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Diagnosing PCVAD in a vaccinated industry

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Summary

1. Vaccination status does not change the methods for diagnosis of disease associates with PCV2. PCVAD will likely be present in some individuals in a vaccinated population.

2. Vaccination will alter infection, immunity, ecology, and disease dynamics. Tools to better define these interactions are emerging. Problem-solving skills and analytical tools have more value than thumb-rules, opinions, and generalizations.

3. The significance of PCVAD in a vaccinated population depends on expectations of vaccine efficacy and is confounded by vaccination timing, vaccination compliance, and perhaps dam vaccination status.

4. Diagnosis of the effect of PCV2 infection in a population, irrespective of vaccination status, is a math problem best solved by analysis of relevant data. Subclinical effects of PCV2 infection is difficult to diagnose by routine "diagnostic tests". Accurate records, agent and disease monitoring, and vaccine field trials are likely to offer better information.

5. Optimizing vaccine use will require quantitative skills. Don't make it more complicated than it needs to be (*Occam's razor).

Introduction / background

Diagnosis of infectious diseases affecting an individual animal is usually fairly straight forward. A diagnosis utilizes clinical signs and/or symptoms and/or lesions and/or evidence for infectious agent(s) to offer a name to a disease with some unspecified level of confidence. Often, the initial diagnosis defines the obvious, *proximate cause*. More challenging is finding and prioritizing the components of etiology (risk factors and agents) when there is more than one present in an individual animal or sampling of animals. Even more daunting is prioritizing etiology on a herd basis since the number of possible etiologic permutations (of disease agents, environmental contributors, management factors) that define *ultimate cause*(s) is seemingly endless. Factual knowledge of husbandry, nutrition, pig flow, environment, diseases, infectious agent ecology, and process improvement tools are the foundations for adding context to the complexities.

Veterinarians attempt to diagnose infectious disease processes by diagnostic testing to establish cause and effect. Yet, the numbers of causes, tests, types of tests and associated costs of diagnosis and testing can overwhelm reasoning capacity or economic benefit. It is fairly easy to assign a *proximate* cause to a disease and intervene with some nostrum. More difficult is assigning *ultimate* causes since there no single test that accomplishes this in population medicine. Ultimate cause(s) are not immediately obvious, may challenge our dogma, and usually require system or process changes rather than a single nostrum. Appropriate diagnostic testing does add value to the overall analysis.

Trying to simplify diagnostic investigations yet maintain accuracy of diagnosis is challenging, in no small part due to definitions and semantics. A "diagnosis" is the name assigned to a disease condition and/or outcome of some analysis. The diagnosis can be general or specific, depending on the information that is available and perspective of the observer. In the examples of diagnoses from one pig below, one is more valued than the others. Yet, none define the risk factors that contribute to disease expression.

1. Clinical diagnosis: (using signs and symptoms): pneumonia
2. Pathologic diagnosis: necrotizing bronchiolitis and suppurative bronchopneumonia
3. Pathologic diagnosis: lymphoid depletion
4. Disease diagnosis: swine influenza
5. Disease diagnosis: PCVAD
6. Etiologic diagnosis: Pneumonia: swine influenza virus and Pasteurella multocida
7. Etiologic diagnosis: Systemic disease: PCV2

A diagnosis by a diagnostic laboratory is based on observations and test results from a population sample, usually from tissue or serum. This is not the same as a *herd diagnosis,* which relies on a knowledgeable veterinarian evaluating all the evidence, including diagnostic laboratory data. The goal is clarity in defining an abnormal condition, either as an individual animal diagnosis or a herd diagnosis. Using principles of epidemiology, disease, and medicine to improve animal health is what veterinary practitioners do.

A disease agent (PCV2) may be significant to the individual affected (individual animal diagnosis) but have seemingly

little impact on herd performance (herd diagnosis); therefore individual animal/test diagnosis must be carefully interpreted when applied to herd diagnosis. Because herds are made up of individual animals, veterinarians that focus on herd information may miss opportunities to improve performance of individual pigs that contribute to herd productivity. And, veterinarians that focus on individual animal afflictions may miss opportunities to improve performance on a herd basis. It is very difficult to do both well. Irrespective of perspective (herd diagnosis vs. individual animal diagnosis), some concepts from a diagnostician that could be pondered before formulating costly intervention strategies include:

