cervid producers, wildlife agencies, the general public, and USDA action agencies such as USDA/APHIS in controlling the spread of TB in humans and animals.

Persistence of Mycobacterium bovis in Vaccinated White –Tailed Deer

ARS researchers at Ames, Iowa, previously demonstrated that *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) used as a vaccine reduced disease severity in White-tailed deer (WTD) upon experimental challenge with virulent *M. bovis*. In an extension of these studies, it was demonstrated that *M. bovis* BCG persists in tissues of WTD for up to 9 months after vaccination. The attenuated live vaccine was primarily detected in lymphoid tissues without evidence of colonization of muscle (i.e., meat potentially consumed by humans); thus, the risk of transmission to humans is minimal. These findings underscore the necessity of continuing detailed safety studies for use of vaccines intended for wildlife that may be consumed by humans.

Scientific Publication:

Palmer M.V., T.C. Thacker, W.R. Waters, S. Robbe-Austerman, S.M. Lebepe-Mazur and N.B Harris. 2010. Persistence of *Mycobacterium bovis* Bacillus Calmette Guerin (BCG) Danish in white-tailed deer (*Odocoileus virginianus*) after oral or parenteral vaccination. Zoonoses and Public Health, 2010 Dec;57(7-8):e206-12.

Detection of Mycobacterium bovis in Deer

Using samples from a heavily infected captive elk and fallow deer herd (~70% prevalence), we demonstrated that two serum-based tests, which detect TB-specific antibodies, provided much improved accuracy as compared to that achieved with the skin test. In association with prior studies by our group, the collective impact is that a blood-based test is now available for use in captive cervids, pending approval by United States Animal Health Association/TB committee and USDA TB program staff for official use in the eradication program. The proposed research results will have a positive benefit for livestock and captive cervid producers, wildlife agencies,

the general public, and USDA action agencies such as USDA/APHIS in controlling the spread of TB in humans and animals.

Scientific Publications:

O'Brien, D.J., Schmitt, S.M., Lyashchenko, K.P., Waters, W.R., Berry, D.E., Palmer, M.V., Mcnair, J., Greenwald, R., Esfandiari, J., Cosgrove, M.K. 2009. Evaluation of Blood Assays for Detection of *Mycobacterium bovis* in White-tailed Deer (Odocoileus Virginianus) in Michigan. Journal of Wildlife Diseases. 45(1):153-164.

Lyashchenko, K.P., Greenwald, R., Esfandiari, J., Chambers, M.A., Vicente, J., Gortazar, C., Santos, N., Correia-Neves, M., Buddle, B.M., Jackson, R., O'Brien, D.J., Schmitt, S., Palmer, M.V., Delahay, R.J., Waters, W.R. 2008. Animal-side Serologic Assay for Rapid Detection of *Mycobacterium bovis* Infection in Multiple Species of Free-ranging Wildlife. Veterinary Microbiology. 132(3-4):283-292.

Waters W.R., Stevens G.E., Schoenbaum M.A., Orloski K.A., Robbe-Austerman S., Harris N.B., Hall S.M., et al. 2011. Bovine tuberculosis in a Nebraska herd of farmed elk and fallow deer: a failure of the tuberculin skin test and opportunitities for serodiagnosis. Vet Med Int. 2011 Apr 14;2011:953985.

Component 4: Respiratory Diseases

Rationale for the research:
In spite of decades of control measures using antibiotics and vaccines, endemic respiratory diseases remain primary health threats to livestock and poultry. The cost of respiratory disease is significant and disease outbreaks often determine the difference between profit and loss for a producer. Most respiratory diseases present themselves as disease complexes involving several primary and secondary viral and bacterial pathogens, complicating control and prevention strategies. The most challenging aspect of dealing with respiratory disease is recognizing that clinical or overt disease is only the tip of the iceberg. The cost goes far beyond the treatment of sick animals and the cost of dead animals. The vast majority of the economic impact is actually due to the hidden cost of sub-clinical disease where animals are infected but show no apparent disease symptoms. Livestock and poultry that develop respiratory diseases have notable decreases in growth performance. Even with livestock and poultry being vaccinated against many of the most common pathogens today, respiratory lesions are still prevalent at slaughter and their impact on weight gain and carcass quality is significant. Important scientific gaps remain in our understanding of respiratory pathogen complexes and the ecological and host interactions that lead to disease and production losses independent of host species. With the current emphasis on reduced usage of antibiotics in livestock and poultry operations, new research approaches are needed to design effective prevention and control programs that will facilitate proper planning, careful attention to livestock and poultry health management, and the discovery of effective countermeasures.

Stakeholders at our September 2005 Animal Health Workshop representing the beef industry ranked respiratory diseases as their 2nd priority and the sheep industry ranked respiratory diseases such as malignant catarrhal fever (MCF) as their 5th priority. The swine industry ranked porcine reproductive and respiratory syndrome virus (PRRSV) as their 1st priority, preventative health management (innate immunity and alternatives to growth promotants and antibiotics) as their 2nd priority, re-emerging diseases such as swine influenza virus (SIV) and porcine circovirus type 2 (PCV2) were their 3rd priority, and the porcine respiratory disease complex (PRDC) their 4th priority. The poultry broiler industry ranked respiratory disease their 3rd priority and characterized the following respiratory pathogens as priority diseases: infectious bronchitis, infectious laryngotracheitis, turkey rhinotracheitis (TRT) and associated swollen head syndrome (SHS) of chickens (avian pneumovirus), colibacillosis (*Escherichia coli*), fowl chorea (*Pasteurella multocida*), turkey coryza (*Bordetella avium*), *Ornithobacterium rhinotracheale* (ORT) of turkeys, and Mycoplasmosis (*Mycoplasma gallisepticum* and *Mycoplasma synoviae*). In addition, the 2005 ARS National Stakeholder (Electronic) Survey ranked infectious bronchitis and infectious laryngotracheitis as priority endemic respiratory diseases.

Because of the sheer number of pathogens involved in respiratory diseases, and the ability of many pathogens to cross the species barrier, ARS concentrated their available resources on priority respiratory pathogens associated with the bovine, ovine, porcine, and poultry respiratory disease complexes. Emphasis was given to the design of experimental animal disease models to test newly discovered technologies and countermeasures, with the eventual goal of validating them under field conditions through strategic partnership with industry.

Research needs:
Research needs identified included identifying and understanding the mechanisms of disease transmission of respiratory pathogens in beef production systems as well as the host responses to respiratory pathogens, including mechanisms of immune evasion and protective immunity. Also recognized as a critical need were epidemiological studies to identify reservoirs of priority respiratory pathogens. However, the scientists were unable to develop research plans that met the expectations of the external review panel and research on bovine respiratory diseases was discontinued for the duration of the cycle.

The transmission of malignant catarrhal fever to bison in western grazing lands is a concern to the sheep industry. Two of the most important gaps in the understanding of the transmission between the two species include the pathogenesis and immune response in sheep and bison associated with infection. Research in this area will help develop intervention strategies to minimize the risk of the sheep spreading the devastating disease to bison.

Respiratory disease in swine is one of the most serious and costly concerns to the industry. Research is needed to elucidate the pathogenesis of monovalent and polymicrobial infections of swine respiratory pathogens. Pathogens included in the swine respiratory research included porcine reproductive and respiratory syndrome virus (PRRSV), swine influenza virus (SIV), *Bordetella bronchiseptica,* and *Haemophilus parasuis*. The mechanisms by which swine respiratory pathogens caused disease due to changes in gene expression of both the porcine host and the bacterial respiratory pathogens during the infectious process are important in developing effective intervention strategies for polymicrobial infections. In addition, research to understand the host responses to respiratory pathogens, including mechanisms of immune evasion and protective immunity are needed.

Research gaps were recognized in the elucidation of the mechanisms of disease transmission of respiratory pathogens in relevant poultry production systems including the interaction and pathogenesis of polymicrobial interactions. Studies are needed to investigate the host response to respiratory pathogens, including mechanisms of immune evasion and protective immunity. In addition, novel vaccine candidates need to be developed and evaluated to a number of pathogens. Improved diagnostic capabilities to enable rapid differential diagnosis of respiratory pathogens on poultry farms are also lacking for many of the common poultry respiratory diseases.

Anticipated Products in Action Plan:
- Develop drug and vaccine delivery systems that target the swine, avian, and ruminant respiratory tract.
- Discover and evaluate alternatives to antibiotics for preventing and treating respiratory diseases of all domestic livestock species.
- Discover diagnostic platforms that can be used to develop on-site tests for respiratory pathogens.
- Discover highly effective vaccines that induce targeted immune responses to prevent colonization of the respiratory tract and prevent shedding and disease transmission in swine and poultry.

- Define pathogen interactions that lead to polymicrobial infections and respiratory disease complexes in swine and poultry.
- Characterize the changes in gene expression underlying porcine cellular responses to infection with respiratory pathogens.
- Characterize global changes in gene expression of porcine bacterial pathogens in response to respiratory infection.
- Define determinants of virulence and characterize mechanisms of infection of respiratory pathogens of cattle, swine, sheep, and poultry.
- Perform genomic and proteomic analysis of ovine and avian respiratory pathogens to determine changes in gene expression during the infection process.
- Identification of microbial genetic variations associated with differences in virulence and disease transmission in sheep, swine, and poultry.
- Characterize mechanisms of immune evasion and protective immunity of swine and poultry pathogens.
- Define the characteristics of aerosol spread for priority respiratory pathogens in relevant poultry production systems.
- Discover differential diagnostics platforms that can be used to develop flock-side tests.

Impact:
The impact of the research included the identification of disease pathogen reservoirs, understanding pathogen transmission, and the discovery and technology transfer of highly effective diagnostics, vaccines, and biotherapeutics to control and potentially eradicate respiratory diseases from poultry flocks and sheep herds.

The overall impact of the research to control and prevent endemic respiratory diseases benefits the swine industry both in producing healthier pigs and reducing the economic impact of respiratory disease. The better understanding of the pathogenesis of disease and the discovery and technology transfer of control measures, including vaccines, may ultimately help eradicate respiratory diseases from swine herds. The overall goal of these projects was to produce scientific information and tools that enable the U.S. swine industry to remain competitive and profitable.

COMPONENT 4: SELECTED ACCOMPLISHMENTS

Malignant Catarrhal Fever Virus.
Nucleic acid based tests for malignant catarrhal fever virus (MCFV) were developed and validated by ARS scientists in Pullman, Washington, including real-time PCR and real-time multiplex PCR that significantly advanced routine MCF diagnosis. An experimental animal model for ovine herpes virus 2 (OvHV-2) infection and disease induction was established, which allows for the study of viral replication and host interaction with the goal of vaccine development. Importantly, it was shown that the lung is the OvHV-2 entry site for initial replication, which is required for viral dissemination and subsequent disease development. The host immune responses to the viral replication in both sheep and bison were defined. A robust immune response concurrent with viral replication in sheep was found, but the immune response in bison was limited. These data indicate that OvHV-2 changes cell tropism during initial replication in the lung of both carrier and clinically susceptible hosts and the ultimate differences

between subclinical infection and disease in these species may depend on virus modulation of immune functions.

Scientific Publication:
Gailbreath K.L., O'Toole D., Taus N.S., Knowles D.P., Oaks J.L., Li H. 2010. Experimental nebulization of American bison (Bison bison) with low doses of ovine herpesvirus 2 from sheep nasal secretions.Vet Microbiol. Jul 14;143(2-4):389-93. Epub 2009 Nov 24.

Swine influenza.
Swine influenza is a highly contagious viral infection in pigs that significantly affects the pork industry due to weight loss and secondary infections. There is also the potential of a significant threat to public health, as occurred in 2009 when the pandemic H1N1 influenza virus strain emerged from reassortment events among avian, swine, and human influenza viruses within pigs. As classic and pandemic H1N1 strains now circulate in swine, an effective vaccine may be the best strategy to protect the pork industry and public health. Current inactivated-virus vaccines available for swine influenza protect only against viral strains closely related to the vaccine strain, and egg-based production of these vaccines is insufficient to respond to large outbreaks. DNA vaccines are a promising alternative because they can potentially induce broad-based protection with more efficient production methods. ARS scientists in Ames, Iowa, working together with scientists at the National Institutes of Health in Bethesda, Maryland, evaluated the potential of monovalent and trivalent DNA vaccine constructs to elicit immunological responses and protect pigs against viral shedding and lung disease after challenge with pandemic H1N1 or classic swine H1N1 influenza virus. Scientists also compared the efficiency of a needle-free vaccine delivery method to that of a conventional needle/syringe injection. The results of these studies demonstrated that DNA vaccination elicits robust serum antibody and cellular responses after three immunizations and confers significant protection against influenza virus challenge. Needle-free delivery elicited improved antibody responses with the same efficiency as conventional injection and could be considered for development as a practical alternative for vaccine administration.

Scientific Publication:
Gorres J.P., Lager K.M., Kong W.P., Royals M., Todd J.P., Vincent A.L., Wei C.J., Loving C.L., Zanella E.L., Janke B., Kehrli M.E. Jr, Nabel G.J., Rao S.S. 2011. DNA vaccination elicits protective immune responses against pandemic and classic swine influenza viruses in pigs. Clin Vaccine Immunol. Nov;18(11):1987-95. Epub 2011 Sep 14.

Glässer's disease in swine.
Respiratory disease remains one of the most important causes of disease to the swine industry. *Haemophilus parasuis* is a bacterium that causes Glässer's disease in swine, a disease characterized by chronic debilitation and often death that costs the swine industry millions in losses annually. However, not all strains of the bacterium cause disease. To date, little is known about genetic differences among *H. parasuis* strains and genetic factors that contribute to its ability to cause disease. Respiratory and systemic diseases caused by *H.parasuis* remain problematic to the swine industry, especially high health status herds. Currently, there are no effective vaccines for *H. parasuis* and most control strategies have not been successful in preventing disease and the resulting loss of pigs. Scientists in Ames, Iowa, compared four

isolates of the bacterium for their ability to cause disease in pigs. Three of the isolates caused disease in the pigs, while pigs given the fourth isolate remained healthy. Pigs that were given the non-disease causing isolate were subsequently protected from disease when exposed to one of the disease causing isolates. Thus, strains of *H. parasuis* that don't cause disease may be useful as vaccines to protect pigs against disease causing strains. In order to better understand the differences between *H. parasuis* isolates and potentially identify the mechanism by which some isolates fail to cause disease, DNA sequencing is being used to compare the genomes of the different isolates. These results will provide information so scientists can develop control strategies and potentially identify vaccine candidates that can be used by swine producers to control losses from this disease and identify whether strains of *H. parasuis* circulating on the farm will cause disease.

Scientific Publication:
Mullins, M.A., Register, K.B., Bayles, D.O., Loving, C.L., Nicholson, T.L., Brockmeier, S.L., Dyer, D.W., Phillips, G.J. 2009. Characterization and Comparative Analysis of the Genes Encoding Haemophilus parasuis Outer Membrane Proteins P2 and P5. *Journal of Bacteriology*. 191(19):5988-6002.

Characterization of H5N1 LPAI Avian Influenza Viruses from North America.
Avian influenza viruses of many different antigenic subtypes (H1-H16) are found commonly in wild birds, but only the H5 and H7 subtypes are known to have the potential for being highly pathogenic in poultry. The H5N1 subtype is of particular importance because of the widespread outbreaks of highly pathogenic avian influenza in Europe, Asia, and Africa, and extensive surveillance of wild birds was conducted in the Americas to evaluate the chance of these highly pathogenic viruses entering the United States through wild birds. Several H5N1 low pathogenic avian influenza (LPAI) viruses were isolated in wild birds by ARS scientists in Athens, Georgia, in collaboration with APHIS and the United States Geological Survey (USGS). These viruses were sequenced and shown to be of North American lineage that are separate from the H5N1 highly pathogenic avian influenza (HPAI) viruses found in Europe, Asia, and Africa. The biologic and sequence characterization of these viruses continue to provide evidence that H5N1 HPAI viruses have not traveled to the Americas in wild birds, and clearly documents that H5N1 LPAI viruses are normally found at a low prevalence level in the Americas. This study also included experimental animal studies conducted in collaboration with The Ohio State University that showed that these viruses did not replicate well in poultry and pose only a small threat of introduction to our poultry populations.

Scientific Publication:
Spackman, E., Swayne, D.E., Suarez, D.L., Senne, D.A., Pedersen, J.C., Killian, M.L., Pasick, J., Handel, K., Pillai, S.P., Lee, C., Stallknecht, D., Slemons, R., Ip, H.S., Deliberto, T. 2007. Characterization of lowpathogenicity H5N1 avian influenza viruses from North America. Journal of Virology. 81(21):11612-11619.

Development of Avian Influenza Virus Rapid Diagnostic Tests.
ARS scientists in Athens, Georgia, developed and bench validated a new real-time reverse transcriptase polymerase chain reaction (RT-PCR) protocols for the rapid detection of the subtypes H6, H9 and H11 of avian influenza viruses. Avian influenza virus has 16 distinct

antigenic subtypes, but certain subtypes are responsible for most diseases outbreaks in poultry. A RT-PCR test for the rapid identification of H6, H9, and H11 subtypes of avian influenza were developed and bench validated. The rapid detection and identification of avian influenza viruses, particularly the H6 and H9 subtypes, provide additional tools to diagnose avian influenza outbreaks. The H6 and H9 subtypes are commonly found in other countries and rapid diagnostic tools are needed to rapidly diagnose if these subtypes infect poultry in the United States.

Scientific Publication:
Das, A., Suarez, D.L. 2007. Development and bench validation of real-time reverse transcriptionpolymerase chain reaction protocols for rapid detection of the subtypes H6, H9, and H11 of avian influenza viruses in experimental samples. Journal of Veterinary Diagnostic Investigation. 19:625-634.

Identification of Virulence Factors for Turkey ORT.
Ornithobacterium rhinotracheale (ORT) is the causative agent of sporadic airsacculitis of turkeys and is one of main causes for post-harvest condemnation of turkey carcasses. This is the first report of the identification of a membrane-bound hemolysin of *O. rhinotracheale* (ORT) from North American isolates from turkeys. The hemolysin could potentially be an important virulence factor for ORT, and appears to be differentially expressed in strains obtained from various sources. Experiments will be designed to test whether the hemolytic phenotype is related to virulence. This knowledge will allow us to design appropriate intervention strategies to control pre-harvest infection.

Scientific Publication:
Tabatabai, L.B., Zehr, E.S., Zimmerli, M.K., Nagaraja, K.V. 2008. Iron acquisition by Ornithobacterium rhinotracheale. Avian Diseases. 52(3):419-425.

Fowl Cholera Peptide Vaccine.
Fowl cholera is an epidemic disease of poultry caused by the bacterium *Pasteurella multocida*. This disease is a major concern to poultry producers and veterinarians and without adequate approved therapeutic response measures. Vaccination can be effective against the disease but safe broadly protective vaccines are currently unavailable on the market. A recombinant peptide vaccine was formulated containing portions of a *P. multocida* protein which is critical to development of disease with all known isolates of the causative bacterium. Administration of the vaccine elicited a specific immune response which protected against disease in birds. This research can be used by vaccine manufacturers to facilitate the formulation of vaccine products with adequate safety and broad efficacy for use by the poultry industry.

Scientific Publications:
Tatum, F.M., Tabatabai, L.B., Briggs, R.E. 2009. Sialic Acid uptake is necessary for virulence of *Pasteurella multocida* in turkeys. Microbial Pathogenesis. 46(6):337-344.

Tatum, F.M., Tabatabai, L.B., Briggs, R.E. 2009. Protection Against Fowl Cholera Conferred by Vaccination with Recombinant *Pasteurella multocida* Filamentous Hemagglutinin Peptides. Avian Diseases. 53(2):169-174.

A Panviral Microarray for Detection of Swine Respiratory Viruses in Clinical Samples.
The continuous emergence of swine viruses has elevated the need for diagnostic platforms that have the ability to detect many known, novel, and emerging pathogenic agents simultaneously. Panviral DNA microarrays represent the most robust approach for massively parallel viral surveillance and detection. The Virochip is a panviral DNA microarray that is capable of detecting all known viruses, as well as novel viruses related to known viral families, in a single assay and has been used to successfully identify known and novel viral agents in clinical human specimens. However, the usefulness and the sensitivity of the Virochip platform have not been tested on a set of clinical veterinary specimens with the high degree of genetic variance that is frequently observed with swine virus field isolates. ARS scientists in Ames, Iowa, investigated the utility and sensitivity of the Virochip to positively detect swine viruses in both cell culture-derived samples and clinical swine samples. The Virochip successfully detected porcine reproductive and respiratory syndrome virus (PRRSV) in serum and influenza A virus in lung lavage fluid. The Virochip also successfully detected porcine circovirus type 2 (PCV2) and porcine respiratory coronavirus (PRCV) in turbinate tissue homogenate. Collectively, these data demonstrate that the Virochip can successfully detect pathogenic viruses frequently found in swine in a variety of solid and liquid specimens, such as turbinate tissue homogenate and lung lavage fluid, as well as antemortem samples, such as serum.

