Title: Monitoring ISU VDL data for signs of emerging diseases - #18-192 IPPA

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Industry Summary:

The overall objective of this endeavor was to develop and apply new tools and algorithms to swine diagnostic data as a means for enhancing the existing systems of monitoring the health of Iowa and US swine.

The number of porcine submissions to the ISU VDL and respective disease diagnosis information based on diagnostic codes (Dx codes) were recovered from the ISU VDL laboratory information and management system (ISU LIMS). Data on pathogen detection reported to the Swine Disease Reporting System (SDRS) from the state of Iowa were recovered and used to monitor agent detection in Iowa. These databases were analyzed and different algorithms were developed and applied for each purpose. To scan the historical number of porcine submissions received at ISU VDL each month, and to forecast the expected number of porcine submissions to be made each month for the coming year, an additive Winters model with logistic transformation was used. To monitor disease diagnosis at ISU VDL, an EARS-C1 algorithm was applied to the database organized by a physiological system, and by pathogen. Moreover, SDRS data of cases submitted from Iowa was monitored using a cyclic regression model for weekly proportion of PCR-positive cases, and to forecast the expected upcoming weekly results for Porcine Reproductive Respiratory Syndrome Virus (PRRSV), Porcine Epidemic Diarrhea Virus (PEDV), Porcine Deltacoronavirus (PDCoV) and Mycoplasma hyopneumoniae (MHP).

Throughout the course of the project period, a novel and greatly improved system and associated software application for incorporating Dx codes into tissue-based (sick pig) case records was developed. Each Dx code is composed of four individual components (i.e., System, Insult type, Tissue or Lesion, and Disease or Etiology). One to any number of Dx codes can be assigned per case. Dx codes are subjective (professional) assessments provided by the diagnostic pathologist responsible for coordinating the case. Each component of a Dx code is a discrete categorical data point, making such data well suited for subsequent summary and analysis. This new system of coding was retrospectively applied to historical tissue-based (sick pig) case submissions, and used to facilitate the monitoring of disease diagnosis objective of this project. Going forward, this new Dx coding system, coupled with the use of state of the art business intelligence (BI) software for summarizing and visualizing such data, will greatly enhance the ability to monitor historical, emerging, and remerging trends in Iowa and US swine.

Overall, the algorithms were able to capture changes in the pattern of porcine submissions to the ISU VDL over time. The scanning of disease diagnosis was able to capture changes in the number of diagnoses by different systems or agents at different weeks during the year of 2019. The cyclic regression model, used to scan state of Iowa information present in the SDRS database for the cyclic pattern of agent detection, was able to characterize a
clear seasonal pattern of detection of PDCoV, PEDV, PRRSV, and MHP. During different weeks of 2019, signals were issued for increased detection of PDCoV, PEDV, and PRRSV.

This project led to the development and application of new tools and algorithms to monitor diagnostic information for signals of emerging and/or re-emerging pathogens in Iowa and US swine. The algorithms and new web-based systems being established aim to provide a platform for Iowa veterinarians and producers to have state-level information, and use it to compare with agent detection at a national level reported in the SDRS project. Veterinarians and producers can compare this aggregate level data (state or nation-wide) to observations and/or existing datasets of their own production system or veterinary clinic. The models and tools developed will continue to be evaluated, updated, and improved over time. When facing signals for increased agent detection, veterinarians and producers can reinforce biosecurity compliance measures as a way to prevent further spread of the agents. The detected signals were periodically discussed with the SDRS Advisory Council during the year of 2019 and the relevant findings were reported in the SDRS monthly written reports, audio reports, and video reports. Monthly SDRS reports are currently available at the Swine Health Information Center (SHIC) webpage https://www.swinehealth.org/domestic-disease-surveillance-reports/. Additionally, the PDF, audio, and video reports can be accessed at the SDRS project webpage https://www.fieldepi.org/sdrs. Interested individuals can sign up to receive the monthly PDF and audio reports by e-mail, by submitting a request to the SDRS project.