1. Diagnostic laboratories make observations (pathology), perform tests, and report results. Reports rarely contain what is unknown, not tested for, or interpretation and perspective outside of personal experience and knowledge.
2. Diagnostic laboratories prefer to report results to veterinarians. The veterinary practitioner has expertise in animal disease, with a more complete knowledge of the herd and production scheme. It is the veterinary practitioner that renders the final diagnosis or herd diagnosis.
3. Some fundamental questions that can be answered by diagnostic testing include: "Is it there?", "Is it important?", "Is it new to the herd?", "What else is involved?"
4. Generally, we only find what we look for. Before requesting diagnostic assistance, practitioners may ponder:
    a. What is the diagnostic question that I wish to answer in this case?
    b. Which tests can be used to answer the question?
    c. What populations should be sampled? Random or targeted sampling?
    d. What type and how many samples are required?
    e. How reliable is the test and how are the results reported?
    f. How will results be interpreted?
    g. How will results be applied to formulation of an intervention strategy? What decision will be influenced by test outcome?
    h. Should I do a test if I am not prepared to interpret the result or act on the outcome?
5. Effective communication throughout the diagnostic chain can enhance value of diagnostic investment. Telephones, emails, videos, photos, web reporting, etc. are all tools that can save time, money, and provide more useful information.
6. The quality of specimens submitted is directly related to the quality of diagnostic information received. Diagnostic laboratories still receive many cases where haphazard or inadequate specimen collection and preservation compromise quality of results. Staff training should be high priority.
7. Tests are complicated and expensive. A practitioner should seek to understand the tests (types, limitations, interpretation) or discuss test selection with a diagnostician. Each case will have unique nuances. Standardized testing strategies can be useful, but can miss unique disease permutations.
8. Interpret results in context. Be aware of what you don't know. Question what you think you know frequently. Test results and observations are not the same as a herd diagnosis.
9. If diagnostic results don't make sense, then there likely is something not right about the process. Review all steps of the diagnostic investigation, from farm observations to sampling to testing to reporting. Misinterpretation of information and errors are not uncommon.

PCVAD

Perhaps the first question to consider is your working definition of porcine circovirus-associated disease (PCVAD). The definition of PCVAD on a *herd basis* usually includes some variation of:

1. A "significant" increase of baseline mortality (records) with clinical signs of wasting
2. The presence of compatible pathologic lesions (lymphoid depletion)
3. The lesions are associated with the presence of PCV2 (IHC).

A diagnosis of PCVAD on a herd basis uses clinical skills, records, and specific disease diagnostic criteria. The sensitivity and specificity by which these are applied varies widely amongst veterinarians, yet the diagnosis of PCVAD on a herd basis is the purview of the herd veterinarian and is not based on a diagnostic test alone.

The diagnostic laboratory provides test (e.g. IHC) results and observational (e.g. lesion) information. This diagnostician is comfortable offering a diagnosis of PCVAD as an individual animal disease; the presence of an etiologic agent associated with a compatible lesion in an animal is sufficient for an etiologic diagnosis: Systemic disease: PCV2 which is not unlike: Systemic disease: PCV2-associated disease (PCVAD). Often, there is more than one disease process or etiology present in an individual. Therefore, depending on the samples provided and bias of the testing strategy, a diagnostic pathologist can also

expand on the etiologic or pathologic possibilities. The outcome of a diagnostic examination is often extrapolated to the population as a whole. Unfortunately in modern swine production, single agents associated with disease are the exception rather than the rule. The sheer number of permutations of etiologies and risk factors challenge the limits of human understanding. It is the wise practitioner who is not misled in this process.

In population medicine, the individual animal has been seemingly ignored yet the population is composed of individual animals. As economics and welfare modulate production, the individual animal likely will be increasingly valued. PCV2-associated disease affects individual animals, usually pigs that have substantial value. Since PCV2 is ubiquitous, finding the virus in a pig or population has little meaning. Finding the virus associated with compatible lesion is very important to the individual pig and, at least to this diagnostician, defines PCVAD. The economic and productivity effects on a population in which PCVAD is confirmed in a couple of individuals becomes a math problem. The herd veterinarian is best positioned to do the math.

Although the clinical effects of PCVAD can be dramatic, it is clear that subclinical effects of infection and disease substantially impact growth and performance. The problem is that the effects are subclinical hence cannot be visually observed with confidence, but the effects can be measured (with a scale or variation measures of productivity, marketing parameters, etc). The subclinical impact of PCV2 was not recognized until effective vaccines were applied. In response to the global epidemic of PCVAD, many pigs are now vaccinated for PCV2. The suppression of clinical disease via vaccination is quite dramatic, with an additional benefit derived from some impact on subclinical infections. This, finally, brings us to the point of this presentation.

PCVAD diagnosis

The short version of this paper is that diagnosis of PCVAD in a vaccinated industry is the same as in an unvaccinated industry. If one or more animals have disease associated with PCV2, then PCVAD is present in the herd. The extent to which PCVAD impacts the herd cannot be deciphered by laboratory analysis; that is the job of the herd veterinarian. From my perspective:

Criteria for assigning a diagnosis of PCVAD to an individual animal are:

1. Animal examined has evidence of disease, e.g. symptoms
2. Lesions compatible with those described for PCV2 are present by gross and/or microscopic examination
3. PCV2 is present (IHC) within the compatible microscopic lesions. Tissues affected are one or more: lymphoid tissues; lung; liver; gut; kidney; CNS; heart and applies to reproductive disease as well (lesions/virus in fetal heart)

Criteria for assigning a group diagnosis of PCVAD

1. PCVAD confirmed in typically affected individuals
2. Group measures are sufficiently deviated from "normal" for system to be recognized

