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Pathogens as their role evolves: a view from the diagnostic laboratory (Kernkamp Lecture)

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Introduction

The emergence of new pathogens is challenging veterinary diagnostic laboratory (VDL) infrastructure as never before. At the same time, new responsibilities such as preparing for the risk of foreign animal diseases and bioterrorism are competing for declining laboratory financial resources, equipment and laboratory space. The objective of this presentation is to increase your awareness of the issues facing the US veterinary diagnostic laboratory system. My hope is that after hearing the presentation, some of you will be compelled to increase your participation as active members of veterinary diagnostic laboratory organizations that influence national and state veterinary laboratory policies.

Why is it important to understand veterinary diagnostic laboratory issues? It is important because animal disease has become increasingly significant as a cause of suboptimal production and economic risk for the swine industry. Or as Senator Steve Dille more concisely stated, “Veterinary diagnostic laboratory programs are important because it is hard to make money with sick pigs”.

Background

There are major differences in how laboratories have met their financial challenges while attempting to remain true to their mission. Some laboratories have pursued a strategy of revenue generation and are now heavily dominated by high volume testing. Other laboratories have reorganized to enhance their ability to provide in depth diagnostic investigations, to develop new and more cost effective diagnostic methods, and to train graduates students in diagnostic medicine. Some laboratories have placed large emphasis on companion animal diagnostics whereas others have focused on production animal medicine. Because the capabilities of veterinary laboratories is dynamic and variable, laboratory users should stay abreast of their laboratory’s capabilities and develop a strong working relationship with a diagnostician to help ensure that their client expectations are met.

The art-of-emerging disease diagnostic investigation

Consultation with well trained diagnostic pathologists brings immediate benefit to emerging disease investiga-

tions. The discussion should be followed by careful animal observation free of time constraints and other distractions. Clinical information should be documented and submitted in detail because it is needed by the pathologist to generate a report that is correct and meaningful. At present, laboratory submission forms are sometimes completed by a lay person and are either useless or contain incorrect information. Important or relevant information is sometimes omitted or is indecipherable and occasionally no information is provided at all. Where possible, historical data and production records should be submitted electronically thereby enabling analysis using high speed computers to uncover biological information hidden in the mass of laboratory and epidemiologic data. Great care should be taken to avoid searching for a narrow list of infectious agents when faced with an unusual disease. It is precisely the wrong approach and sometimes leads to over-conclusion and erroneous diagnostic endeavors. Instead, subroutines used for diagnostic investigations should be expanded to include a complete physical examination and complete necropsy. Several animals displaying typical signs at various stages of disease should be necropsied and a full set of tissues collected for histopathology and other laboratory tests.

Laboratory results should be evaluated with an “open mind” through a process of inductive and deductive reasoning. Diagnostic hypotheses should be developed, investigated and continually refined while separating what you know from what you think you know. Avoid disbelieving or dismissing laboratory data if the results cannot be related to a specific disease entity because pre and post analytical errors are far more common than analytical errors. By studying a similar pattern of laboratory data in a large series of cases, confidence in the existence of a new disease or syndrome will emerge and will increase as similar findings are reported by others. When the findings have been replicated several times, a disease or syndrome will assume an increasing degree of believability.

Emerging diseases: contemporary swine clinician skills to optimize success

The contemporary swine clinician must have the ability to carefully observe and describe diseases; correlate history, physical examination, clinical signs, and production record data; must know when, how, what type and to what

James E. Collins

extent of laboratory investigations to undertake; must understand and interpret the significance of the laboratory results obtained; must use knowledge of pathological principles to formulate possible diagnoses; must develop hypotheses about underlying mechanism(s), and must be able to explain the basic mechanisms underlying the major disease processes to the farm manager/owner. To be most effective the clinician must seek ways to protect the swine industry from emerging diseases by broadening diagnostic investigations beyond pathogens of known economic significance while being unconstrained by the fear of damaging the swine industry from unduly harsh regulatory responses.

The “health” of the US Veterinary Diagnostic Laboratory System

The “health” and capabilities of the US Veterinary Diagnostic Laboratory system can be assessed by briefly reviewing strengths and weaknesses.