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**Scientific Abstract:** Veterinary diagnostic laboratories (VDLs) are continuously receiving swine case submissions and samples for testing. The use of diagnostic information for monitoring analyte detection and disease diagnosis is useful to understand the macro-epidemiological aspects associated with the megatrends of agent detection and disease diagnosis. We developed models to 1) monitor the number of monthly porcine submissions received at the ISU VDL; 2) monitor and predict the cyclic pattern of nucleic acid detection of PRRSV, PEDV, and PDCoV and MHP by PCR testing from case submissions originating from farms located in Iowa that are being reported to the Swine Disease Reporting System (SDRS) project; and 3) monitor the number of cases with the different types of disease diagnosis being derived from tissue-based (sick-pig) diagnostic cases submissions processed at the ISU VDL. To monitor monthly submissions at the ISU VDL, 5 years of historical data (2014-2018) composed by the monthly counts of porcine submissions were used to fit an additive Winters model with logistic transformation using the PROC ESM procedure available in the SAS software. The findings were used to forecast the expected number of monthly porcine submissions to the ISU VDL, with a 95% confidence interval (CI), for 2019. To monitor the cyclic pattern of detection of PRRSV, PEDV, PDCoV, and MHP information reported to the SDRS project, a cyclic regression model was applied to the information for cases from the state of Iowa. Historical data (2016-2018) composed by the weekly percentage of PCR-positive submissions, for each of the agents, were used to fit a cyclic robust regression model using the PROC ROBUSTREG procedure available on SAS. The findings were used to forecast the expected weekly percentage of PCR-positive submissions, with a 95% CI, for 2019. To monitor weekly counts of disease diagnosis at ISU VDL a 7-week window composed by the previous weekly counts of diagnosis by system or agent was used to fit an EARS-C1 algorithm using the R software, for 2019. The findings were used to monitor the upcoming weekly counts of diagnosis based on three standard deviations from the mean counts of the previous 7-week window.

During 2019: The number of porcine submissions received at ISU-VDL was above expected in May and October. The proportion of PRRSV-positive submissions crossed 95% CI boundaries at weeks 45-49. The proportion of PEDV-positive submissions crossed 95% CI boundaries at weeks 2, 6, 8, 12, 16, 25, 34, 47, 50. The proportion of PDCoV-positive submissions crossed 95% CI boundaries at weeks 7-8, 10-12, 15, 18, 24, 45-47, 49-50. Different
weeks had signals for an increased number of diagnoses for each of the eight monitored systems or one or more of the 20 monitored endemic agents.

Results from the model described herein and web-based systems being established to summarize and share such information present as a promising new development for keeping veterinarians and producers more informed about trends and signals of out-of-normality occurring in the findings of swine health related diagnostic work. Monitoring SDRS information was able to assess the seasonal cyclic patterns of PRRSV, PEDV, PDCoV, and MHP detection using the test results reported to the SDRS by multiple VDLs. When facing signals for increased agent detection, veterinarians and producers can reinforce biosecurity compliance measures as a way to prevent the potential spread of the agents.

Introduction: The US swine industry has recent experiences with the emergence and/or re-emergence of pathogens, including new variants of PRRSV and Senecavirus A, novel enteric coronaviruses (PEDV, PDCoV), and clinical nervous system-associated viruses. The economic impact of emerging pathogens in livestock operations can be influenced by the time to detect and respond to such challenges. The application of statistically sound algorithms to veterinary diagnostic results for purposes of monitoring or attempting to predict endemic and emerging pathogen activity is rather limited. Thus, there is an opportunity to develop and evaluate the application of scientifically derived algorithms to swine diagnostic data as a means for enhancing the existing systems of monitoring the health of Iowa and US swine.