Helpful but not criteria: There is pursuit of understanding of roles of confounding etiologies and risk factors sufficient to place PCV2 in context (agents, timelines, etc)

Criteria for assigning a diagnosis of subclinical effects of PCV2 infection

These are nebulous. Subclinical effects of "immune stimulation" are widely recognized. The magnitude of a subclinical effect probably does vary with agent, circumstance, and permutations of those. In the absence of an understanding of the role of subclinical infection, my perspective is:

1. PCV2 is confirmed present in the group; PCV2-associated disease can be found in one or more individuals if sought
2. Application of PCV2 vaccine results in a measurable and statistically significant improvement in a valued measure of performance

Additional comments regarding PCVAD:

1. Epidemics of high mortality are easily diagnosed
2. Endemic or subclinical disease needs context (accurate records and analysis)
   a. Vaccination response is nearly diagnostic
   b. On-farm trials are useful in this assessment
3. It is useful to identify any other agents/cofactors present and contributing
   a. Implement appropriate interventions
   b. Monitor response
   c. Create timelines for alleged infections and clinical diseases
4. Serology and quantitative PCR add data but not confidence to diagnostic process
5. Genomics/sequencing/RFLP generally confuse diagnostic process
6. The concept of Occam's Razor* is appealing when pondering PCVAD

What are some of the confounders to diagnostic processes and/or interpretation of evidence and/or our thought pro-

cess? Variation in practices precludes generalizations and rules but I do start with some basic assumptions:

1. PCV2 infection of pigs is ubiquitous
    a. Seroconversion occurs 10 weeks +/- 6 weeks
    b. Substantial variation exists in exposure dose / timing and in susceptibility / maternal antibody
2. Vaccine is being used widely
    a. Mitigates clinical disease and lesions
    b. Decreases but does not eliminate viral load in pig and environment
    c. Age and timing of vaccinations will vary…gilts/ sows/boars/offspring
    d. Particular product selected will vary
    e. The vaccine dose, number of doses, and antigenic mass will vary
    f. Compliance will vary
    g. Other disease may confound efficacy in some situations
    h. Maternal immunity may confound efficacy in some situations/products
3. Humans are innovative to the point of whimsical
    a. Vaccination strategies will vary by age, stage, circumstances, location
    b. Perceptions (opinion) can trump realities (data) in everyday practices
    c. Many of our concerns are related to failed processes
        i. Implementation and compliance to procedures
        ii. Failure to control confounders (other diseases, risk factors)
    d. Data provides a perception of more confidence in a decision
4. Evidence is more than data; evidence-based decisions are preferable

There are various diagnostic tools available to swine practitioners for PCV2 specifically and disease generally. Balancing the value of these tools with ability to make better decisions on the farm is a challenge for most of us.

1. Clinical Assessments: preferably by a knowledgeable veterinarian
    a. Defined clinical syndrome(s) present
    b. Biased by experience and mindset
    c. Wide variation of sensitivity and specificity between observers
2. Subclinical Assessments: determine what to measure
    a. Records
    b. Field trials
    c. Some prudence required in assigning cause and/or cure
3. Pathology: You miss more by not looking than by not knowing
    a. Gross lesions, microscopic lesions
    b. Adds confidence in aligning clinical disease with alleged etiology
4. Agent detection:
    a. IHC: useful for corroborating agent with lesion
    b. PCR, quantitative PCR, gene sequencing, RFLP
        i. Useful research tools
        ii. Useful epidemiology tools
        iii. Helps determined current infection status. PCV2 is endemic, therefore expected to be present; interpret results in context of clinical situation and records
        iv. Utility of PCR is likely over-rated for PCV2
    c. Isolation: adds little useful information for PCV2
5. Serology:
    a. Endemic agents: establish when infection generally occurring
    b. External/epidemic agents: determine if infection has occurred
    c. Can imply but does not establish causality
    d. Immunity to infection or disease may not be measurable by serology
        i. Detected antibody does not equal immunity
        ii. Immunity does not equal detectable antibody
    e. Utility is likely over-rated for PCV2

References: Web resources

1. http://www.vetmed.iastate.edu/departments/vdpam/swine/diseases/pcv2/releated_links.asp

2. http://www.thepigsite.com/pmws/

3. http://www.vetmed.iastate.edu/departments/VDPAM/vdl.aspx

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*ADDENDUM:

*What is Occam's Razor?

accessed 01July08: http://math.ucr.edu/home/baez/physics/General/occam.html

Occam's (or Ockham's) razor is a principle attributed to the 14th century logician and Franciscan friar; William of Occam which states that *"Entities should not be multiplied unnecessarily."*

Isaac Newton stated the principle: *"We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances."*

In the words of Einstein: "… More complex theories have frequently been proposed... In my view, such more complicated systems and their combinations should be considered only if there exist physical-empirical reasons to do so." Or more succinctly: ***"Everything should be made as simple as possible, but not simpler."***