Strengths

University affiliation. The faculty and staff in US veterinary diagnostic laboratories are well educated and highly motivated. University affiliated laboratories integrated with veterinary colleges or veterinary science departments can bring sophisticated and expensive laboratory methods to bear on diagnostic investigations. For example, the University of Minnesota Advanced Genetic Analysis and Advanced Computational Biology Centers bring new ways to study the evolution and movement of swine pathogens within and among production systems. University affiliation also enables veterinary laboratories to train veterinary students (future clients), producers and veterinarians in diagnostic medicine. In addition, diagnostic problems requiring further research can be efficiently transferred to research laboratories to find solutions. Solutions, knowledge and products (intellectual property) can then be transferred from the research laboratory to the field, so called “translational research”.

Accredited veterinary diagnostic laboratories affiliated with major universities that have strong public health, federal and state agricultural and natural resource collaborations are well positioned to respond to emerging diseases because of the wide range of expertise, facilities and equipment available. Universities, however, need to develop internal structures that enable faster responses to emerging disease threats. The ideal veterinary laboratory for today’s swine health challenges is staffed by diagnosticians well versed in production medicine, computer records, epidemiology, molecular biology and laboratory pathology. The range of laboratory services offered should include the “tried and true methods” of cell culture, electron microscopy, bacterial culture, histopathology, and animal inoculation as well as advanced molecular diagnostic methods. Regrettably, some veterinary laboratories

have “moth balled” their electron microscopes and have closed their virology cell culture sections in response to reduced funding yet these are the very techniques that enable a full range of unknown organism detection. It is noteworthy that conventional diagnostic methods often prove superior to the “sexier” DNA-based methods when searching for novel pathogens and solving difficult diagnostic problems.

US Veterinary Diagnostic Laboratory System Accreditation. Animal disease diagnosis and surveillance in the United States is the combined responsibility of publicly funded state and federal diagnostic laboratories. Ensuring the quality of diagnostic and surveillance efforts is essential for safeguarding the health and well being of our herds and flocks, companion animals, wildlife, zoo and exotic species, and the general public. Equally critical is assuring our trading partners that importation of animals and live animal products from the United States is safe.

Emergence and re-emergence of infectious diseases, including national program diseases such as tuberculosis; rapid global transport that increases the threat of foreign animal disease introduction into the United States; and the use of bioweapons, most of which are zoonotic agents, all impart a heightened sense of importance to reliable, quality diagnostic laboratory results. At present, 45 laboratories in the United States (some of which are multiple laboratories included in one state laboratory system) and 2 laboratories in Canada have full AAVLD accreditation status. (Excerpt from AAVLD Accreditation White Paper, McElwain et al, www.AAVLD.org).

There is no accreditation body in other countries equivalent to AAVLD. As a result, the international community has increasingly relied on organizations that use International Organization of Standards (ISO) as a guide. United States producers increasingly rely on export of animals and animal products to prosper. International acceptance of diagnostic laboratory results from individual animal and population-based testing is therefore critical to maintain open avenues of trade. The AAVLD Accreditation Committee has adopted more rigorous and independent standards recognized by the Office International des Epizooties (OIE) (OIE is the international animal health organization). The new standards are roughly equivalent to ISO17025 (<http://www.iso.ch/iso/en/ISOOnline.frontpage>).

National Animal Health Laboratory Network. The task of national animal disease surveillance is shared between publicly-funded state animal health laboratories, represented by the AAVLD, and federal animal health laboratories administered through the USDA’s Animal and Plant Health Inspection Service (APHIS). This partnership safeguards the health of our nation’s livestock and poultry, companion animals and wildlife, and protects the public from diseases common to animals and humans.

Pathogens as their role evolves: a view from the diagnostic laboratory

The nation's public health and food supply is at constant risk from accidental or malicious introduction of exotic animal diseases. The threats include obvious ones like foot and mouth disease (FMD), as well as agents that affect animals and humans, such as avian influenza, anthrax, bovine spongiform encephalopathy (BSE) and West Nile virus. The USDA Safeguarding Review identified the need for a state-of-the-art National Animal Health Laboratory Network (NAHLN). A national strategy combining the nation's federal, state, and local resources, the NAHLN, established in 2002 has begun to function in response to animal health emergencies, including bioterrorist events, as well as newly emerging and foreign animal diseases. Animal industries, regulatory agencies, and public health benefit from the communications and proficiency fostered by this network. Since 2002 the US has seen the introduction of exotic Newcastle disease, avian influenza and BSE. They were controlled as a result of collaborative interactions between NAHLN and USDA. Importantly, the NAHLN strengthens current state-based laboratory testing for export of animals and live animal products, and ensures that tests meet international quality standards to guarantee access of animals and animal products to global markets.