Objectives:

The overall objective of this endeavor was to develop and apply new tools and algorithms to swine diagnostic data as a means for enhancing the existing systems of monitoring the health of Iowa and US swine.

Algorithms were developed and applied to three different types of porcine diagnostic data.

1. Monitoring and predicting the expected number of porcine submissions at ISU VDL.
2. Monitoring pathogen-level detection from Iowa swine being reported to the SDRS.
3. Monitoring disease diagnosis made on tissue-based (sick pig) case submissions at ISU VDL.

Additionally, observations related to this work were discussed with the SDRS Advisory Council periodically throughout the year of 2019, and the relevant findings were reported in the SDRS monthly written reports, audio reports, and video reports.

Materials & Methods:
The monitoring of the ISU VDL information requires a different set of algorithms depending on the data and the question. Specific approaches using different statistical procedures were developed to monitor the total number of porcine cases received each month at the ISU VDL, monitor agent detection from case submissions originating from farms located in Iowa being reported to the SDRS, and to monitor disease diagnosis in tissue-based (sick pig) cases received at ISU VDL.

The procedures adopted are here described:
1. Monitoring and predicting the expected number of porcine submissions at ISU VDL:

Total counts of porcine diagnostic case submissions received at the ISU VDL were retrieved from the ISU Laboratory Information Management System (ISU LIMS). A statistical model to scan the total counts, normalize the data, forecast the monthly totals for the upcoming year and its 95% CI was developed. A model selection considering a time series smoothing model accounting for simple, double, linear, damped trend, seasonal, Winter additive or multiplicative nature of the data, and with additional transforming procedure as log, square root, logistic, and box-cox was developed using PROC ESM commands in SAS (SAS v.9.4, SAS Institute Inc., Carry, NC). Model selection was based on the akaike information criterion (AIC), whereas the model with the smallest AIC was further used to forecast the number of porcine submissions for each month in the upcoming year, and its 95% CI. A SAS statement using data steps was created to capture the number of submissions case submissions received, forecasted results, and 95% CI. The final consolidated information was plotted using the PROC SGPANEL procedure in SAS.
2. Monitoring pathogen-level detection from Iowa swine being reported to the SDRS:

The SDRS has been aggregating anonymized veterinary diagnostic records from 4 major United States swine-centric veterinary diagnostic laboratories (VDLs): Iowa State University, University of Minnesota, South Dakota State University, and Kansas State University. Currently, PCR based detection for Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), Porcine Epidemic Diarrhea Virus (PEDV), Porcine Deltacoronavirus (PDCoV), Transmissible Gastroenteritis Virus (TGEV), and *Mycoplasma hyopneumoniae* (MHP) are being aggregated and reported to the SDRS. Weekly counts of the PCR-positive and total number of case submissions from the four VDLs originating from farm sites located in the state of Iowa were retrieved from the SDRS database. A function to calculate the percentage of positive submissions was applied. Each year was considered and organized in a cycle composed of 52 observations corresponding to 52 weeks. Weekly data from 3 years of historical data (2016 - 2018) were used to construct the baseline for each agent detection. A SAS PROC ROBUSTREG procedure was used to fit a cyclic regression model to monitor the proportion of PCR-positive submissions, and forecast the expected upcoming year weekly results. A 95% CI for each predicted weekly value was calculated using the SAS DATA STEP procedure using the predicted standard error value for each weekly result captured from the output of the robust regression model. An outbreak signal was defined as the point in time when the percentage of observed PCR-positive submissions exceeded the number of expected PCR-positive submissions. State of Iowa’s historical results, the 2019 predicted results with 95% CI for the predicted weekly result, and weekly percentage of positive submissions were plotted using SAS PROC SGPANEL procedure for PRRSV, PDEV, PDCoV, and MHP. TGEV has a limited number of positive results, and thus TGE was not eligible to be included in the model.