Scientific Publication:
Nicholson T.L., Kukielka D., Vincent A.L., Brockmeier S.L., Miller L.C., Faaberg K.S. 2011. Utility of a panviral microarray for detection of swine respiratory viruses in clinical samples. J Clin Microbiol. 2011 Apr;49(4):1542-8. Epub 2011 Jan 26.

Development of Real-Time Polymerase Chain Reaction Assays for Rapid Detection and Differentiation of Wild-Type Pseudorabies and Gene-Deleted Vaccine Viruses.
ARS scientists in Ames, Iowa, validated a real-time PCR assay for Pseudorabies virus surveillance. Pseudorabies virus (PRV), the cause of Aujeszky's disease, was eradicated from the U.S. domestic swine herd but continues to circulate in the feral swine population and thus continues to pose a threat for the commercial swine industry. A critical need for the current PRV surveillance program in the United States is the rapid detection of PRV. Real-time polymerase chain reaction (real-time PCR) is a valuable diagnostic technique that can rapidly identify infectious agents in clinical specimens. Diagnostic performance of the real-time PCR assay developed as a testing method confirmed that it is a rapid, accurate assay that is adaptable to a variety of PCR platforms currently in use by diagnostic laboratories around the world and can provide reliable results on an array of clinical samples.

Scientific Publications:
Ma W., Lager K.M., Richt J.A., Stoffregen W.C., Zhou F., Yoon K.J. 2008. Development of real-time polymerase chain reaction assays for rapid detection and differentiation of wild-type pseudorabies and gene-deleted vaccine viruses. J Vet Diagn Invest. 2008 Jul;20(4):440-7.

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Component 5: Reproductive and Neonatal Diseases

Rationale for the research:
Reproductive performance is the foundation of a successful food animal production system. Sows need to deliver as many healthy pigs as possible to ensure an efficient and cost effective pork production system. Cows need to deliver healthy calves to produce wholesome meat and milk. The reproductive health of poultry egg-layers and breeders directly impacts egg yield and the ability to seed broiler houses with quality stock. A multitude of infectious and metabolic diseases can decrease reproductive performance. Preventing reproductive and neonatal diseases will better enable an animal to realize its full production potential. However, as our food animal production systems have become more efficient there has been a concomitant decrease in the reproductive performance of dairy cows and our livestock and poultry industries continue to experience significant neonatal morbidity and mortality.

The decline in fertility of dairy cows is multifactorial. Epidemiological studies indicate that factors such as dystocia, retained placenta, metritis and ovarian cysts associated with infertility are conditions that develop secondary to metabolic diseases such as hypocalcemia and ketosis. Herds suffering low pregnancy rates are generally experiencing multiple management inefficiencies including constant exposure to infectious diseases such as bovine viral diarrhea virus (BVDV) and *Neospora caninum* (neosporosis) leading to an increase in early embryonic mortality and late term abortions. There are also common underlying metabolic diseases that further compromise immune functions and contribute to poor estrus expression and/or detection, extended anovulatory periods, and low conception rates. Hypocalcemia and negative energy balance are major metabolic challenges to the cow. Marked negative changes in energy balance and reduced immunocompetence influence gonadotropic and metabolic hormones. New research is needed to understand the metabolic effects of lactation on reproduction and understanding mechanisms linking disease to poor conception and early embryonic mortality.

The reproductive health of beef and dairy cows also impacts the health of neonates. Nearly one in 11 calves born alive dies before it is weaned. Failure of passive transfer of maternal antibody and failure to develop an immune system capable of staving off common pathogens are major factors affecting morbidity and mortality of neonates. Understanding the ontogeny of the development of the immune system in neonates to a fully functional adult immune system will be critical to improve survival on farms where exposure to infectious agents is rapidly increasing due to congregation of large numbers of animals at one site.

The ARS animal health reproductive and neonatal diseases research program focused on three strategic areas: 1) understanding the pathogenesis of disease; 2) understanding mechanisms of disease-protection *in utero*; and 3) the development of highly effective diagnostics, vaccines, and biotherapeutics to prevent and control priority diseases. Resources were directed to solve problems in following key areas: eradication of bovine viral diarrhea (BVD); *Neospora caninum* (neosporosis); and the reproductive health of the dairy cow.

Stakeholders at our September 2005 Animal Health Workshop representing the dairy industry ranked reproductive and neonatal diseases as their 2nd priority. The National Cattleman's Beef Association (NCBA) Fiscal Year 2005 Emerging Cattle Health and Issues Working Group

identified BVD and neosporosis on their list of animal disease research priorities. Additional diseases that also impact reproductive performance, neonatal health, and egg production are addressed in Component 4 and include the following action plan research components: porcine reproductive and respiratory syndrome and mycoplasmosis of poultry.

Research Needs:
Several critical gaps existed in our scientific knowledge of BVDV disease pathogenesis. These gaps included the need to understand what constitutes a protective immune response, particularly for fetal protection. The mechanisms of immune tolerance that lead to persistent infections *in utero* need to be determined to enable their prevention. In addition, BVDV-induced immune suppression may impede the development of effective vaccines. Improved diagnostics that enable detection of cows pregnant with persistently infected fetuses have been evaluated. The impact of BVDV in non-bovine species on a national BVDV control and eradication program was investigated as well as interference from newly emerging BVDV variants and other pestivirus species.

Successful management of *Neospora*-induced disease in cattle requires a thorough understanding of epidemiology, in particular identification of a small reservoir host (e.g. rodents), other definitive hosts (e.g. canids), and development of field pen-side diagnostic tests. Prevention of neosporosis would be best achieved through the development of highly efficacious vaccines against *Neospora caninum* infection of adult cows, either oocyst-derived or arising from cyst reactivation.

The etiology, epidemiology, and pathology of infectious and metabolic diseases that affect reproductive performance were investigated and characterized. In addition, the ability of neonatal calves to respond immunologically to vaccines was assessed using TB vaccine as a model.

Anticipated Products In Action Plan:
- Discovery of methods to diagnose cattle pregnant with fetuses that are persistently infected with BVDV.
- Scientific information to increase our understanding of the epidemiology and transmission patterns of *N. caninum* in dairy and beef herds, and the role of dogs and wild canids and small rodents in the infection cycle.
- Field diagnostic tests for rapid identification of neosporosis in dairy and beef herds.
- A recombinant vaccine against *N. caninum* tachyzoites that is highly effective in preventing abortion and reactivation of tissue cysts.
- Scientific information to determine the role of infectious and metabolic diseases that result in decreased reproductive performance.
- Development of management tools to prevent infectious and metabolic diseases that affect reproductive efficiency.
- Discovery of effective diagnostics, vaccines, and biotherapeutics to support reproductive health management protocols.

Impact:
Gaps were recognized in the diagnostic tests, vaccines and scientific information that elucidates the causes of persistently infected ruminants with BVDV. In addition, information on how certain viruses (e.g., pestiviruses) are able to attack the host immune system which will provide science-based strategies for vaccine or biotherapeutic intervention. This research will assist in the development of countermeasures and integrated protocols to enable more effective prevention or eradication of BVDV in U.S. cattle herds.

Neosporosis-associated abortion control will improve the reproductive efficiency of U.S. dairy and beef herds. An important gap was identified in lack of understanding about the interaction between host reservoirs and cattle in the transmission of *N. caninum.* This knowledge is important in the development and transfer of new and unique vaccine strategies to control neospora-associated diseases.

Gaps in the causes of reproductive diseases, effective countermeasures and integrated protocols to increase the overall reproductive performance of U.S. dairy herds have helped the dairy industry were identified. In addition, information on the immune response in neonatal calves to vaccination is critically needed as a crucial piece of information for improved intervention strategies to maintain the health of calves.

COMPONENT 5: SELECTED ACCOMPLISHMENTS

Wildlife Present a Potential Source of Bovine Viral Diarrhea Virus (BVDV) for Cattle.
Bovine Viral Diarrhea Virus (BVDV) is a costly disease that affects cattle and other ruminants. The virus has many nasty effects, including fever, diarrhea, respiratory and reproductive disease, abortion, birth defects, and death. BVDV is thought by many to be the most important endemic viral disease of cattle, with economic losses estimated at about $50 to $100 per cow. Design of effective programs geared toward the eradication of BVDV in domestic cattle will require an understanding of BVDV infections in wild ungulates, which are frequently in contact with domestic cattle. ARS scientists in Ames, Iowa, investigated the potential for white-tailed deer does to become persistently infected and serve as a source of infection for our domestic cattle herds. White-tailed does were infected with BVDV during the first trimester of pregnancy. Infection resulted in death or reproductive failure (abortion, readsorption, stillbirth) in 11 out of 13 naïve does. Histological and immunohistochemical examination of persistently infected fawns revealed that BVDV antigen was distributed widely throughout many tissues and cell types, most notably epithelium and vascular endothelium, consistent with that reported in cattle. In contrast to cattle, lymphocytes exhibited only very rare positive staining. These findings indicate that BVDV infection results in clinically severe reproductive disease in deer and that there may be differences in the way the virus behaves in deer compared to cattle. These findings suggest that the impact of BVDV reproductive disease in deer may be under appreciated and that because the virus may be spread differently from deer than cattle, different control strategies may be needed. This preliminary information is important for both cattle and captive deer producers.

Scientific Publication:
Ridpath, J.F., Mark, C., Chase, C.L., Ridpath, A.C., Neill, J.D. 2007. Febrile response and decrease in circulating lymphocytes following acute infection of white tail deer fawns with either a BVDV1 or a BVDV2 strain. Journal of Wildlife Diseases. 43(4):653-659.

Dairy Calf Immune Responses.
The effect of early vaccination on the capability of B cells from pre-ruminant calves were tested for their ability to respond using ovalbumin and *Mycobacterium bovis*, strain bacillus Calmette-Guen (BCG). Vaccination of 3-week-old calves with ovalbumin resulted in the production of IgG1 and IgG2 antibodies. Vaccination with BCG did not elicit a measurable antibody response. In a second study, when calves were vaccinated with both BCG and ovalbumin, antibody responses occurred. This work demonstrated that calves B cells are capable of responding to antigens.

Scientific Publication:
Foote M.R., Nonnecke B.J., Beitz D.C., Waters W.R. 2007. Antigen-specific B-cell responses by neonatal calves after early vaccination. J Dairy Sci. Nov; 90(11):5208-17.

Hypocalcemia in Dairy Cows.
The periparturient cow undergoes a transition from non-lactating to lactating at calving. The animal is tremendously challenged to maintain calcium homeostasis. Those that fail can develop milk fever, a clinical disorder that is life threatening to the cow and predisposes the animal to a variety of other disorders. The physiological factors that cause milk fever and strategies for prevention of milk fever focused on the effects diet cation-anion difference can have on tissue sensitivity to parathyroid hormone. Another major risk factor for milk fever is hypomagnesemia, which is observed when animals are fed inadequate amounts of magnesium, or some factor is present in the diet that prevents adequate absorption of magnesium. Moderate hypomagnesemia impairs the ability of the cow to maintain calcium homeostasis and hypocalcemia occurs. These findings have been widely used by the dairy industry in the control of milk fever.

Scientific Publication:
Goff, J.P. 2008. The monitoring, prevention, and treatment of milk fever and subclinical hypocalcemia in dairy cows. Vet J. Apr;176(1):50-7. Epub 2008 Mar 14.

Component 6: Enteric Diseases

Rationale for the research:
Enteric diseases affect animals and humans universally and are the cause of significant production losses and mortality. Several enteric pathogens are zoonotic and considered food safety pathogens that pose major public health concerns. The problems associated with food safety pathogens are addressed under National Program 108, Food Safety. Endemic enteric diseases of livestock and poultry remain economically important causes of production losses. Although many enteric diseases can be prevented through sound biosecurity measures and good management practices, significant scientific gaps remain in our understanding of commensal (harmless beneficial microorganisms) versus pathogenic infections, polymicrobial infections and enteric disease complexes, disease transmission, and the ecological and host interactions that lead to disease and production losses. With the continued concern over the use of antibiotics in animal production, there is a need to find safe and practical alternatives to prevent and control enteric diseases. Research is needed to identify the pathogens responsible for many enteric diseases, molecular tools for epidemiological studies, and the discovery of improved diagnostics and vaccines that can be integrated in the design of effective prevention and control programs.

The ARS animal health enteric diseases research program used available resources to focus on one key priority enteric disease of cattle, Johne's disease; and more broadly on enteric diseases of poultry with an emphasis on the gut microbiome and its impact on nutrition and health.

Stakeholders at our September 2005 Animal Health Workshop representing the dairy industry ranked Johne's disease as their 1st priority; stakeholders representing the turkey industry ranked Poult Enteric Mortality Syndrome (PEMS) as the third most important disease after avian influenza and avian pneumovirus; and stakeholders representing the poultry broiler industry ranked enteric diseases as their 4th priority with Runting-Stunting Syndrome of broilers (RSS) the most important disease.

Research Needs:
Completion of the sequencing of the *Mycobacterium paratuberculosis* genome provides new research tools to identify *M. paratuberculosis*-specific genes and proteins that may be useful as diagnostic tools or vaccine candidates. Genomic and proteomic analyses of *M. paratuberculosis* are needed to identify immunogens that may be differentially expressed in subclinical and clinical stages of disease. In concert with studies in microbial genomics, studies on host immune responses during the different stages of disease are needed to ascertain potential mechanisms that contribute to inflammation and disease. Unique microbial genomic sequences and host responses are needed to implement a technology-driven vaccine discovery program.

Poultry enteric diseases include Poult Enteritis Mortality Syndrome (PEMS), Runting-Stunting Syndrome of broilers (RSS), as well as several unclassified enteric diseases. The exact causes of many of these diseases remain unknown. PEMS affects young turkeys and is probably the most severe form of enteric disease. PEMS was first reported in North Carolina in 1991. Since then, PEMS and similar disease conditions have been reported in most regions where turkeys are commercially produced including; the Southeastern United States, Texas, California, Arkansas, and Missouri. Since its emergence in 1991, outbreaks of PEMS have cost the turkey industry

millions of dollars in losses annually. Although there are no detailed financial studies, it is estimated that PEMS outbreaks cost the North Carolina turkey industry $34 million in losses in 1995 alone, making it the most economically devastating disease of turkeys. The exact cause of PEMS is unknown but is thought to be associated with avian astroviruses, avian reoviruses, and avian rotaviruses infections. Determining the cause of PEMS and other enteric diseases of poultry has been difficult because many enteric viruses cannot be grown in the laboratory and available virus detection tests lack sensitivity and specificity. Moreover, enteric diseases can be caused by two or more infectious agents, working independently but causing clinically similar conditions, or working in concert in so called polymicrobial infections to form enteric disease complexes with primary and secondary pathogens. Accordingly, molecular tools are needed to identify enteric disease viruses and understand the epidemiology and pathogenic pathways responsible for disease and production losses. There is also a need to understand the processes that regulate host response to enteric infection to develop effective strategies to prevent enteric disease.

The Animal Health Action Plan identified a significant list of research priorities and anticipated products expected from research on enteric diseases and that now serve to help measure the national program's progress during the last 5 years in meeting the needs of cattle and poultry producers. The following list of anticipated products from the Action Plan is followed by the expected impact of the research and a sampling of relevant accomplishments.

Anticipated Products In Action Plan:

- Comparative analyses of the *M. paratuberculosis* proteome leading to the development of highly sensitive and specific diagnostic tests for detection of *M. paratuberculosis* for cattle and sheep through identification and characterization of unique bacterial genes and proteins.
- Host immune response analyses to understand the mechanisms of control in early stages of disease and the switch in immunity that results in progression from subclinical to clinical disease.
- Highly effective vaccine platform that prevents subclinical disease, shedding of *M. paratuberculosis,* and progression to clinical disease.
- Identify factors associated with the risk of enteric diseases.
- Identify modulators of stress in production systems that affect enteric disease development.
- Discovery of cytokines and their expression profiles that govern processes involved in host defense during enteric infections.
- Identify and characterize pathogens responsible for poultry enteric disease complexes
- Pathogen-specific markers useful for molecular or immunological detection.
- Molecular tools to study the epidemiology and ecology of enteric pathogens.
- Strategies that enhance the clearance of enteric pathogens.
- Discovery of immunointervention strategies to prevent the development of enteric infections.

Impact:
The research program provided information on key host-pathogen responses during the infection process that contribute to the development and application of genomic-based diagnostic tests and vaccines to prevent and control Johne's disease. The poultry enteric research program provided information to detect pathogens responsible for enteric disease complexes, understand the relationship of enteric pathogens to each other and host co-evolution, and tools that enable the prevention and control of enteric diseases.

COMPONENT 6: SELECTED ACCOMPLISHMENTS

Understanding the Pathogenesis of Johne's Disease.
Paratuberculosis (Johne's disease) is a chronic wasting enteric disease of ruminants caused by infection with a bacterial pathogen designated as *Mycobacterium avium* subsp. paratuberculosis. Economic losses are estimated to be $200/infected cow/year and are the result of animal culling, reduced milk production, poor reproductive performance, and reduced carcass value. Prevalence of Johne's disease in the U.S. dairy cattle population is estimated to be 22 to 40 percent. ARS scientists in Ames, Iowa, have produced several novel monoclonal antibodies (highly specific antibodies engineered to bind to a very precise mark or "epitope" on an antigen) against *Mycobacterium avium* subsp. *paratuberculosis*. These antibodies have enabled scientists to follow disease progression as the bacterial pathogen infects its host and have opened up new areas of research in pathogenesis and diagnostic studies. Importantly, ARS scientists have also identified antibodies produced in sheep infected with Johne's disease that react to both a sheep protein and a protein produced by *Mycobacterium avium* subsp. *paratuberculosis*. This finding suggests that the host immune response may not be able to distinguish between self proteins and this bacterial pathogen. This new information provides the first clues to the immunopathology observed in Johne's disease and may suggest an autoimmune component to this disease.

Scientific Publications:
Bannantine, J.P., Paustian, M., Waters, W.R., Stabel, J.R., Palmer, M.V., Li, L., Kapur, V. 2007. Profiling Host Antibody Responses to *Mycobacterium avium* subspecies *paratuberculosis* Infection Using Protein Arrays. Infection and Immunity. 76(2):739-749.

Bannantine, J.P., Radosevich, T.J., Stabel, J.R., Sreevatsan, S., Kapur, V., Paustian, M. 2007. Development and Characterization of Monoclonal Antibodies and Aptamers Against Major Antigens of *Mycobacterium avium* subsp. *paratuberculosis*. Clinical and Vaccine Immunology. 14(5):518-526.

Bannantine, J.P., Radosevich, T.J., Stabel, J.R., Berger, S., Griffin, J.F., Paustian, M. 2007. Production and Characterization of Monoclonal Antibodies Against a Major Membrane Protein of *Mycobacterium avium* subsp. *paratuberculosis*. Clinical and Vaccine Immunology. 14(3):312-317.

Bannantine, J.P., Waters, W.R., Stabel, J.R., Palmer, M.V., Li, L., Kapur, V., Paustian, M. 2008. Development and Use of a Partial *Mycobacterium avium* subspecies *paratuberculosis*. Protein Array. Proteomics. 8(3):463-474.

Bannantine, J.P., Rosu, V., Zanetti, S., Rocca, S., Ahmed, N., Sechi, L.A. 2008. Antigenic Profiles of Recombinant Proteins from *Mycobacterium avium* subsp. *paratuberculosis* in Sheep with Johne's Disease. Veterinary Immunol Immunopath, 122(1-2):116-125.

Identification of Novel Antigens in Johne's Disease.
Diagnosis of cattle infected with Johne's is difficult due to the long incubation time between infection and the onset of clinical disease. ARS scientists in Ames, Iowa, identified six novel proteins that may be candidates for an improved diagnostic test for Johne's disease. The scientists identified the proteins through the use of a newly developed 96-spot protein assay. Studies using the protein assay have determined that some proteins can be detected as early as 70 days after infection of cattle with *M. paratuberculosis*. Early diagnosis of infected cattle will allow improved control strategies on a herd basis through isolation and culling of infected animals.

Scientific Publications:
Yakes, B.J., Lipert, R.J., Bannantine, J.P., Porter, M.D. 2008. Impact of Protein Shedding on Detection of *Mycobacterium avium* subsp. *paratuberculosis* by a Whole-Cell Immunoassay Incorporating Surface-Enhanced Raman Scattering. Clinical and Vaccine Immunology. 15(2):235-242.