Rapid adoption of new technology by veterinary diagnostic laboratories is a strength of the US laboratory system. In each decade since the 1960's an important new diagnostic method was developed and adopted by VDL: Fluorescent antibody technique – 1960s, electron microscopy -1970s, Elisa-1980s, PCR-1990s, molecular epidemiology and Internet -2000.

The provision of transparent and unbiased laboratory results by VDL, in partnership with swine veterinarians, enables the veterinarians and pig producers to “sort out” (Joe Connor; personal communication) the usefulness of diagnostic testing. VDL provide the bad news and good news with equal facility unconstrained by administrative and business pressures.

Improved integration of VDL with state laboratories and Colleges of Veterinary Medicine and specialization holds further promise for gaining efficiencies and expertise and for better mobilization of research activity. Collaboration among state laboratories such as the Department of Health, Department of Agriculture and Department of Natural Resources is leading to better integration and coordination of services. Duplicate programs, especially those with large capital and program expenses, can often be eliminated or scaled down. Laboratory specialization and consolidation among US laboratories can lead to better utilization of state and national resources.

Capturing revenue from licensing and royalty income, although unpopular among some groups, can be a good thing by stimulating innovation and by generating revenue to reinvest in diagnostic test development and

infrastructure.

Good public relations. The public's understanding of the value of veterinary diagnostic laboratories to the “public good” has increased dramatically in recent years because of several zoonotic disease outbreaks such as CWD, BSE, bird flu, West Nile, TB and the risk of bioterrorism...the public “gets it”.

Weaknesses

Increased dependence on laboratory user fee income has led to several unintended consequences. A quote from Dr. G. Kee Jim, Feedlot Health Management Services, Okotoks, Alberta, Canada is appropriate to veterinary diagnostic laboratory funding: “A client's worse day being a vet's (veterinary diagnostic laboratory's) best day is not a sustainable business model.” In the 1970s the U of MN VDL went from 100% state support to 25% state support today. This trend is widespread in higher education and veterinary diagnostic laboratories generally. The availability of user fee income has proven essential for laboratory survival but the greater dependence on fee income poses several risks to the well being of agriculture. Revenue generation has diverted resources away from diagnostic investigation, the correct VDL mission. It also has decreased the thoroughness of diagnostic investigations as VDL move to a competitive, high volume testing strategy leading to a culture of competition instead of collaboration and information sharing.

Lack of organizational structure and funding model that enables rapid mobilization of CVM resources to address and solve a problem. The University of Minnesota is to be congratulated for establishing the “Rapid Agricultural Response Fund” to mobilize resources to address emerging disease issues. The administration of the funds now needs to facilitate urgent diagnostic investigations or the fund risks morphing into small grants program. (I would water down this last sentence)

Premise identification and traceability. “We have the best QA/QC laboratory system available to ensure accurate results, we just can't tell you what animal or premise the sample/animal is from”.

Funding decline caused by increased competition for state and federal resources for animal disease investigation and increasing costs threaten to decrease laboratory submissions thereby reducing disease surveillance. The need to generate revenue is leading to increasing competition and decreasing collaboration among VDLs. The synergy created through collaboration is being threatened as VDLs compete for business. VDLs must operate as efficiently as a business without becoming one. Return on investment should not be a major driving force for tests offered by VDL. VDL directors must persuade academic and legislative leaders that revenue generation is a short term thinking that will ultimately threaten the

James E. Collins

viability of VDLs.

Failure to adapt to the needs of modern agriculture, food safety and public health. University pressure to increase NIH research that is more prestigious and more lucrative, but of limited relevance to agriculture, should not ignore the role played by the VDLs.

What is needed?

Veterinarians and producers must understand the major issues facing the US Veterinary Diagnostic Laboratory system and then seek active participation from key local, national and international animal health organizations such as AAVLD, NAHLN advisory board, VDL advisory committees, Board of Animal Health or equivalent. Veterinarians and producers must play a greater role in achieving the proper balance of VDL effort and resource allocation for serving the public good. The capacity of the US laboratory system must be expanded to meet the surge capacity caused by unusual and emergency animal diseases. The USDA National Veterinary Services Laboratories should dedicate more time, effort and funding to standardizing diagnostic techniques that can be used at state, regional, and national levels and national training, proficiency testing, and quality assurance to ensure uniform test results. Funding for federal and state facility upgrades to meet bio-containment requirements for affordable Biosafety level 2 and 3 diagnostic and research facilities. And, more emphasis must be placed on animal experiments as a means of diagnostic investigation.