Yakes, B.J., Lipert, R.J., Bannantine, J.P., Porter, M.D. 2008. Detection of *Mycobacterium avium* subsp. *paratuberculosis* by a Sonicate Immunoassay Based on Surface-Enhanced Raman Scattering. Clinical and Vaccine Immunology. 15(2):227-234.

New Viruses Detected in the Guts of Turkeys.
The discovery of novel viruses in turkeys may help veterinarians unravel some of the mysteries of viral enteric diseases that affect poultry. Each year, enteric disorders such as Poult Enteritis Mortality Syndrome (PEMS) in young turkeys and Runting Stunting Syndrome (RSS) in chickens cause tremendous economic losses to the poultry industry worldwide due to increased mortality rates, decreased weight gain and treatment costs. Decades of research indicate that certain viruses may be the culprit for viral enteric diseases, but no single agent has been identified. ARS scientists in Athens, Georgia, used a new powerful tool called "Metagenomics" to detect and sequence nucleic acid of all the RNA (ribonucleic acid) viruses present in the gut of turkeys affected by enteric syndromes. Metagenomics, a molecular technique, is the study of a collection of genetic material from a mixed community of organisms. The technology allows scientists to look at a complex environmental sample, sequence all the viral nucleic acid in the sample and analyze it as a single genome. ARS scientists extracted and analyzed nucleic acid from poultry intestine samples collected from five different turkey flocks affected by enteric diseases. The intestinal virus metagenome contained thousands of pieces of nucleic acid representing many groups of known and previously unknown turkey viruses. As suspected, avian viruses such as astrovirus, reovirus and rotavirus—common in the gut of birds and implicated in some enteric diseases—were verified. The detection of numerous small, round RNA viruses, such as the members of the *Picornaviridae* family, long thought to be a major constituent in the turkey gut also was confirmed. However, ARS scientists found many previously unknown turkey viruses such as picobirnavirus, a small double-stranded RNA virus implicated in enteric disease in other agricultural animals. A calicivirus also was identified in poultry for the first time.

Caliciviruses are found in different animals and have been implicated for years in enteric diseases in humans. Discovering this treasure trove of virus sequences puts researchers a step closer to understanding viral communities in poultry, and will help scientists determine which viruses are associated with enteric diseases and which organisms are not.

Scientific Publication:
Day J.M., Ballard L.L., Duke M.V., Scheffler B.E., Zsak L. (2010). Metagenomic analysis of the turkey gut RNA virus community. Virol J. 12;7:313.

Direct-fed Microbials Improve the Gut Health in Broiler Chickens.
Probiotics modulate gut immunity and enhance natural resistance against avian coccidiosis. Direct-fed microbials are live microorganisms which confers a health benefit on the host by balancing its intestinal microbes. Recently, much attention has been paid to the role of direct-fed microbials on the immune system (i.e., immunomodulation) and their effects on the interaction between gut microflora and host immune system development. In order to develop a novel control strategy for poultry diseases and to reduce antibiotics uses, scientists in Beltsville, Maryland, investigated the immune mechanisms and possibility of immune enhancement using various direct-fed microbials products. Feeding dietary direct-fed microbials significantly improved intestinal structure and enhanced gut health as revealed by increased villus height and crypt depth compared with normal controls. These studies provided a rational scientific basis for future studies to investigate direct-fed microbials as immunopotentiating agents to enhance host protective immunity against enteric pathogens in broiler chickens.

Scientific Publication:
Lee, K.W., Lee, S.H., Lillehoj, H.S., Li, G.X., Jang, S.I., Park, M.S., Kim, D.K., Lillehoj, E.P., Neumann, A.P., Rehberger, T.G., Siragusa, G.R., Babu, U.S. 2010. Effects of Direct-Fed Microbials on Growth Performance, Gut Morphometry, and Immune Characteristics in Broiler Chickens. Poultry Science. 89:203-216.

Biotherapeutics Antibodies Feed Supplements for Poultry Health.
ARS scientists have worked with industry to develop novel biotherapeutic antibodies as feed supplements to enhance the disease resistance of poultry flocks to gastrointestinal pathogens that impact food safety and production gains. Applied advanced technologies in avian immunology and genomics have led to identifying novel molecules that have been shown to enhance host innate immunity, decrease early mortality, and reduce the use of antibiotics in poultry production. These innovations will reduce economic losses due to enteric diseases in poultry and will decrease the use of many antibiotics that are associated with human drug resistances. These novel dietary immunomodulation strategies to enhance poultry health have implications for human health, farm animal security, and increasing the production capabilities of poultry industries worldwide.

Scientific Publication:
Lee S.H., Lillehoj H.S., Park D.W., Jang S.I., Morales A., García D., Lucio E., Larios R., Victoria G., Marrufo D., Lillehoj E.P. 2009. Protective effect of hyperimmune egg yolk IgY antibodies against Eimeria tenella and Eimeria maxima infections. Vet Parasitol.;163(1-2):123-6.

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NP 103 Component 7: Parasitic Diseases

Rationale for the research:
Parasites represent one of the most diverse groups of organisms that live on a host (ectoparasites) or within a host (endoparasites) and are responsible for hundreds of insidious diseases ranging from enteric diseases to vector-borne hemoparasitic infections. The livestock and poultry industries are severely affected by significant losses in animal production due to lower weight gain, anemia, diarrhea, and death. Nematode infections in cattle and the cost of combating these parasites costs beef producers over $1 billion per year. Many parasites are invasive and exotic to the United States and impact international trade. With the advent of climate change, parasites may spread to new areas increasing their impact on various animal species. Most importantly, the emergence of drug resistant parasites against many commonly used pharmaceutical drugs has huge economic implications.

Stakeholders at the September 2005 Animal Health Planning Workshop representing the beef industry ranked anti-parasitic drug resistance as their 5th priority; the dairy industry ranked hemoparasites as their 5th priority; the equine industry ranked diseases that impact international movement of horses such as Piroplasmosis (Equine Babesiosis) as their 1st priority; and the sheep and goat industries ranked internal parasites as their 2nd priority. The poultry broiler industry identified enteric diseases such as coccidiosis their 4th priority. The National Cattleman's Beef Association (NCBA) Fiscal Year 2005 Emerging Cattle Health and Issues Working Group identified Anaplasmosis on their list of animal disease research priorities.

Research Needs:
Anti-helminthic resistance to drugs such as Ivermectin and Fenbendazole has been observed world-wide in nematodes of cattle and small ruminants, particularly in sheep-producing countries. Although the number of reports is low, there has been documentation of a significant increase in drug resistance in nematodes of cattle. The drug resistance appears to vary according to host, parasite, and region. This is an area of critical importance and research towards identifying and working on developing an understanding of the mechanisms of resistance as well as alternative strategies is critical for successful animal production.

Avian coccidiosis is a serious protozoan disease of poultry. Currently it is the cause of the largest level of antibiotic use. Due to the concerns for the development of antibiotic resistance due to the wide scale use of antibiotics, there is a need for alternative strategies for control of coccidia in poultry. As a result, developing an improved vaccine that is cross protective against a number of protozoan species is needed.

Research is needed to discover vector related contributions to the risk of anaplasmosis in areas within the United States characterized as endemic and the discovery of parasite antigen structure associated with high transmission efficiency. In addition, developing improved diagnostic and control strategies for equine piroplasmosis is important research due to the fact it is considered a foreign animal disease in the United States. The constant movement of horses internationally for breeding or competition purposes makes our ability to detect the parasite as well as treat infected horses critical to well-being of the billion dollar equine industry.

Anticipated Products In Action Plan:

- Develop molecular-based techniques to rapidly speciate and quantify *Eimeria* oocysts in litter samples.
- Develop rapid tests to identify drug resistance markers in *Eimeria* field isolates.
- Discover recombinant vaccines that are safe and effective against heterologous field challenges with mass vaccination capability to prevent outbreaks of coccidiosis in poultry farms.
- Investigate and document drug resistance related to parasite species; e.g., *Haemonchus contortus*, *H. placei*, *Cooperia punctata*, *C. oncophora*, *Ostertagia ostergii*, *Nematodirus helvetianus*, and trichostrongyles.
- Determine the effect of different production and management systems on the manifestation of drug resistance in sheep, dairy, cow-calf, and feedlot operations.
- Identify molecular probes to better define parasite species in the field.
- Identify molecular markers of drug resistance based on mode of action and measure the allele frequency of parasite genes involved in drug resistance.
- Identify patterns of gene flow in nematode populations to manage drug resistance in different production systems to reduce the impact of drug resistance on productivity.
- Determine the transmission competence of vectors within the United States and trading partners (Canada).
- Develop vaccines which prevent production losses from clinical disease and transmission (transfection technology is the center of our vaccine strategy for babesiosis).
- Determine if current chemotherapeutics for *Anaplama marginale* and *Babesia caballi* are effective in clearing persistent infections.

Impact:
A greater understanding of the extent and type of drug resistance in nematodes of U.S. cattle and sheep, especially as related to the type and phase of farm management is critical to the well-being of livestock production systems. Improved molecular probes for speciating nematodes in the farm environment and for identifying markers of drug resistance are needed as the range of species of parasites spread due to climate change. Reduction in the incidence and effects of nematode infections in cattle and sheep by allowing fact-based application of appropriate anti-helminthic compounds is needed as resistance levels to the current products increases. Data supporting and aiding decisions on import/export restrictions and novel vaccines which prevent clinical disease and block vector borne- transmission and the hemoparasites such as *Anaplasma* or *Babesia* is critically needed by the various livestock industries.

Avian coccidiosis is an important problem to the poultry industry. Treatment for coccidiosis by antibiotics is of concern for development of antimicrobial resistance as coccidiostat-resistant protozoa are developing. As a result, alternative strategies are critical. Scientists in Beltsville, Maryland, are working to develop alternatives to antibiotics including development of novel vaccines. The research developed will help control this serious problem while reducing the levels of antimicrobial agents administered to poultry.

COMPONENT 7: SELECTED ACCOMPLISHMENTS

Survey of Cattle Parasites and Resistance to Drug Therapy. Intestinal parasites have been a problem for livestock for many years. Conservative estimates are that gastrointestinal parasites cost the American cattle industry over $2 billion dollars per year. This cost is based on the treatment with chemicals (anthelmintics) to kill intestinal worms and the decreased productivity and growth of livestock infected with parasites. This easily makes gastrointestinal worms or nematodes the most costly parasitic infection of American cattle. Although the drugs currently used to control cattle intestinal worms worldwide are generally effective and safe, global resistance by parasites to drugs is rapidly on the rise. A national survey of cattle intestinal parasites and their response to anti-parasiticide treatment was conducted in collaboration with the APHIS and two university collaborators. The results of a study of randomly selected cattle operations demonstrated a wide distribution of resistance to anthelmintic treatment. In nearly all cases, the most resistant species of parasite was *Cooperia* species, in particular *Cooperia punctata*. While historically this parasite was a minor species infecting cattle, with the emergence of resistance to anti-parasiticide treatment, it has become a predominant pathogen. These results demonstrate that overuse of anthelmintics has not only selected for drug resistant intestinal parasites, but has also changed the population dynamics of parasites on pasture and has resulted in a species with an increased ability to cause damage to livestock. Additional research is being conducted to assess potential genetic markers that can be used to identify anthelmintic resistant parasites which will aid in developing new intervention and control strategies to control important species of intestinal parasites in cattle. These are critical fist steps in investigating the increasing problem of resistance to products that kill parasites and using population genetics to quantify the resistance of intestinal parasites and identifying genetic markers associated with drug resistance in intestinal worms.

Scientific publications:

Gasbarre L.C., Smith L.L., Lichtenfels J.R., Pilitt P.A. 2009. The identification of cattle nematode parasites resistant to multiple classes of anthelmintics in a commercial cattle population in the US.Vet Parasitol. Dec 23;166(3-4):281-5. Epub 2009 Aug 26.

Gasbarre L.C., Smith L.L., Hoberg E., Pilitt P.A. 2009. Further characterization of a cattle nematode population with demonstrated resistance to current anthelmintics. Vet Parasitol. 2009 Dec 23;166(3-4):275-80. Epub 2009 Aug 26.

Developing Improved Vaccine Strategies in Poultry.

Avian coccidiosis is an intestinal disease of poultry caused by protozoa in the genus *Eimeria*. Coccidiosis is the most important infectious disease affecting productivity in commercial broilers worldwide, causing over $ 350 million annual loss to the U.S. poultry industry alone. Although vaccine usage is increasing, application of anticoccidial drugs, such as ionophores or synthetic drugs remain the predominant control method. With the concern of emergence of antibiotic resistance, strategies to reduce the use of antimicrobials in food production animals are needed. In addition, the emergence of drug-resistant *Eimeria* strains found in a poultry facility, and subsequent lower performance, has forced producers to adopt alternative strategies, such as alternating between two drugs or rotating drugs. While coccidiosis vaccines have proven to be effective, there have been reports of increased costs associated with vaccination. Currently,

effective vaccination requires administering live oocysts to non-immune birds, which provides protection. However there often appears to be reduced vaccine efficacy which may be due to variability in the uptake of *Eimeria* oocysts in the vaccines administered to chicks by conventional methods. Thus, a significant number of chicks do not receive a sufficient dose of vaccine to develop resistance against challenge infection, while other chicks receive too many oocysts resulting in shedding high numbers of oocysts in litter. This research is utilizing existing technology to develop new vaccines for controlling the disease and improve consistency of delivery of live *Eimeria* oocyst vaccines. Novel delivery systems for vaccinating against *Eimeria* are being developed. These systems include using a recombinant attenuated Salmonella vaccine to deliver *Eimeria* antigens and encapsulated oocysts inside gelatin beads fed to day-old chicks to reduce intake variability. Developing improved vaccine strategies to control coccidiosis in poultry is important to reduce the need for antibiotics, which is a major goal of USDA disease control strategies.

Scientific Publication:
Konjufca V., Jenkins M., Wang S., Juarez-Rodriguez M.D., Curtiss R. 3rd. 2008. Immunogenicity of recombinant attenuated *Salmonella enterica* serovar *Typhimurium* vaccine strains carrying a gene that encodes Eimeria tenella antigen SO7.Infect Immun. 2008 Dec;76(12):5745-53. Epub 2008 Sep 22.

Babesiosis and Horses.
Equine piroplasmosis is a disease caused by blood parasites of the *Babesia* family. It is considered a foreign animal disease in the United States and every effort has been made to prevent its entry into the U.S. horse population. The presence of this organism would prove very expensive to the equine industry due to blocking of export and importation of horses. During 2010 the United States encountered the reemergence of babesiosis, also known as piroplasmosis in the equine population. Babesiosis in horses is caused by two distinct parasites, *Babesia equi* (now *Theileria equi*) and *Babesia caballi*. In order to begin developing strategies to control and re-eliminate the organism for the U.S. equine population and in response to the needs of the USDA/APHIS, ARS scientists in Pullman, Washington, developed a method to eliminate persistent infection and transmission risk from horses infected with *B. caballi.* This has proven critical to the equine industry as it has resulted in owners of infected horses being able to treat their horses to enable them to resume their prior functions. In contrast, the second parasite *T. equi*, has proven more difficult to clear from infected horses. Research by scientists has resulted in the sequencing and annotating the genome of *B. equi.* It was discovered that this parasite is taxonomically between other *Babesia* organisms and a different blood borne parasite, *Thieleria*. The genetic information also determined that *T. equi* lacks a gene family that produces a classical antigenic variation. This discovery will enable scientists to begin further research exploring and developing alternative intervention strategies to control this foreign disease entity in the U.S. equine population.

Scientific Publications:
Goff W.L., Johnson W.C., Molloy J.B., Jorgensen W.K., Waldron S.J., Figueroa J.V., Matthee O., Adams D.S., McGuire T.C., Pino I., Mosqueda J., Palmer G.H., Suarez C.E., Knowles D.P., McElwain T.F. 2008. Validation of a competitive enzyme-linked immunosorbent assay for

detection of Babesia bigemina antibodies in cattle. Clin Vaccine Immunol. Sep;15(9):1316-21. Epub 2008 Jul 16.

Short M.A., Clark C.K., Harvey J.W., Wenzlow N., Hawkins I.K., Allred D.R., Knowles D.P., Corn J.L., Grause J.F., Hennager S.G., Kitchen D.L., Traub-Dargatz J.L.2012. Outbreak of equine piroplasmosis in Florida. J Am Vet Med Assoc. 2012 Mar 1;240(5):588-95.

Scoles G.A., Hutcheson H.J, Schlater J.L., Hennager S.G., Pelzel A.M., Knowles D.P. 2011. Equine piroplasmosis associated with Amblyomma cajennense Ticks. Emerg Infect Dis. ct;17(10):1903-5.

Schwint O.N., Ueti M.W., Palmer G.H., Kappmeyer L.S., Hines M.T., Cordes R.T., Knowles D.P., Scoles G.A. 2009. Imidocarb dipropionate clears persistent Babesia caballi infection with elimination of transmission potential. Antimicrob Agents Chemother. Oct;53(10):4327-32. Epub 2009 Jul 20.

New Vaccine Strategies for Controlling Bovine Babesiosis.

Babesia bovis and *Babesia bigemina* are important causative agents of bovine babesiosis, known as cattle tick fever (CTF), which was a significant problem in the southern United States until the 1940s, when the tick vectors were eradicated by intensive dipping of cattle with chemicals to kill the ticks (acaracides). However, the ticks that spread CTF are present in a buffer zone along the Rio Grande and have begun to spread, and thus pose the threat of an outbreak of CTF in the Mexico-United States border regions. The threat of reintroducing CTF into the United States from Mexico has increased because (1) the USDA/APHIS surveillance program involves only ticks; no surveillance is performed to identify cattle carrying the babesia organism; (2) at least a million cattle that may carry babesia come from Mexico each year; (3) ticks resistant to current control chemicals have been reported in northern Mexico and the southern United States; (4) there is an increase in the number of wild deer along the border that can carry the ticks and babesia; and (5) there is no drug or vaccine approved for use in the United States to treat CTF. The lack of a vaccine for control of CTF leaves U.S. cattle vulnerable to the disease upon reintroduction. It is estimated that the cost of controlling vector ticks alone in the first year, should they spread outside the current quarantine zone into the United States, is over $1.3 billion. Critical progress was made in developing a long-acting anti-babesial and anti-tick vaccine by placing anti-tick genes into babesia organisms that are incapable of causing disease. To date, a green fluorescent protein gene was inserted into *B. bovis* and expression demonstrated. The insertion or alteration of genes in *B. bovis* will allow scientists to identify genes and proteins which induce protective immunity against the ticks in cattle. In addition, this technique will allow scientists to identify the virulence genes used by *B. bovis* and identify new and novel vaccine candidates. This information is critical for the development of anti-babesial vaccines including those which block transmission between animals.

Scientific Publications:

Bastos R.G., Ueti M.W., Knowles D.P., Scoles G.A. 2010. The *Rhipicephalus* (Boophilus) *microplus* Bm86 gene plays a critical role in the fitness of ticks fed on cattle during acute *Babesia bovis* infection. Parasit Vectors. Nov 19;3:111.

Suarez, C.E., McElwain, T.F. 2008. Transient transfection of purified *Babesia bovis* merozoites. Experimental Parasitology. 118(4):498-504.

Component 8: Transmissible Spongiform Encephalopathies

Rationale for the research

Scrapie of sheep, bovine spongiform encephalopathy (BSE) of cattle, chronic wasting disease (CWD) of deer and elk, and variant Creutzfeldt-Jacob disease (vCJD) of humans are all fatal neurodegenerative disorders classified as transmissible spongiform encephalopathies (TSEs). There are no effective treatments or cure. The origin of TSEs has yet to be determined but scientific evidence indicates that the causal agents are abnormal prion proteins that induce a catalytic conversion of the normal host protein into an abnormal form. The abnormal prion proteins are transmissible and in most cases appear to be resistant to degradation. The discovery in 1996 that BSE of cattle is the cause of vCJD in people represented an unforeseen emerging zoonosis. That discovery has raised concern in the public health community that other TSEs such as CWD could evolve to cause disease in people. Although there is no evidence that CWD is zoonotic, TSEs have now been shown to be able to cross the species barrier, both experimentally and under natural conditions.

To date, only four cases of BSE have been found in the United States. The first case was found December 2003 in a cow imported from Canada and is estimated to have cost the U.S. beef industry $3.2 billion to $4.7 billion from the loss of beef and offal exports. The three subsequent cases were in cows born and raised in the United States. The first United States indigenous case was found in a downer cow in Texas, November 2004; the second indigenous cow was found on a farm in Alabama, March 2006; the third indigenous case was recently found on a diary farm in California, April 2012. The finding of three indigenous cases of BSE, and the number of scrapie and CWD cases reported annually in the United States continues to raise concerns about the public health risks of animal TSEs.

Despite being caused by misfolding of a host encoded protein, we now know that BSE exists as more than one strain. The form first identified has been termed classical BSE. This is the form associated with the feed-borne epizootic in the United Kingdom. More recently, two other forms have been identified and can be broadly referred to as atypical BSE, or specifically defined as High-type (H-type) or Low-type (L-type) BSE based upon their migration pattern relative to classical BSE on a Western blot. Neither H-type nor L-type BSE is associated with the feed-borne epizootic. Based on various forms of evidence, H-type and L-type BSE are generally believed to be spontaneous in nature rather than feed-borne, as is the case for classical BSE. The three indigenous U.S. BSE cases were reported as “atypical.” The first two indigenous BSE cases reported in 2004 and 2006 were reported as H-Type BSE, while the case in 2012 an L-type BSE.

ARS scientists have made significant contributions to the understanding of the atypical H-Type BSE cases found in the United States. ARS identified the first genetic case of BSE, and showed that it is a heritable polymorphism. ARS scientists have also contributed to the understanding of atypical BSE as a potential spontaneous TSE in cattle. This information supports, for the first time, the presence of three different etiologies (spontaneous/sporadic, genetic, and infectious/feedborne) of BSE in cattle. Previously, only humans were known to have three separate etiologies for TSEs. In collaboration with APHIS and a team of Italian researchers, ARS has shown that the United States and Italian diagnostic techniques are equivalent in identifying

classical, H-type, and L-type BSE, an important contribution that helped identify the April 2012 atypical L-type BSE case in California.

Stakeholders at the September 2005 Animal Health Planning Workshop representing the wildlife, sheep, and goat industries ranked TSE research as their 1st priority; representatives of the beef industry ranked TSE research as their 6th priority. Diseases in Component 8 include classical and atypical BSE, scrapie, and CWD. Additional selected accomplishments for BSE are captured under Component 2.

Research Needs:
The Institute of Medicine of the National Academies published a guidance document November 2003 calling for a National Prion Research Program (Advancing Prion Science: Guidance for the National Prion Research Program – free download available from the National Academies Press at http://www.nap.edu/catalog.php?record_id=10862). Key recommendations from the National Academies report included funding basic research to elucidate: 1) the structural features of prions; 2) the molecular mechanisms of prion replication; 3) the mechanisms of pathogenesis of TSEs; and 4) the physiological function of the normal prion protein. In addition, the National Academies report recommended a comprehensive applied research program in diagnostics, testing blood for evidence of TSEs, epidemiological studies to monitor the occurrence of TSEs in human and animals, and research that will lead to strategies to prevent and treat TSEs.

The White House Office of Science and Technology Policy (OSTP) created a federal Interagency Working Group (IWG) on Prion Science in September 2004. ARS and the NIH co-led the IWG with participation Food and Drug Administration, APHIS, Centers for Disease Control and Prevention, Department of Defense, and Enivironmental Protection Agency. The working group determined that although significant scientific advances had been made, the research conducted to date had yet to deliver many of the concrete solutions needed to safeguard people and animals from these devastating diseases. A critical concern was the potential for environmental, genetic, or iatrogenic events that could lead to new variant TSEs that are infectious and zoonotic (transmissible from animals to humans). The following six priorities were selected by the IWG on Prion Science to maximize the impact of a National Prion Research Program:

1. Nature and origin of prion agents
2. Pathobiology of prion strains
3. Determinants of transmissibility and epidemiology
4. Genetics of disease susceptibility
5. Diagnostics, detection, and surveillance
6. Prevention and treatment

These six interrelated priorities represent areas with critical gaps in our knowledge base. They were selected with the aim of establishing strategic collaborations that will produce benefits by aligning core competencies across federal agencies.

Because TSE clinical studies in livestock and cervids require several years to reach an end-point, the associated expenses and resources needed to implement a research program, and the need for

multidisciplinary research teams, ARS integrated its prion research laboratories located in Ames, Iowa, Pullman, Washington, and Albany, California, into a national coordinated research program in 2004. ARS focused its core competencies and the available resources of its national coordinated research program on six research needs: 1) understand infectivity, tissues tropism, and pathogenesis; 2) identify determinants of host range specificity; 3) understand the molecular mechanisms of prion replication; 4) strain characterization and determinants of virulence; 5) develop ante-mortem (live) pre-clinical animal tests; and 6) discover cost effective methods of prion inactivation. These research needs were the basis for determining the anticipated products that are expected from the research, and that now serve to help measure the national program's progress during the last five years in meeting the needs of animal producers, researchers, and action and regulatory agencies. The following list of anticipated products from the Action Plan is followed by the expected impact of the research and a sampling of relevant accomplishments.

Anticipated Products In Action Plan:

- Sensitive and specific ante-mortem tests that are rapid and scalable.
- Establish the biochemical, pathological, and epidemiological profile of atypical TSE strains and unusual isomers of the prion protein.
- Determine the pathogenesis of TSEs, including establishing route(s) of prion migration in the host, amplification of the agent, and disease expression.
- Conduct interspecies transmission studies to determine the host range specificity and resulting risk of TSEs to other animal species.
- Enhanced rapid methods of agent detection to protect the human environment.
- Cost effective methods of inactivating TSE agents.
- Identify and characterize genotypic variations and functional genomic mechanisms associated with disease susceptibility or resistance.

Impact:

The impact of the research included scientific information to enable regulatory and action agencies to promulgate science-based control programs. The development of diagnostics and countermeasures has enhanced current federal and state control and eradication programs for scrapie and CWD and will continue to enable the prevention and containment of future occurrences of BSE.

COMPONENT 8: SELECTED ACCOMPLISHMENTS

Characterization of Atypical Bovine Spongiform Encephalopathy Cases in the United States.
Scientists at ARS and APHIS in Ames, Iowa, reported that the first two indigenous BSE cases in the United States were "atypical." Using a variety of laboratory diagnostic methods to conduct the analyses, the scientists did not detect any definite spongiform lesions in the BSE-positive brains of the atypical cases and observed smaller quantities of the abnormal prion agent when compared to typical BSE cases. Only a few atypical BSE cases have been reported in cattle from France, Germany, Japan, the Netherlands, and the United Kingdom and there is a paucity of peer-reviewed published data on atypical BSE. Important questions include the tissue distribution of abnormal prions in atypical cases. To date, we know that cases have occurred in different breeds of cattle with different genotypes; that the majority of cases occur in older cattle; and that very

few of the animals have typical clinical symptoms of BSE. Further research is needed to determine the frequency of these atypical cases, their pathogenesis in cattle, and, if possible, the origin of such novel BSE phenotypes.

Scientific Publication:
Richt, J.A., Kunkle, R.A., Alt, D., Nicholson, E.M., Hamir, A.N., Czub, S., Kluge, J., Davis, A.J., Hall, S.M. 2007. Identification and characterization of two bovine spongiform encephalopathy cases diagnosed in the United States. Journal of Veterinary Diagnostic Investigation. 19(2):142-154.

Confirmatory Laboratory Tests to Detect Classical and Atypical BSE Forms.
ARS scientists in Ames, Iowa, obtained brain samples from cases of United States and Italian Classical (C-) type, U.S. High (H-) type, and an Italian Low (L-) type BSE to compare the ability of two sets of immunohistochemical (IHC) and Western blot (WB) confirmatory protocols to detect C- and atypical (L- and H-type) BSE forms. The study showed that the IHC and WB BSE confirmatory protocols were equally able to recognize C-, L- and H-type BSE forms and to discriminate between their different immunohistochemical and molecular phenotypes. Importantly, for the first time, one of the two sets of BSE confirmatory protocols proved effective in identifying the L-type BSE form. This finding helped validate the suitability of the BSE confirmatory tests for BSE surveillance currently in place in the United States.

Scientific Publication:
Porcario C., Hall SM, Martucci F., Corona C., Iulini B., Perazzini A.Z., Acutis P., Hamir A.N., Loiacono C.M., Greenlee J.J., Richt J.A., Caramelli M., Casalone C. 2011. Evaluation of two sets of immunohistochemical and Western blot confirmatory methods in the detection of typical and atypical BSE cases. BMC Res Notes. 2011 Sep 29;4:376.

Experimental Interspecies Transmission Studies of Transmissible Spongiform Encephalopathies in Cattle.
Experimental cross-species transmission of TSE agents provides valuable information for potential host ranges of known TSEs. Some interspecies transmission studies have been conducted by inoculating disease-causing prions intracerebrally (IC) rather than orally; the latter is generally effective in intraspecies transmission studies and is considered a natural route by which animals acquire TSEs. The "species barrier" concept for TSEs resulted from unsuccessful interspecies oral transmission attempts. Oral inoculation of prions mimics the natural disease pathogenesis route whereas IC inoculation is rather artificial; however, it is very efficient since it requires smaller dosage of inoculum, and typically results in higher attack rates and reduces incubation time compared to oral transmission. A species resistant to a TSE by IC inoculation would have negligible potential for successful oral transmission. To date, results indicate that cattle are susceptible to IC inoculation of scrapie, transmissible mink encephalopathy (TME), and CWD but it is only when inoculated with TME do they develop spongiform lesions or clinical disease similar to BSE. Importantly, cattle are resistant to oral transmission of scrapie or CWD; susceptibility of cattle to oral transmission of TME has not yet determined.

Scientific Publication:
Hamir A.N., Kehrli M.E. Jr., Kunkle R.A., Greenlee J.J., Nicholson E.M., Richt J.A., Miller J.M., Cutlip R.C. 2011. Experimental interspecies transmission studies of the transmissible spongiform encephalopathies to cattle: comparison to bovine spongiform encephalopathy in cattle. J Vet Diagn Invest. 2011 May;23(3):407-20.

Experimental Transmission of Chronic Wasting Disease from Elk and White-tailed Deer to Fallow Deer.
Final observations on experimental transmission of chronic wasting disease (CWD) from elk and white-tailed deer to fallow deer from a 5-year study were reported. During the study, 13 fawns were inoculated intracerebrally with CWD-infected brain material from white-tailed deer and 3 other fawns were kept as uninoculated controls. Animals were euthanized at 7, 24, 26, months post-inoculation (MPI), and between 29-37 and 51-60 MPI. Only five of the deer kept between 51 and 60 MPI became sick and were euthanized. Microscopic lesions of spongiform encephalopathy were observed in only these five animals; however, abnormal prions were detected in tissues of the central nervous system by immunohistochemistry, Western blot, and by a commercial rapid test in all animals that survived beyond 24 months post-infection. This study demonstrated that intracerebrally inoculated fallow deer not only amplify CWD prions, but also develop lesions of spongiform encephalopathy. These results provide information on the potential risk of CWD transmission across different cervid species, and contributes to understanding CWD transmission in wild and captive cervids.

Scientific Publication:
Hamir A.N., Greenlee J.J., Nicholson E.M., Kunkle R.A., Richt J.A., Miller J.M., Hall M. 2011. Experimental transmission of chronic wasting disease (CWD) from elk and white-tailed deer to fallow deer by intracerebral route: final report. Can J Vet Res. 2011 Apr;75(2):152-6.

Accumulation of Prion Scrapie in the Placentas of Goats.
Domestic goats are a natural and experimental host of scrapie and bovine spongiform encephalopathy. Goats are also susceptible to experimental infection with CWD and Creutzfeldt Jakob disease. Distribution of prion scrapie is similar in the tissues of scrapie-infected sheep and goats but no data are available on the potential shedding of the agent through the placenta, the presumed route of transmission of ovine scrapie. ARS scientists in Pullman, Washington, studied the accumulation of prion scrapie in the placentas of goats with naturally acquired classical scrapie in comparison to field cases of classical ovine scrapie. The results of these studies showed that prion scrapie accumulates in the shed placentas of goats with naturally acquired scrapie. Although these levels were low in most caprine samples, the caprine placenta may contribute to prion contamination of kidding facilities and transmission to co-housed sheep or goats.

Scientific Publication:
O'Rourke K.I., Zhuang D., Truscott T.C., Yan H., Schneider D.A. 2011. Sparse PrP(Sc) accumulation in the placentas of goats with naturally acquired scrapie. BMC Vet Res. 2011 Feb 1;7:7.

APPENDIXES

APPENDIX 1 – *Research Projects in National Program 103*
APPENDIX 2 – *Publications by Research Project*
APPENDIX 3 – *ARS Technology Transfer*
APPENDIX 4 – *Research Collaborations*
APPENDIX 5 – *Retrospective Electronic Survey Results*

APPENDIX 1

National Program 103 – Animal Health
ACCOMPLISHMENT REPORT 2007 – 2011

List of Research Projects

Project Number	Project Title, Scientists Assigned, and Location
1265-31320-075-00D	**DETERMINANTS OF AVIAN COCCIDIOSIS INFECTION AND PATHOGENICITY;** Mark Jenkins (P) and Raymond Fetterer; Beltsville, Maryland
1265-32000-082-00D	**EPIDEMIOLOGY AND CONTROL OF NEOSPORA CANINUM AND RELATED PROTOZOA;** Wenbin Tuo (P) and Jitender Dubey; Beltsville, Maryland
1265-32000-083-00D	**GENOMIC AND IMMUNOLOGIC STRATEGIES TO IMPROVE MILK PRODUCTION EFFICIENCY AND CONTROL MASTITIS;** Anthony Capuco (P) and Theodore Elsasser; Beltsville, Maryland
1265-32000-084-00D	**USING GENOMICS TO DEFINE AND CONTROL PARASITIC INFECTIONS IN CATTLE;** Dante Zarlenga (P), Tad Sonstegard, Robert Li, and Curtis Van Tassel; Beltsville, Maryland
1265-32000-085-00D	**INTEGRATED BIOSYSTEMATICS AND TAXONOMY FOR PARASITES AMONG UNGULATES AND OTHER VERTEBRATES;** Eric Hoberg (P) and Katarzyna Miska; Beltsville, Maryland
1265-32000-086-00D	**AVIAN GENOMIC AND IMMUNOLOGIC APPROACHES FOR CONTROLLING MUCOSAL PATHOGENS;** Hyun Lillehoj (P); Beltsville, Maryland
1265-32000-088-00D	**GENETIC AND IMMUNE STRATEGIES TO CONTROL MUCOSAL PATHOGENS OF SWINE;** Joan Lunney (P), Joseph Urban, Jr., Dante Zarlenga, and Harry Dawson; Beltsville, Maryland
1940-32000-050-00D	**COUNTERMEASURES TO CONTROL FOREIGN ANIMAL DISEASES OF SWINE;** Manuel Borca (P), James Zhu, and Jonathan Arzt; Orient Point, New York
1940-32000-052-00D	**FOOT-AND-MOUTH DISEASE VIRUS (FMDV) HOST-PATHOGEN INTERACTIONS;** Luis Rodriguez (P), Aida Rieder, James Zhu, William Golde, Marvin Grubman, Manuel Borca, Teresa De Los Santos, and Jonathan Arzt; Orient Point, New York
1940-32000-053-00D	**FOOT-AND-MOUTH DISEASE VIRUS (FMDV) COUNTERMEASURES DISCOVERY;** Marvin Grubman (P), Teresa De Los Santos, William Golde, Aida Rieder, Luis Rodriguez, and James Zhu; Orient Point, New York

* For the sake of consistency, projects are listed and organized in Appendix 1 and 2 according to the ARS project number used to track projects in the Agency's internal database. A (P) after a scientist's name indicates the project's principal investigator.

Project Number	Project Title, Scientists Assigned, and Location
1940-32000-054-00D	**VESICULAR STOMATITIS VIRUS (VSV) HOST-PATHOGEN INTERACTIONS;** Luis Rodriguez (P), Jonathan Arzt, and James Zhu; Orient Point, New York
1940-32000-055-00D	**ADVANCED VACCINES FOR FOOD-AND-MOUTH DISEASE AND CLASSICAL SWINE FEVER;** Luis Rodriguez (P); Orient Point, New York
3625-32000-079-00D	**CHARACTERIZATION AND ENHANCEMENT OF IMMUNE RESPONSES OF CALVES;** Brian Nonnecke (P) and Randy Sacco; Ames, Iowa
3625-32000-081-00D	**GENOMIC AND IMMUNOLOGICAL ANALYSIS OF SPIROCHETE DISEASES;** Richard Zuerner (P) and David Alt; Ames, Iowa
3625-32000-082-00D	**COUNTERMEASURES TO PREVENT AND CONTROL TUBERCULOSIS IN CATTLE AND WILDLIFE RESERVOIRS;** Wade Waters (P), Mitchell Palmer, and Tyler Thacker; Ames, Iowa
3625-32000-084-00D	**COUNTERMEASURES TO PREVENT AND CONTROL BRUCELLOSIS IN LIVESTOCK AND WILDLIFE RESERVOIRS;** Steven Olsen (P), Betsy Bricker, and Fred Tatum; Ames, Iowa
3625-32000-086-00D	**TRANSMISSION, DIFFERENTIATION, AND PATHOBIOLOGY OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES;** Eric Nicholson (P), Robert Kunkle, and Justin Greenlee; Ames, Iowa
3625-32000-087-00D	**COUNTERMEASURES TO CONTROL AND SUPPORT ERADICAITON OF BOVINE VIRAL DIARRHEA VIRUS (BVDV);** Julia Ridpath (P) and John Neill; Ames, Iowa
3625-32000-088-00D	**SWINE VIRAL DISEASES PATHOGENESIS AND IMMUNOLOGY;** Marcus Kehrli (P), Andrew Cheung, Kay Faaberg, Kelly Lager, Laura Miller, and Amy Vincent; Ames, Iowa
3625-32000-089-00D	**THE PORCINE RESPIRATORY DISEASE COMPLEX (PRDC);** Susan Brockmeier (P), Crystal Loving, Tracy Nicholson, and Karen Register; Ames, Iowa
3625-32000-093-00D	**GENOMIC AND IMMUNOLOGICAL CHARACTERISTICS OF JOHNE'S DISEASE;** Judith Stabel (P) and John Bannantine; Ames, Iowa
3625-32000-094-00D	**IDENTIFICATION OF FACTORS ASSOCIATED WITH IMMUNE SUPPRESSION AND MASTITIS;** John Lippolis (P) and Timothy Reinhardt; Ames, Iowa
3625-32000-098-00D	**COUNTERMEASURES TO CONTROL VIRAL DISEASES OF CATTLE;** Julia Ridpath (P), John Neill, Brian Nonnecke, Karen Register, and Randy Sacco; Ames, Iowa
3625-32000-099-00D	**COUNTERMEASURES TO CONTROL BACTERIAL DISEASES OF CATTLE;** Randy Sacco (P), Robert Briggs, Brian Nonnecke, Louisa Tabatabai, and Fred Tatum; Ames, Iowa

Project Number	Project Title, Scientists Assigned, and Location
5325-32000-008-00D	**DETECTION OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY AGENTS IN LIVESTOCK, WILDLIFE, AGRICULTURAL PRODUCTS, AND THE ENVIRONMENT;** Robert Hnasko (P), John Carter, Christopher Silva, and Larry Stanker; Albany, California
5348-32000-024-00D	**CONTROL OF GAMMAHERPESVIRUS-ASSOCIATED MALIGNANT CATARRHAL FEVER IN RUMINANTS;** Hong Li (P), Donald Knowles, and Naomi Taus; Pullman, Washington
5348-32000-026-00D	**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES: THE ROLE OF GENETICS, STRAIN VARIATION, AND ENVIRONMENTAL CONTAMINATION IN DISEASE CONTROL;** Katherine O'Rourke (P), Donald Knowles, David Schneider, and Stephen White; Pullman, Washington
5348-32000-027-00D	**DETERMINANTS OF ANAPLASMA MARGINALE TRANSMISSION AT THE VECTOR/PATHOGEN INTERFACE;** Glen Scoles (P), Lowell Kappmeyer, Donald Knowles, Susan Noh, Massaro Ueti, and Stephen White; Pullman, Washington
5348-32000-028-00D	**IMMUNOLOGIC AND PHARMACOLOGICAL INTERVENTIONS OF VECTOR-BORNE BABESIOSIS;** Donald Knowles (P), Lowell Kappmeyer, Glen Scoles, Carlos Suarez, and Massaro Ueti; Pullman, Washington
5348-32000-029-00D	**HOST IMMUNOGENETICS PREDICT CLINICAL DISEASES IN OVINE PROGRESSIVE PNEUMONIA VIRUS INFECTED SHEEP;** Lynn Hoesing (P), Lowell Kappmeyer, Donald Knowles, and Stephen White; Pullman, Washington
5430-32000-001-00D	**COUNTERMEASURES TO CONTROL AND ERADICATE RIFT VALLEY FEVER (RFV);** William Wilson (P), Lee Cohnstaedt, Barbara Drolet, Dana Nayduch, and Scott McVey; Manhattan, Kansas
5430-32000-002-00D	**VIRUS-VECTOR-HOST INTERACTIONS OF ARBOVIRAL DISEASES OF LIVESTOCK;** Barbara Drolet (P), Lee Cohnstaedt, Dana Nayduch, Scott McVey, and William Wilson; Manhattan, Kansas
5438-32000-029-00D	**GENETIC AND BIOLOGICAL DETERMINANTS OF RESPIRATORY DISEASE SUSCEPTIBILITY;** Carol Chitko Mckown (P), Michael Clawson, Gregory Harhay, and Michael Heaton; Clay Center, Nebraska
6226-32000-010-00D	**DEVELOPMENT OF ALTERNATIVE APPROACHES TO ANTIBIOTICS FOR CONTROLLING BACTERIAL RESPIRATORY PATHOGENS IN POULTRY;** William Huff (P), Narayan Rath, Geraldine Huff, and Ann Donoghue; Fayetteville, Arkansas
6406-32000-010-00D	**COUNTERMEASURES TO PREVENT AND CONTROL AVIAN MYCOPLASMOSIS;** Scott Branton (P), Spencer Leigh, Joseph Purswell, and Jeffrey Evans; Mississippi State University, Mississippi

Project Number	Project Title, Scientists Assigned, and Location
6612-32000-048-00D	**APPLICATION OF BIOLOGICAL AND MOLECULAR TECHNIQUES TO THE DIAGNOSIS AND CONTROL OF AVIAN INFLUENZA AND OTHER EMERGING POULTRY PATHOGENS;** Erica Spackman (P), David Swayne, Claudio Afonso, Mary Pantin-Jackwood, and David Suarez; Athens, Georgia
6612-32000-049-00D	**NEWCASTLE DISEASE EPIDEMIOLOGY, PATHOGENESIS, AND CONTROL;** Claudio Afonso (P), Patti Miller, and David Suarez; Athens, Georgia
6612-32000-052-00D	**GENOMIC STRATEGIES FOR CONTROL OF MAREK'S DISEASE VIRUS;** Stephen Spatz (P) and Laszlo Zsak; Athens, Georgia
6612-32000-053-00D	**GENOMIC AND FUNCTIONAL ANALYSIS OF THE MUCOSAL IMMUNE RESPONSE AND ITS ROLE IN PROTECTION AGAINST RESPIRATORY PATHOGENS IN POULTRY;** Darrell Kapczynski (P), Mary Pantin-Jackwood, Erica Spackman, David Suarez, and David Swayne; Athens, Georgia
6612-32000-054-00D	**EPIDEMIOLOGY, PATHOGENESIS AND COUNTERMEASURES TO PREVENT AND CONTROL ENTERIC VIRUSES OF POULTRY;** James Day (P) and Laszlo Zsak; Athens, Georgia
6612-32000-056-00D	**EPIDEMIOLOGY, PATHOGENESIS, AND COUNTERMEASURES TO PREVENT AND CONTROL AVIAN METAPNEUMOVIRUS INFECTION;** Qingzhong Yu (P) and Laszlo Zsak; Athens, Georgia

APPENDIX 2

National Program 103 – Animal Health
ACCOMPLISHMENT REPORT 2007 – 2011

Publications by Research Project

1265-31320-075-00D

DETERMINANTS OF AVIAN COCCIDIOSIS INFECTION AND PATHOGENICITY; Mark Jenkins (P) and Raymond Fetterer; Beltsville, Maryland

Belli, S.I., Ferguson, D.J., Slapetova, I., Katrib, M., Slapeta, J., Flowers, S.A., Miska, K.B., Tomley, F., Shirley, M.W., Wallach, M.G., Smith, N.C. 2009. Conservation of proteins involved in oocyst wall formation in Eimeria maxima, Eimeria tenella and Eimeria acervulina Antibodies to Eimeria maxima gametocyte antigens cross-react with Eimeria tenella and E. acervulina: Implications for vaccine development. International Journal for Parasitology. 39:1063-1070.

Berezin, V.E., Bogoyavlenskyi, A.P., Khudiakova, S.S., Alexuk, P.G., Omirtaeva, E.S., Zaitceva, I.A., Tustikbaeva, G.B., Barfield, R.C., Fetterer, R.H. 2010. Immunostimulatory complexes containing Eimeria tenella antigens and low toxicity plant saponins induce antibody response and provide protection from challenge in broiler chickens. Veterinary Parasitology. 167:28-35.

Igarashi, M., Zulpo, D.L., De Cunha, I.A., Barros, L., Pereira, V., Taroda, A., Navarro, I.T., Vidotto, O., Vidotto, M.C., Jenkins, M.C., Garcia, J.L. 2010. Toxoplasma gondii: humoral and cellular immune response of BALB/c mice immunized via intranasal route with rTgROP2. Brazilian Journal of Veterinary Parasitology. 19:210-216.

Jenkins, M.C., Fetterer, R.H., Miska, K.B. 2009. Co-infection of chickens with Eimeria praecox and Eimeria maxima does not prevent development of immunity to Eimeria praecox or Eimeria maxima. Veterinary Parasitology 161:320-323.

Kim, S., Cox, C.M., Stuard, L.H., Dalloul, R.A., Miska, K.B., Jenkins, M.C., Fetterer, R.H. 2010. Molecular Cloning and Functional Characterization of the Avian Macrophage Migration Inhibitory Factor (MIF). Developmental and Comparative Immunology. 34:1021-1032.

Fetterer, R.H., Jenkins, M.C., Miska, K.B., Cain, G.C. 2010. Metam sodium reduces viability and infectivity of Eimeria oocysts. Journal of Parasitology. 96:632-637.

Kim, S., Miska, K.B., Mcelroy, A., Jenkins, M.C., Fetterer, R.H., Cox, C., Stuard, L., Dalloul, R. 2009. Molecular cloning and functional characterization of avian interleukin-19. Molecular Immunology. 47:476-484.

Kniel, K., Shearer, A., Cascarino, J., Wilkins, G., Jenkins, M.C. 2007. High hydrostatic pressure and uv light treatment of produce contaminated with eimeria acervulina as a cyclospora cayetanensis surrogate. Journal of Food Protection. 70:2837-2842.

Jenkins, M.C., Allen, P., Wilkins, G., Klopp, S., Miska, K.B. 2008. Eimeria praecox infection ameliorates effects of e. maxima infection in chickens. 155:10-14.

Miska, K.B., Jenkins, M.C., Trout, J.M., Santin, M., Fayer, R. 2009. Detection and comparison of giardiavirus (GLV) from different assemblages of giardiia duodenalis. Journal of Parasitology. 95(5):1197-2000.

Miska, K.B., Schwarz, R.S., Jenkins, M.C., Rathinam, T., Chapman, D. 2010. Molecular characterization and phylogenetic analysis of Eimeria from turkeys and gamebirds, and the implication on the evolutionary relationships OF Eimeria FROM galliforme birds. Journal of Parasitology. 96:982-986.

* For the sake of consistency, projects are listed and organized in Appendix 1 and 2 according to the ARS project number used to track projects in the Agency's internal database. A (P) after a scientist's name indicates the project's principal investigator.

Perez, V.G., Jacobs, C.M., Barnes, J., Jenkins, M.C., Kuhlenschmidt, M.S., Fahey, G.C., Parsoms, C.M., Pettigrew, J.E. 2011. Effect of corn distillers dried grains with solubles and Eimeria acervulina infection on growth performance and the intestinal microbiota of young chicks. Poultry Science. 90:958-964.

Schwarz, R.S., Fetterer, R.H., Miska, K.B., Rosenberg, G.H. 2009. Coccidian Merozoite transcriptome analysis from Eimeria maxima in comparison to Eimeria tenella and Eimeria acervulina. Journal of Parasitology. 96:49-57.

Schwarz, R.S., Klopp, S., Miska, K.B., Jenkins, M.C. 2009. Genomic analysis of Eimeria spp. populations in relation to performance levels of broiler chicken farms in Arkansas and North Carolina. U.S.A. Journal of Parasitology. 95:871-880.

Stuard, L.H., Miska, K.B., Jenkins, M.C., Fetterer, R.H., Cox, C.M., Kim, S., Dalloul, R.A. 2010. Expression of innate immunity genes during Eimeria praecox infection in chickens. Experimental Parasitology. 127:714-718.

1265-32000-082-00D

EPIDEMIOLOGY AND CONTROL OF NEOSPORA CANINUM AND RELATED PROTOZOA; Wenbin Tuo (P) and Jitender Dubey; Beltsville, Maryland.

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GENOMIC AND IMMUNOLOGIC STRATEGIES TO IMPROVE MILK PRODUCTION EFFICIENCY AND CONTROL MASTITIS; Anthony Capuco (P) and Theodore Elsasser; Beltsville, Maryland.

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USING GENOMICS TO DEFINE AND CONTROL PARASITIC INFECTIONS IN CATTLE; Dante Zarlenga (P), Tad Sonstegard, Robert Li, and Curtis Van Tassel; Beltsville, Maryland.

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INTEGRATED BIOSYSTEMATICS AND TAXONOMY FOR PARASITES AMONG UNGULATES AND OTHER VERTEBRATES;
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AVIAN GENOMIC AND IMMUNOLOGIC APPROACHES FOR CONTROLLING MUCOSAL PATHOGENS; Hyun Lillehoj (P); Beltsville, Maryland.

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FOOT-AND-MOUTH DISEASE VIRUS (FMDV) HOST-PATHOGEN INTERACTIONS; Luis Rodriguez (P), Aida Rieder, James Zhu, William Golde, Marvin Grubman, Manuel Borca, Teresa De Los Santos, and Jonathan Arzt; Orient Point, New York.

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COUNTERMEASURES TO PREVENT AND CONTROL BRUCELLOSIS IN LIVESTOCK AND WILDLIFE RESERVOIRS; Steven Olsen (P), Betsy Bricker, and Fred Tatum; Ames, Iowa.

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TRANSMISSION, DIFFERENTIATION, AND PATHOBIOLOGY OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES; Eric Nicholson (P), Robert Kunkle, and Justin Greenlee; Ames, Iowa.

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COUNTERMEASURES TO CONTROL AND SUPPORT ERADICAITON OF BOVINE VIRAL DIARRHEA VIRUS (BVDV);
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SWINE VIRAL DISEASES PATHOGENESIS AND IMMUNOLOGY; Marcus Kehrli (P), Andrew Cheung, Kay Faaberg, Kelly Lager, Laura Miller, and Amy Vincent; Ames, Iowa.

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IDENTIFICATION OF FACTORS ASSOCIATED WITH IMMUNE SUPPRESSION AND MASTITIS; John Lippolis (P) and Timothy Reinhardt; Ames, Iowa.

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COUNTERMEASURES TO CONTROL VIRAL DISEASES OF CATTLE; Julia Ridpath (P), John Neill, Brian Nonnecke, Karen Register, and Randy Sacco; Ames, Iowa.

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DETECTION OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY AGENTS IN LIVESTOCK, WILDLIFE, AGRICULTURAL PRODUCTS, AND THE ENVIRONMENT; Robert Hnasko (P), John Carter, Christopher Silva, and Larry Stanker; Albany, California.

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CONTROL OF GAMMAHERPESVIRUS-ASSOCIATED MALIGNANT CATARRHAL FEVER IN RUMINANTS; Hong Li (P), Donald Knowles, and Naomi Taus; Pullman, Washington.

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES: THE ROLE OF GENETICS, STRAIN VARIATION, AND ENVIRONMENTAL CONTAMINATION IN DISEASE CONTROL; Katherine O'Rourke (P), Donald Knowles, David Schneider, and Stephen White; Pullman, Wsahington.

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DETERMINANTS OF ANAPLASMA MARGINALE TRANSMISSION AT THE VECTOR/PATHOGEN INTERFACE; Glen Scoles (P), Lowell Kappmeyer, Donald Knowles, Susan Noh, Massaro Ueti, and Stephen White; Pullman, Washington.

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HOST IMMUNOGENETICS PREDICT CLINICAL DISEASES IN OVINE PROGRESSIVE PNEUMONIA VIRUS INFECTED SHEEP; Lynn Hoesing (P), Lowell Kappmeyer, Donald Knowles, and Stephen White; Pullman, Washington.

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COUNTERMEASURES TO CONTROL AND ERADICATE RIFT VALLEY FEVER (RFV); William Wilson (P), Lee Cohnstaedt, Barbara Drolet, Dana Nayduch, and Scott McVey; Clay Center, Nebraska.

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GENETIC AND BIOLOGICAL DETERMINANTS OF RESPIRATORY DISEASE SUSCEPTIBILITY; Carol Chitko Mckown (P), Michael Clawson, Gregory Harhay, and Michael Heaton; Manhattan, Kansas.

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DEVELOPMENT OF ALTERNATIVE APPROACHES TO ANTIBIOTICS FOR CONTROLLING BACTERIAL RESPIRATORY PATHOGENS IN POULTRY; William Huff (P), Narayan Rath, Geraldine Huff, and Ann Donoghue; Fayetteville, Arkansas.

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APPLICATION OF BIOLOGICAL AND MOLECULAR TECHNIQUES TO THE DIAGNOSIS AND CONTROL OF AVIAN INFLUENZA AND OTHER EMERGING POULTRY PATHOGENS; Erica Spackman (P), David Swayne, Claudio Afonso, Mary Pantin-Jackwood, and David Suarez; Athens, Georgia

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NEWCASTLE DISEASE EPIDEMIOLOGY, PATHOGENESIS, AND CONTROL; Claudio Afonso (P), Patti Miller, and David Suarez; Athens, Georgia.

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GENOMIC STRATEGIES FOR CONTROL OF MAREK'S DISEASE VIRUS; Stephen Spatz (P) and Laszlo Zsak; Albany, Georgia.

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GENOMIC AND FUNCTIONAL ANALYSIS OF THE MUCOSAL IMMUNE RESPONSE AND ITS ROLE IN PROTECTION AGAINST RESPIRATORY PATHOGENS IN POULTRY; Darrell Kapczynski (P), Mary Pantin-Jackwood, Erica Spackman, David Suarez, and David Swayne; Athens, Georgia.

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6612-32000-054-00D

EPIDEMIOLOGY, PATHOGENESIS AND COUNTERMEASURES TO PREVENT AND CONTROL ENTERIC VIRUSES OF POULTRY; James Day (P) and Laszlo Zsak; Athens, Georgia.

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EPIDEMIOLOGY, PATHOGENESIS, AND COUNTERMEASURES TO PREVENT AND CONTROL AVIAN METAPNEUMOVIRUS INFECTION; Qingzhong Yu (P) and Laszlo Zsak; Athens, Georgia.

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APPENDIX 3

National Program 103 – Animal Health
ACCOMPLISHMENT REPORT 2007 – 2011

Technology Transfer

Over the 5-year cycle of NP 103, the following highlight NP 103 technology transfer outcomes:

- Inventions: 62
- Patents filed: 19
- Patents approved: 7
- Biological material inventions: 30
- Biological material licenses from inventions: 20

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APPENDIX 4

National Program 103 – Animal Health
ACCOMPLISHMENT REPORT 2007 – 2011

Research Collaborations

Number of Cooperative Research and Development Agreements (CRADAs): 37
Number of Trust Funds: 97
Number of Reimbursables: 225

External Grant Sources of Funding for National Program 103 Projects 2007-2011

Grants from universities usually involved cooperative research projects jointly conducted with university partners. In many cases this funding originated from third parties, such as the USDA National Institute for Food and Agriculture, National Institutes of Health, USAID, National Science Foundation, and other industry, non-profit, and government sources.

University	Government	International	Industry	Misc
90	76	27	111	13

UNIVERSITIES:
Aarhus University
Arizona State University
Clemson University
Colorado State University
Iowa State University
Kansas State University
Langston University
Louisiana State University
Michigan State University
Mississippi State University
Montana State University
New Mexico State University
North Carolina State University
Northern Arizona University
Ohio State University
Oklahoma State University
Pennsylvania State University
South Dakota State University
Texas A&M University
The University of Queensland
Tufts University
Tuskegee University
University of Texas Medical Branch (UTMB)
University of Alaska
University of California
University of Connecticut
University of Delaware
University of Georgia
University of Iowa
University of Maryland
University of Massachusetts
University of Minnesota
University of Pennsylvania
University of Texas
University of Utah
University of Wisconsin
Wake Forest University
Washington State University

RESEARCH ORGANIZATIONS:
Agriculture Professional Services
Alpaca Research Foundation (ARF)
St. Jude Children's Research Hospital

COMPANIES:

Agrilabs, Inc.
Agtech Products
Alphavax, Inc.
Axiss France SAS - Pancosma Bioactives
Biocis Pharma Ltd.
Biodetection Instruments, LLC
Biomune Company
Boehringer Ingelheim Animal Health
Chembio Diagnostic Systems, Inc.
Chesapeake Perl, Inc.
Chronix Biomedical
Cobb-Vantress, Inc
Colorado Quality Research, Inc.
Concurrent Analytical, Inc.
Diversa Corporation
DNA Solutions, Inc.
Fort Dodge Laboratories
Genvec, Inc.
Guardian Biotechnologies
Hematech
HIPRA
HMS Veterinary Development, Inc.
IDEXX Laboratories, Inc.
Imagilin Technology, LLC
Indian Immunologicals, Ltd
Investigacion Aplicada, S.A. de C.V.
Kerry's Nursery
Long Branch Co., Inc.
Merial
Microbio Test
Monsanto Company
Nippon Zeon Company, Ltd
Novartis Animal Health UK Ltd.
Novartis Animal Health US, Inc.
Novus International, Inc.
Pancosma S.A.
Pfizer Animal Health, Pfizer, Inc.
Piggen Canada, Inc.
Prionics AG
Prosetta Bioconformatics, Inc.
Replikins, Inc.
Rock River Laboratory, Inc.
Rural Technologies, Inc.
S. S. Steiner, Inc.
Seppic
Townsends Inc.
Vaxin, Inc.
Veterinary Medical Research Development (VMRD)
Viridax Corporation
Vital Probes, Inc.

INDUSTRY:

American Egg Board
American Jersey Cattle Association
National Pork Board
U.S. Poultry and Egg Association
USA Poultry and Egg Export Council

GOVERNMENT:

Canadian Food Inspection Agency, Canada
Centers for Disease Control and Prevention, Department of Health and Human Services
Environmental Protection Agency
European Commission, Europe
National Institutes of Health, Department Of Health and Human Services
National Science Foundation
National Veterinary Research & Quarantine Service (NVRQS), Republic of Korea
NSW Department of Primary Industries, Australia
Office of Naval Research
Rural Development Administration, Republic of Korea
U.S. Agency for International Development (USAID)
U.S. Army Medical Research and Material Command
USDA Animal and Plant Health Inspection Service (APHIS)
USDA Foreign Agricultural Service (FAS)
USDA National Institute of Food and Agriculture (NIFA)

GOVERNMENT [CONTINUED]:
U.S. Department of Defense
U.S. Department of Homeland Security
U.S. Department of State
U.S. Geological Survey, Department of the Interior
U.S.-Israel Binational Science Foundation, Israel

NON-GOVERNMENT ORGANIZATIONS:
Bill and Melinda Gates Foundation
Biotechnology Research and Development Center (BRDC)
Civilian Research and Development Foundation
Food and Agricultural Organization of the United Nations
Foundation Alliance Biosecure
Institute for Animal Health
Kansas Bioscience Authority
The World Organisation for Animal Health (OIE)

Outgoing Funding to Support ARS Research Programs 2007-2011

Specific Cooperative Agreements

U. S. UNIVERSITIES:
Arizona State University
Colorado State University
Georgia Institute of Technology
Iowa State University
Michigan State University
Mississippi State University
North Dakota State University
Ohio State University
Ohio State University Research Foundation
Oklahoma State University
South Dakota State University
Stephen F. Austin State University
Texas A&M University
University of Alaska
University of Arkansas
University of California
University of Connecticut
University of Delaware
University of Georgia
University of Idaho
University of Illinois
University of Iowa
University of Kentucky
University of Minnesota
University of Missouri
University of Nebraska
University of Washington
University of Wyoming
University Texas Medical Branch
Virginia Commonwealth Unit
Virginia Polytechnic Institute and State University
Washington State University
Washington University

INTERNATIONAL UNIVERSITIES:
Chung-Ang University, Republic of Korea, South Korea
Danish Technical University, Denmark
Erasmus University, Netherlands
Federal University of Santa Maria, Brazil
Flanders Interuniversity Institute for Biotechnology, Belgium
Free University of Brussels, Belgium
Gyeongsang National University, Republic of Korea, South Korea
Monash University, Australia
Polo Universitario, Italy
Technical University, Germany
University of Copenhagen, Denmark
University of Hong Kong, Hong Kong
University of Manitoba, Canada
University of Santiago de Compostela, Spain
Warsaw University of Life Sciences, Poland

INTERNATIONAL RESEARCH ORGANIZATIONS:
Agricultural Research Council – Onderstepoort, South Africa
Argentina Instituto de Biotechnologia (INTA), Argentina
Canada Food Inspection Agency, Canada
Centro de Investigación en Sanidad Animal, Spain
Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australia
Elizabeth Macarthur Agriculture Institute, Australia
Erasmus Medical Center, Netherlands
Food and Agricultural Organization of the United Nations, Indonesia
Food and Agricultural Organization of the United Nations, Egypt
Indian Veterinary Research Institute, India
Institut de Biologia Molecular de Barcelona, Spain
Instituto Nacional de Investigacion y Tecnologia Agraria y Alementaria, Spain
Institute for Animal Health, United Kingdom
Institute for Novel and Emerging Infectious Diseases, Germany
Instituto Nacional de Technolgia Agropecuaria (INIA), Argentina
Instituto Zooprofilattico Sperimentale del Piemonte, Italy
International Livestock Research Institute, Kenya
Italian Reference Centre for Animal TSE, Italy
l'Istituto Zooprofilattico Sperimentale del Piemonte, Italy
Kenya Agriculture Research Institute, Kenya
Kenya Department of Veterinary Services, Kenya
National Agricultural Research Center, Pakistan
National Center for Veterinary Diagnostics, Vietnam
National Commission for Research and Technology, Argentina
National Veterinary Research and Quarantine Service, Republic of Korea, South Korea
Onderstepoort Veterinary Institute, South Africa
Parco Tecnologico Padano, Italy
Philippine Animal Health Center, Philippines
Russian Research Laboratory, ARRIAH at Vladimir, Russia
South African National Institute for Communicable Diseases, South Africa
State Research Center of Virology and Biotechnology, Georgia
Teagasc, Republic of Ireland
Veterinary Laboratories Agency, United Kingdom

INTERNATIONAL COMPANIES:
Guardian Biotechnology, Inc., Canada
Indian Immunological Ltd., India
Investigación Aplicada, S.A., Mexico
Laboratorios HIPRA, S.A., Spain
Pancosma, France
Prionics Ag, Switzerland
Seppic Inc., France

APPENDIX 5

National Program 103 – Animal Health
ACCOMPLISHMENT REPORT 2007 – 2011

2011 Stakeholder Survey PowerPoint

National Program Assessment
Electronic Stakeholder Survey
Animal Health National Program

September 2011

Cyril Gerard Gay, DVM, Ph.D
Senior National Program Leader
Animal Production and Protection

Purpose

- Conduct a “National” Program Assessment
- Obtain genuine, authentic, factual information
- Assess program in a cost effective manner
- Assess whether the national program had impact
- Stakeholders and partners:
  - Producers and Farmers
  - University scientists
  - Industry
  - Trade associations
  - Scientific associations
  - Federal government agencies
  - State government agencies

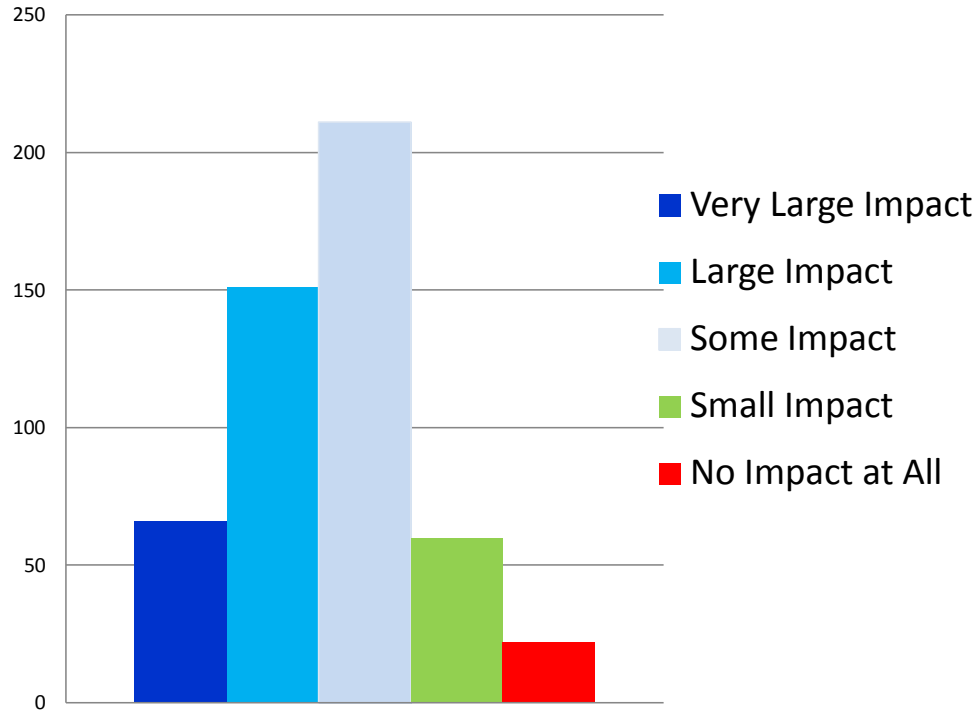
Survey Design

- Web-based survey created in “Survey Tracker”
- Survey consists of 14 questions
- Survey design: Cyril Gay and Sharon Drumm
- Database of answers stored on ARS web server
- Survey administered by Michael Witles
- Regulated process: Paperwork Reduction Act, OMB 83-I Form
- Survey submitted to 1000 persons via e-mail
- Data collected over a three month period
- Goal: 30-50% respondents

Results

- 510 respondents
- 128 producers and farmers
- 55,000 entries to assess in Excel

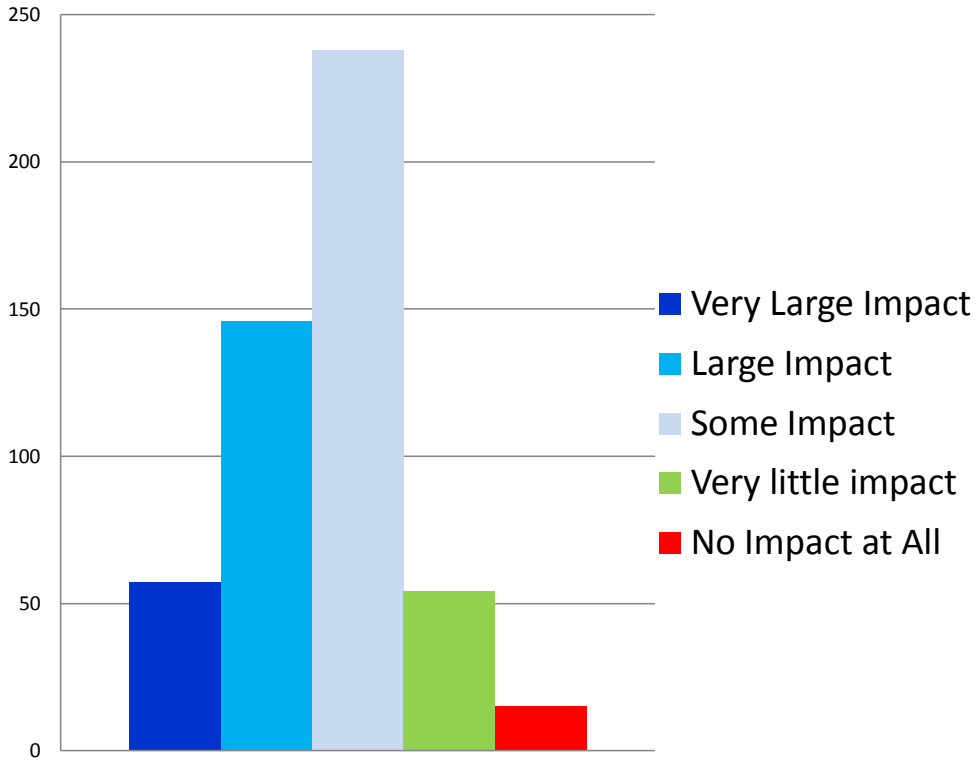
Is the Program having an Impact?



***Number of Respondents Total 510**

84% of respondents thought the program had at least some impact

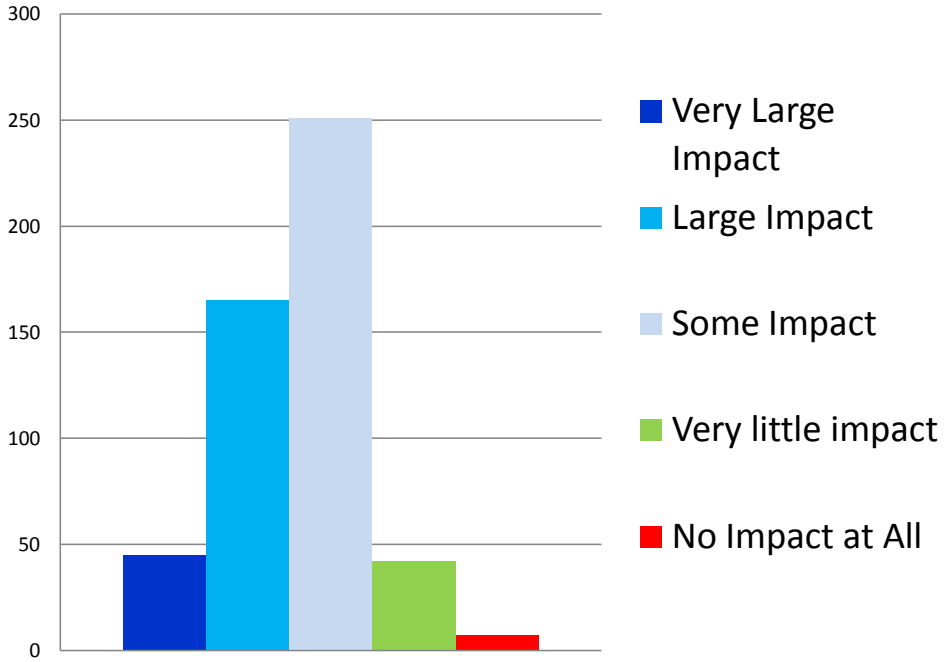
Impact of Program for Priority Diseases



***Number of Respondents Total 510**

86.5% of respondent thought the program had at least some impact

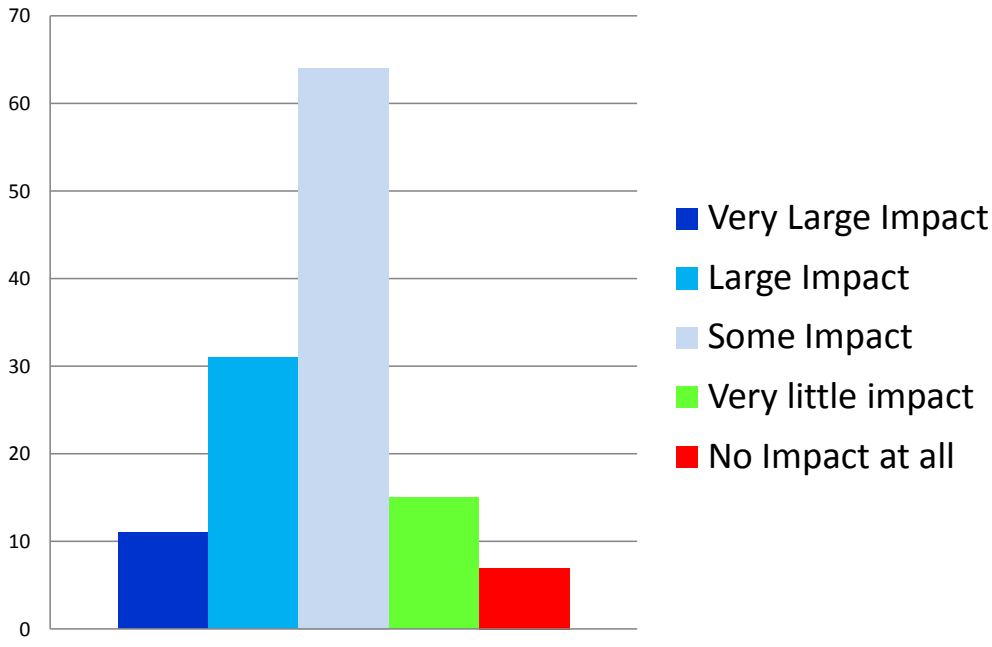
Program Impact Last 5-Years



***Number of Respondents Total 510**

90.4% of respondents thought the program had at least some impact

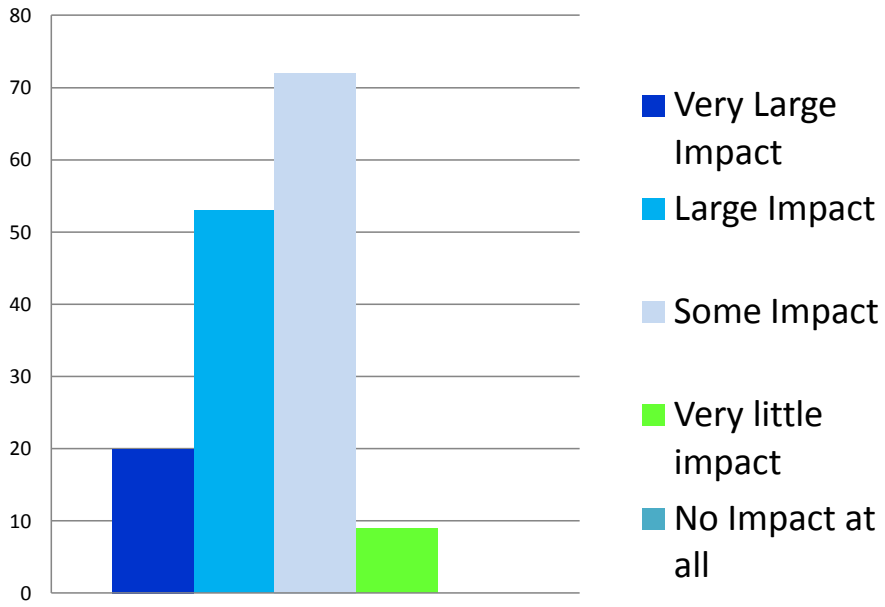
Producers and Farmers Program Impact Last 5-Years



***Number of Respondents Total 128**

83% of respondents thought the program had at least some impact

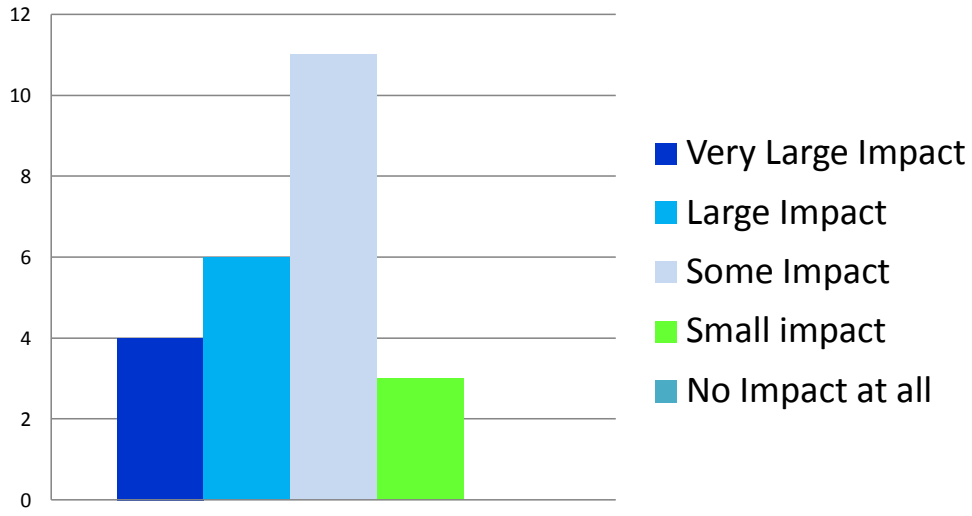
Universities Program Impact Last 5-Years



***Number of Respondents Total 154**

94% of respondents thought the program had at least some impact

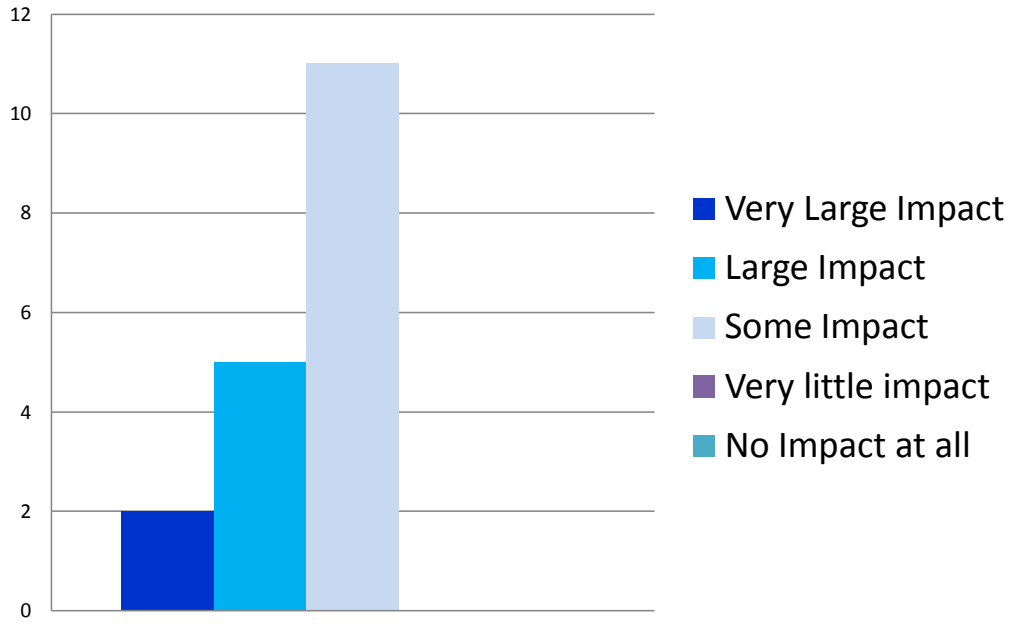
U.S. Government Agencies Program Impact Last 5-Years



***Number of Respondents Total 24**

87.5% of respondents thought the program had at least some impact

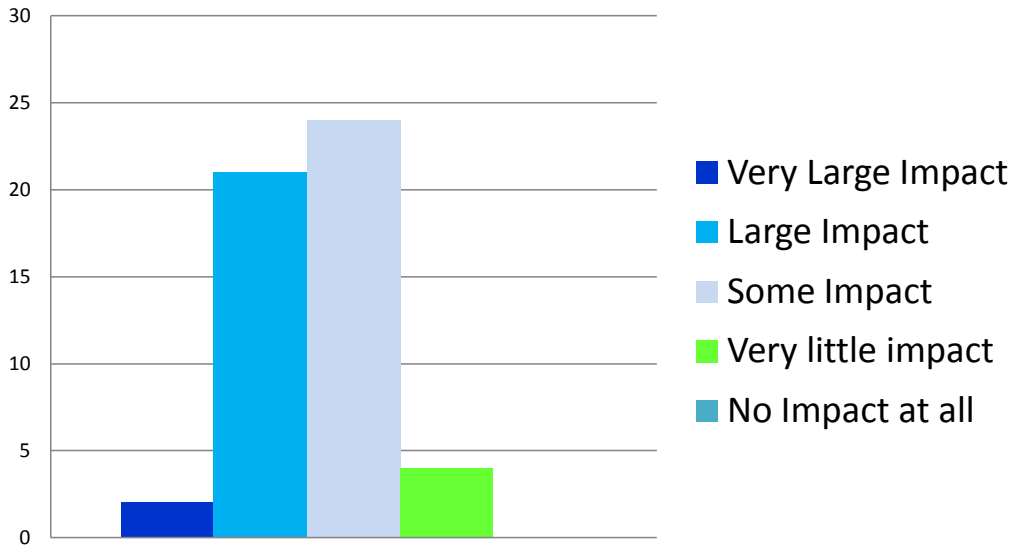
State Governments Program Impact Last 5-Years



***Number of Respondents Total 18**

100% of respondents thought the program had at least some impact

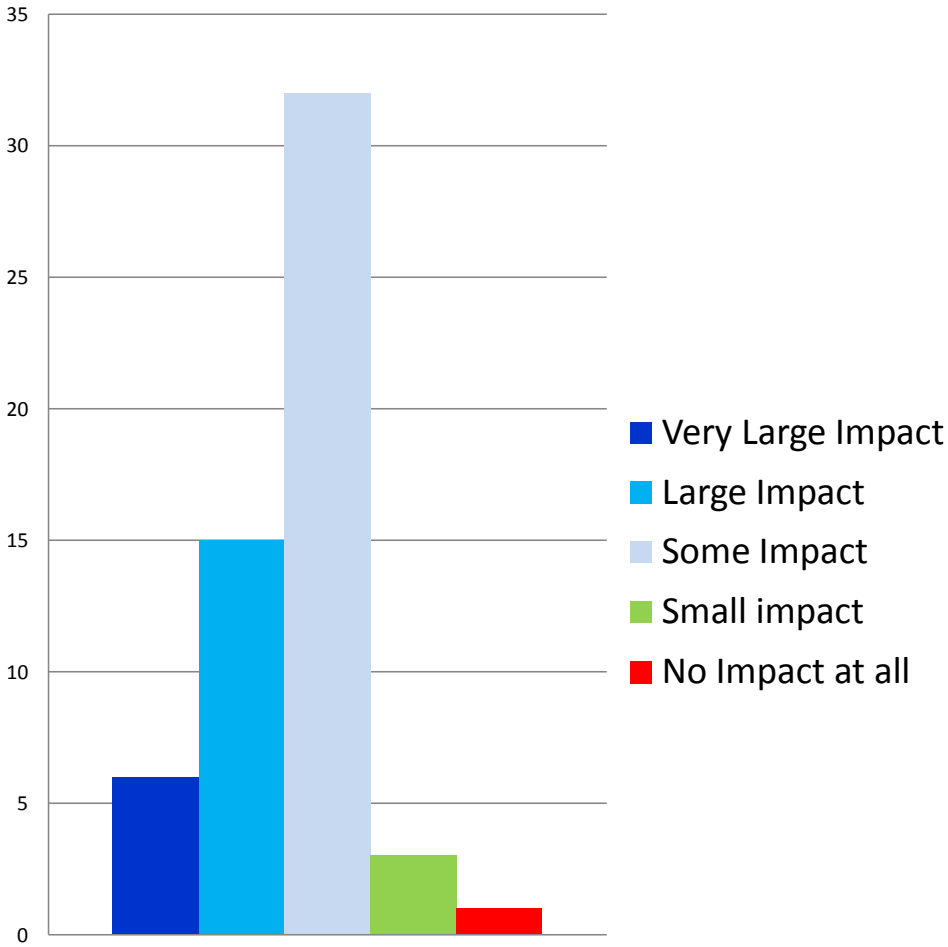
Pharmaceutical Companies Program Impact Last 5-Years



***Number of Respondents Total 51**

92% of respondents thought the program had at least some impact

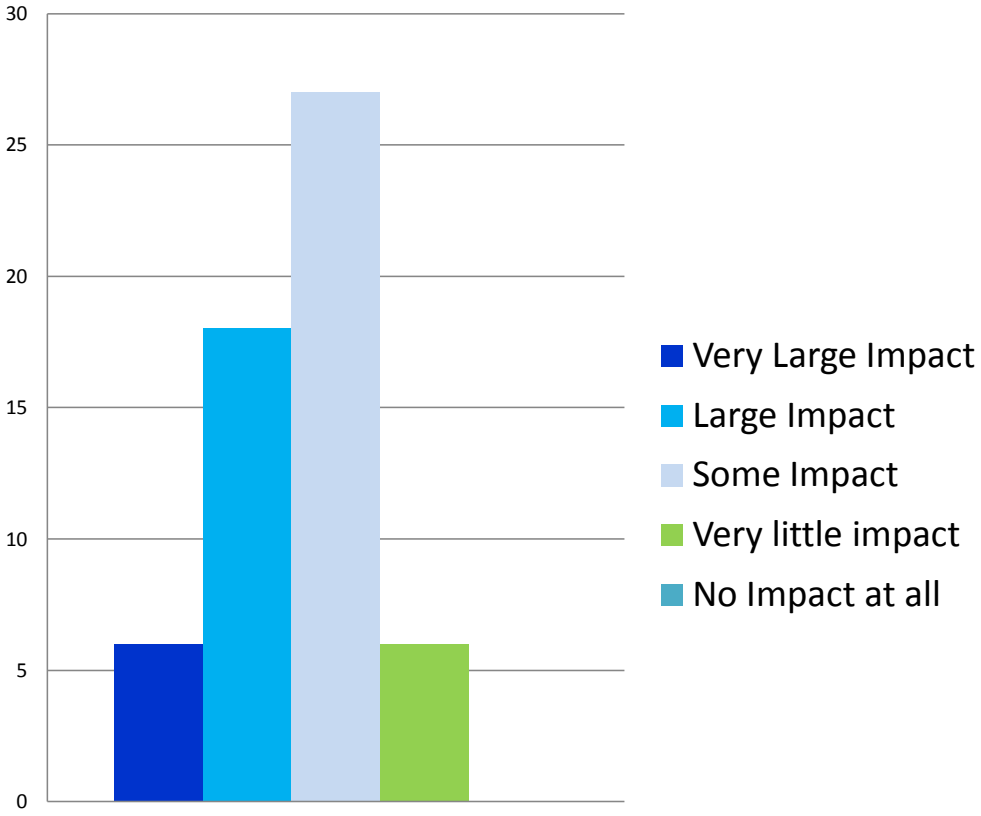
Program Impact: Beef Stakeholders



***Number of Respondents Total 57**

93% of respondents thought the program had at least some impact

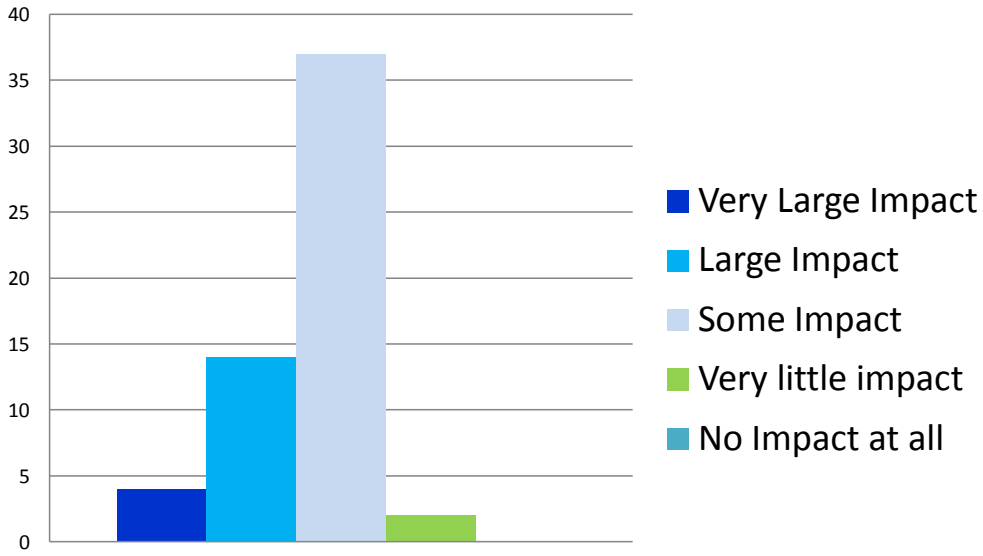
Beef Stakeholders Program Impact for Priority Diseases



***Number of Respondents Total 57**

89% of respondents thought the program had at least some impact

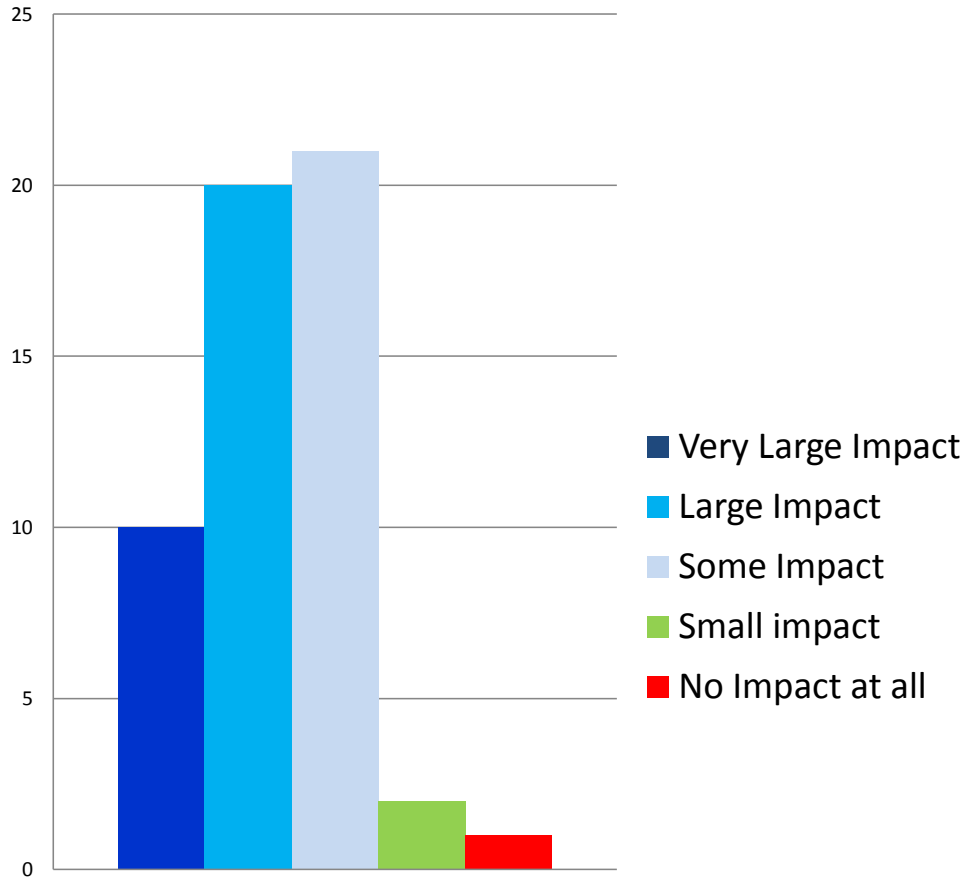
Beef Stakeholders Program Impact Last 5-Years



***Number of Respondents Total 57**

97% of respondents thought the program had at least some impact

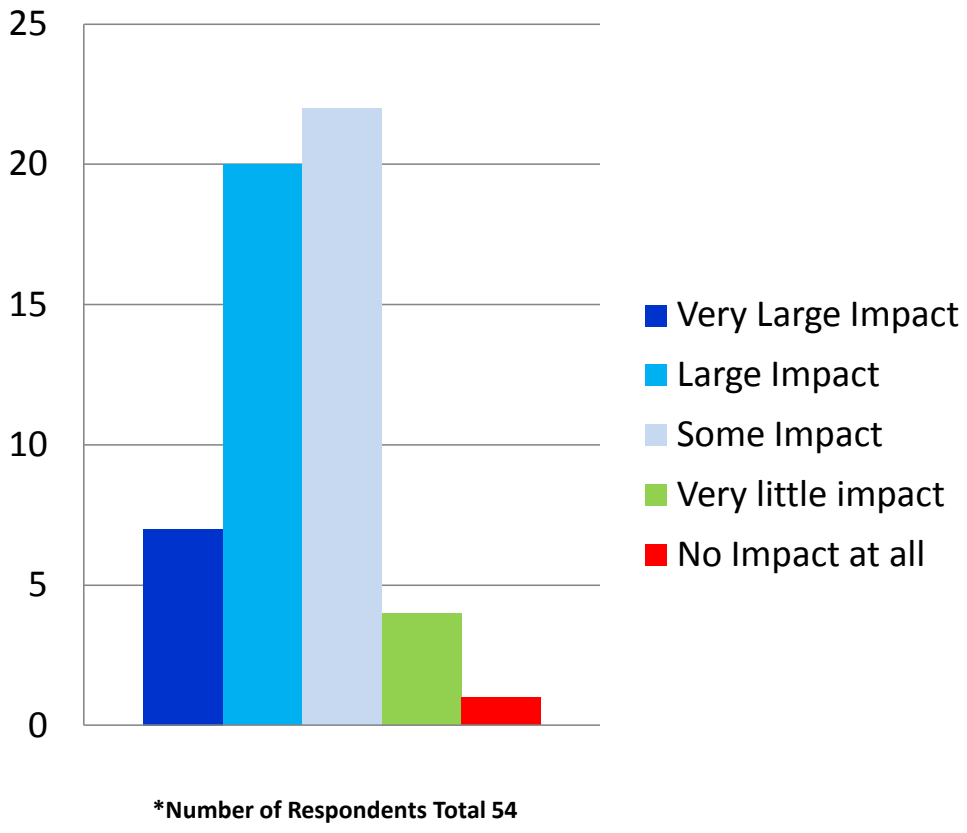
Program Impact: Poultry Stakeholders



***Number of Respondents Total 54**

94% of respondents thought the program had at least some impact

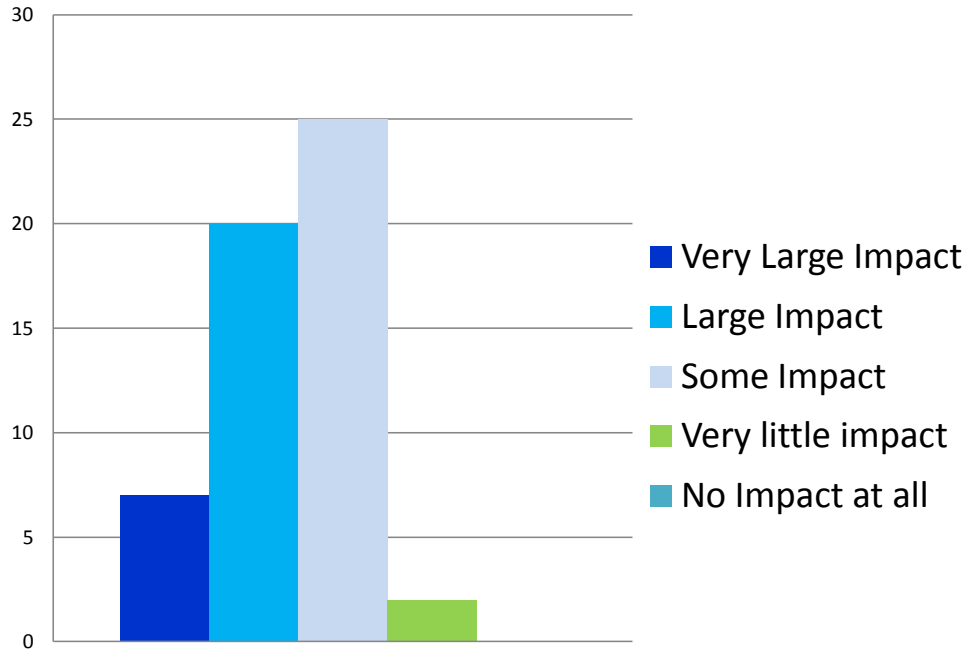
Poultry Stakeholders Program Impact for Priority Diseases



***Number of Respondents Total 54**

91% of respondents thought the program had at least some impact

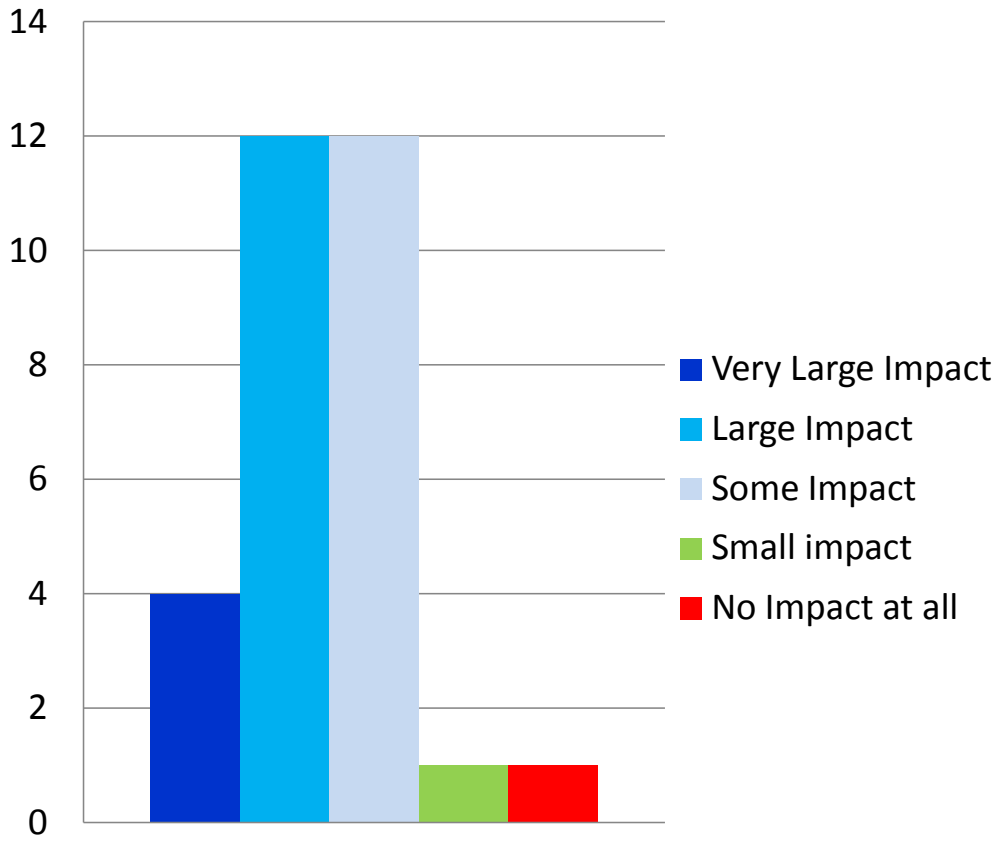
Poultry Stakeholders Program Impact Last 5-Years



*Number of Respondents Total 54

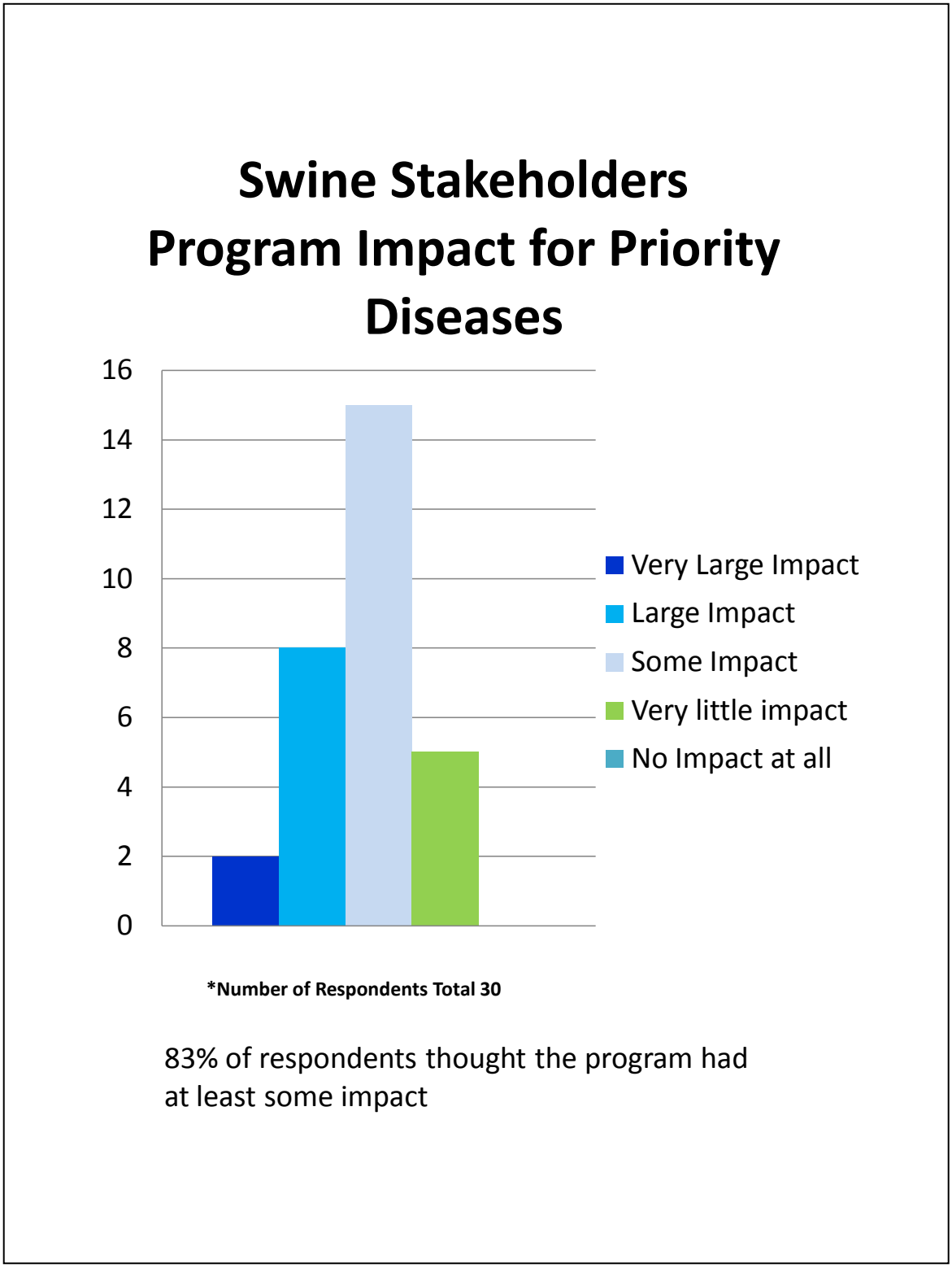
96% of respondents thought the program had at least some impact

Program Impact: Swine Stakeholders



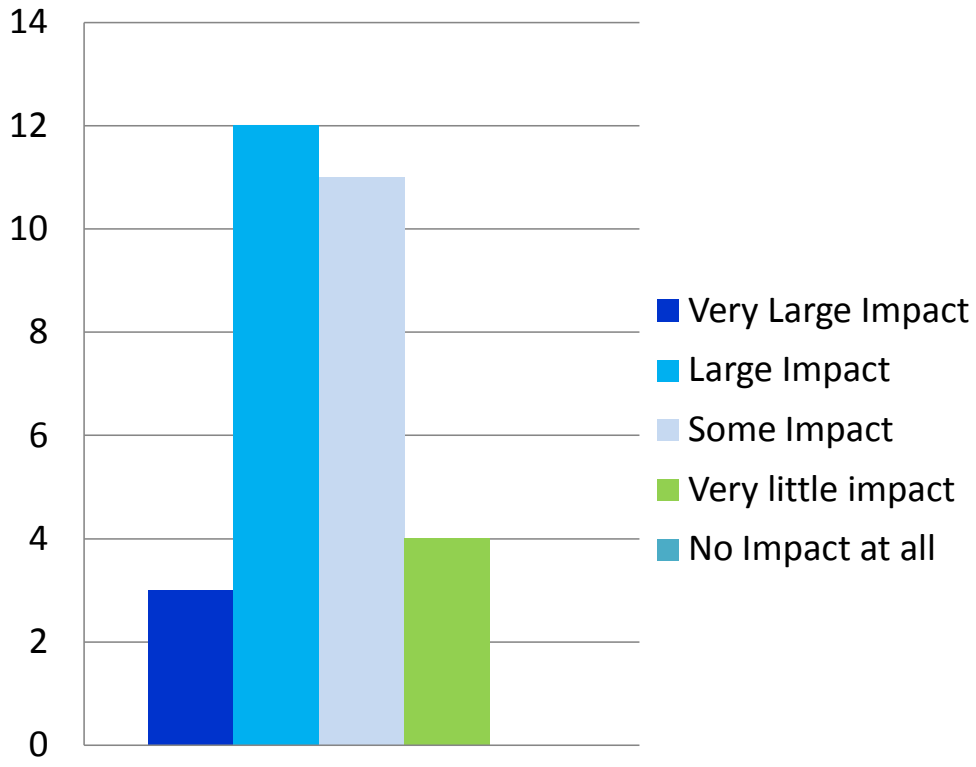
***Number of Respondents Total 30**

93% of respondents thought the program had at least some impact



83% of respondents thought the program had at least some impact

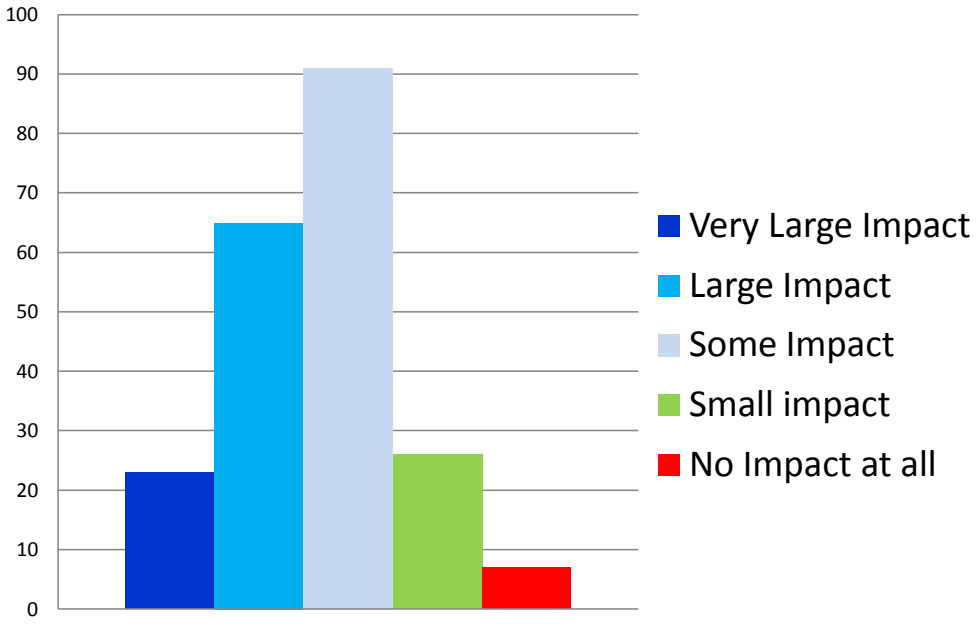
Swine Stakeholders Program Impact Last 5-Years



***Number of Respondents Total 30**

87% of respondents thought the program had at least some impact

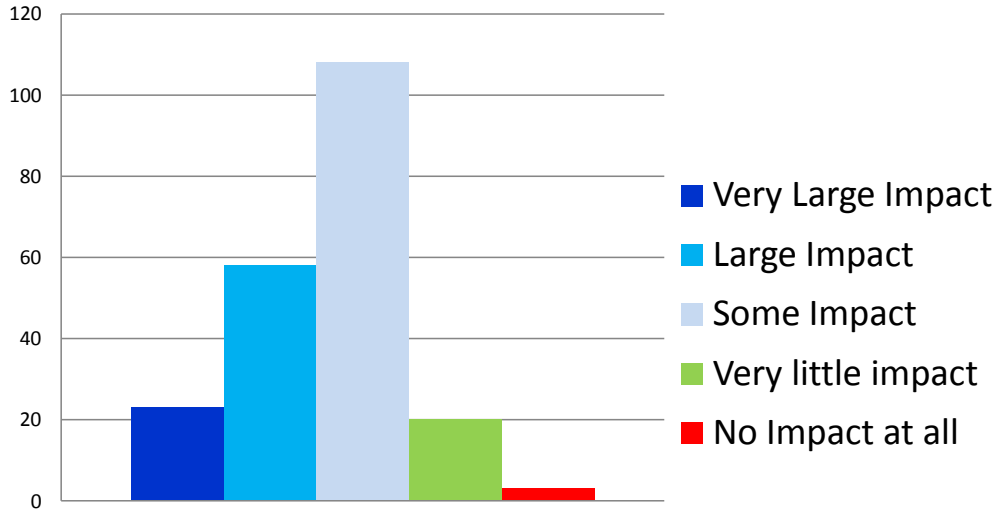
Program Impact: Dairy Stakeholders



***Number of Respondents Total 212**

84% of respondents thought the program had at least some impact

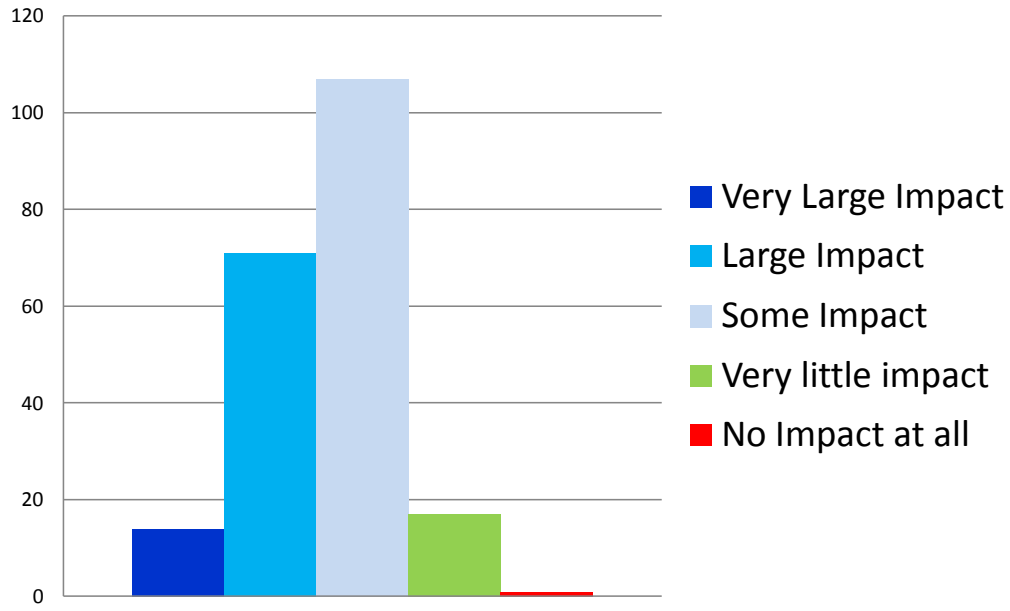
Dairy Stakeholders Program Impact for Priority Diseases



***Number of Respondents Total 212**

89% of respondents thought the program had at least some impact

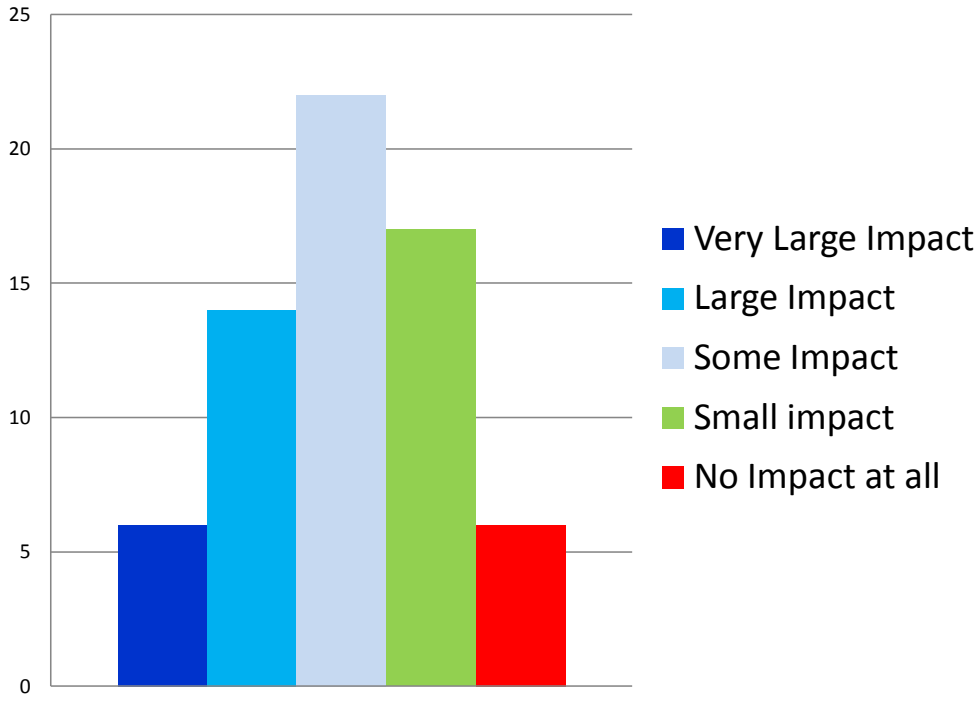
Dairy Stakeholders Program Impact Last 5-Years



***Number of Respondents Total 210**

91% of respondents thought the program had at least some impact

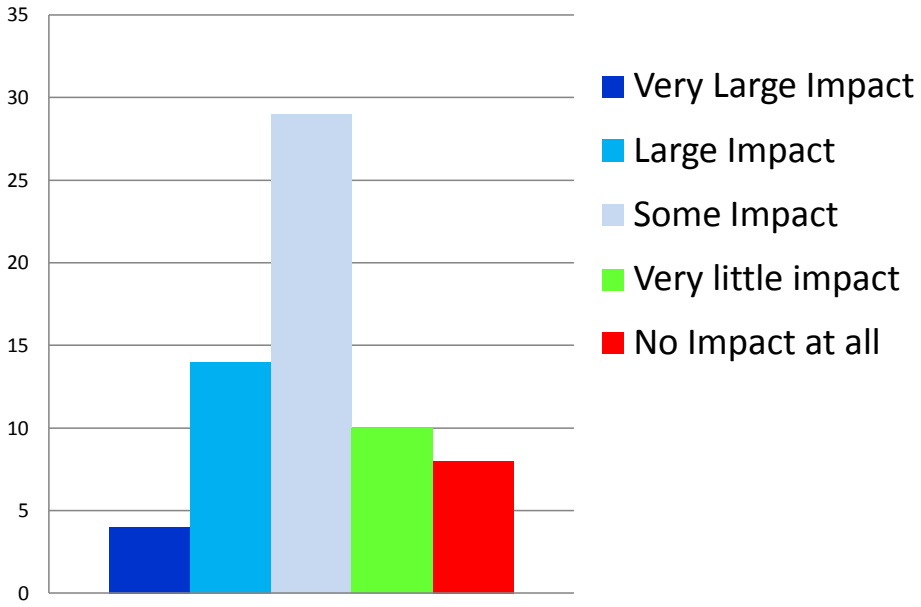
Program Impact: Sheep and Goats Stakeholders



***Number of Respondents Total 65**

64% of respondents thought the program had at least some impact

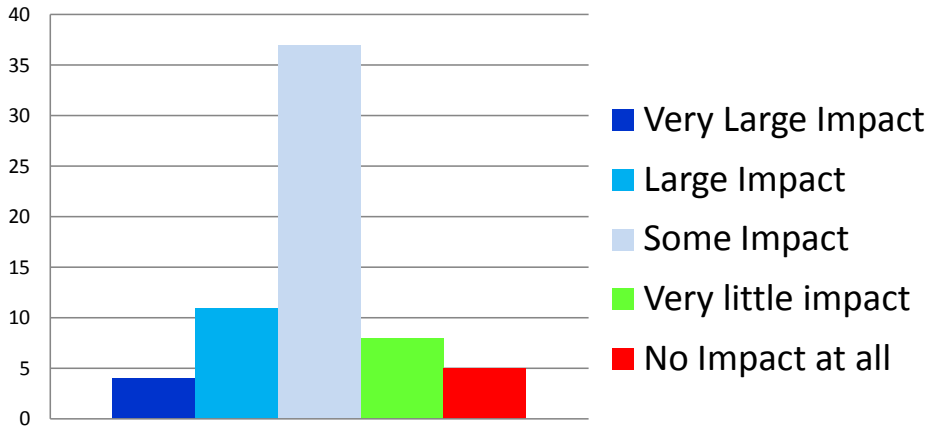
Sheep and Goats Stakeholders Program Impact for Priority Diseases



***Number of Respondents Total 65**

72% of respondents thought the program had at least some impact

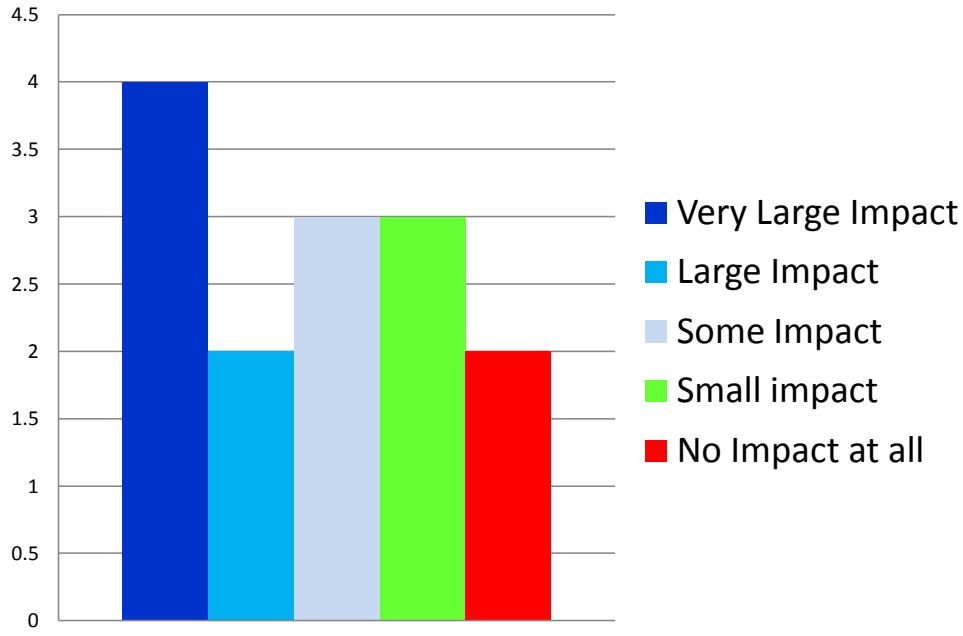
Sheep and Goats Stakeholders Program Impact Last 5-Years



***Number of Respondents Total 65**

80% of respondents thought the program had at least some impact

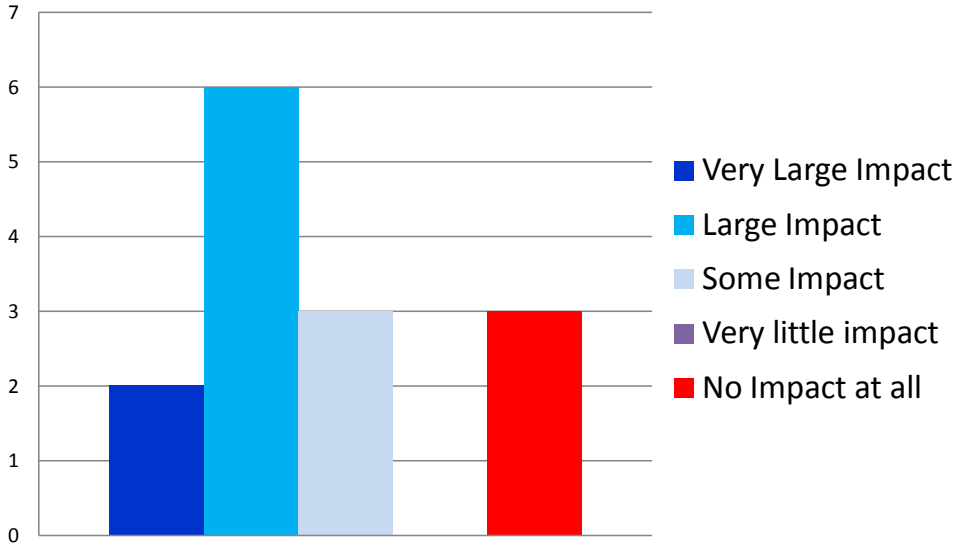
Program Impact Wildlife and Captive Game Species



***Number of Respondents Total 14**

64% of respondents thought the program had at least some impact

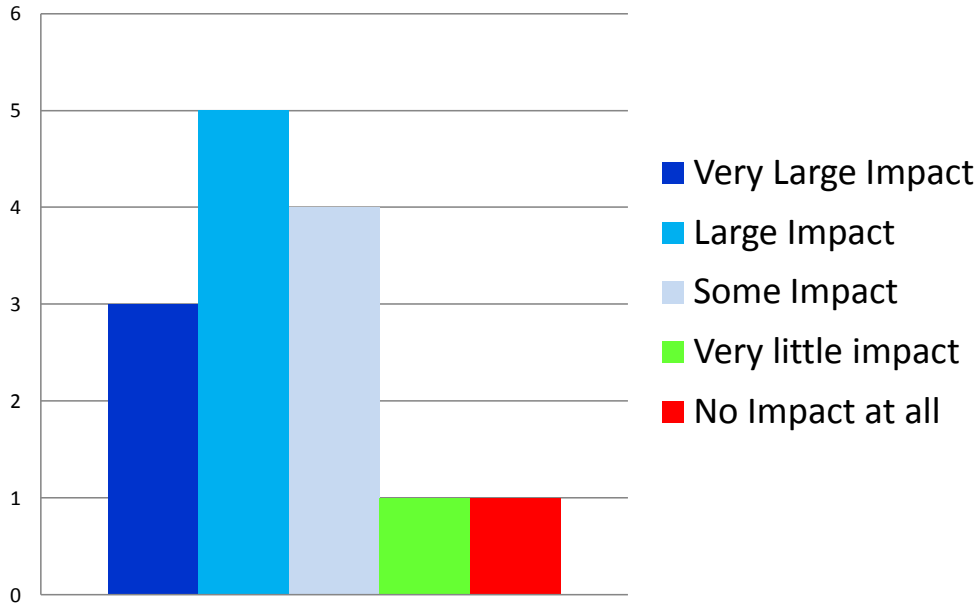
Wildlife and Captive Game Species
Program Impact for Priority Diseases



***Number of Respondents Total 14**

79% of respondents thought the program had at least some impact

Wildlife and Captive Game Species
Program Impact Last 5-Years



***Number of Respondents Total 14**

86% of respondents thought the program had at least some impact

Next Steps

- Complete data assessment
- Distribute report to the 1000 stakeholders and partners that were contacted
- Write National Program Assessment Report
- Hold national program assessment panel

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