3. Monitoring disease diagnosis made on tissue-based (sick pig) case submissions at ISU VDL.

Throughout the course of the project period, a novel and greatly improved system and associated software application for incorporating diagnostic codes (Dx codes) into ISU VDL’s tissue-based (sick pig) case records was developed. Each Dx code is composed of four individual components (i.e., System, Insult type, Tissue or Lesion, and Disease or Etiology). One to any number of Dx codes can be assigned per case. Dx codes are subjective (professional) assessments provided by the diagnostic pathologist responsible for coordinating the case. Each component of a Dx code is a discrete categorical data point, making such data well suited for subsequent summary analysis. This new system of coding was retrospectively applied to historical tissue-based (sick pig) case submissions, and used to facilitate the monitoring of disease diagnosis objective of this project. Additionally, efforts were made to on-board the use of a commercially available business intelligence (BI) software (Microsoft BI®) for use in summarizing and visualizing Dx Code information via customized (web-based) dashboards. To monitor disease diagnosis at ISU VDL, submissions having a Dx code assigned were retrieved from ISU LIMS, organized under the SAS environment, and displayed on a user-friendly online informatics tool to summarize and report the key diagnosis associated with diseases found in tissues organized by physiologic systems and etiology. The 8 monitored systems were: respiratory, enteric, nervous, integument, systemic, musculoskeletal, urogenital, and cardiovascular-blood-endocrine-immune. The 20 monitored agents/diseases were *Streptococcus suis*, *Streptococcus sp.*, *E. coli*, *Haemophilus parasuis*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae*, *Salmonella sp.*, *Mycoplasma hyorhinis*, *Bordetella bronchiseptica*, *Trueperella pyogenes*, *Actinobacillus pleuropneumoniae*, *Clostridium sp.*, coccidiosis, mulberry heart disease, porcine proliferative enteritis − *Lawsonia intracellularis*, PRRSV, Influenza A, rotavirus, porcine circovirus (PCV2), porcine epidemic diarrhea (PED). An EARS-C1 algorithm was implemented under R version 3.6.0 (R Core Team, 2016) to scan and monitor the weekly number of submissions diagnosed by the system and by an agent for signals for increased diagnosis in a specific system or agent.

Results:

1. Monitoring and predicting the expected number of porcine submissions at ISU VDL.

To monitor the monthly porcine submissions received at the ISU VDL, using five years of historical information (2014-2018), a Winters additive model with logistic transformation had the best fit (based on AIC), and was used for predicting the expected monthly number of cases during the year of 2019 (Figure 1A). During 2019, months of May and October had the received number of submissions outside of the 95% CI of the predicted results (Figure 1B).
Monitoring pathogen-level detection from Iowa swine being reported to the SDRS:
The cyclic regression model was able to confirm and characterize the cyclic pattern of detection for the percentage of positive submissions for PRRSV, PEDV, PDCoV, and MHP for the state of Iowa (Figure 2). During the year of 2019 outbreak signals were detected in Iowa for PRRSV at weeks 45-49 (Figure 2A). Out of normality signals for PDCoV were detected at weeks 7-8, 10-12, 15, 18, 24, 45-47, 49-50 using the cyclical model employed on this weekly information (Figure 2B). Also, signals for PEDV were detected at weeks 2, 6, 8, 12, 16, 25, 34, 47, 50 (Figure 2C).

Figure 1. Predicted number of porcine submissions by month to the ISU VDL. A- Historical data used to train the model and to forecast the predicted total number of porcine submissions to be received by month at ISU VDL during the upcoming year. Line: predicted number of cases. Bullets: real number of cases. Blue band: 95% confidence interval for the predicted value. B- Predicted number of total porcine submissions for 2019 at ISU VDL filled with the actual number of submissions (by month) received at ISU VDL.
3. Monitoring disease diagnosis made on tissue-based (sick pig) case submissions at ISU VDL.
As mentioned above, to aid in the long-term impact of this effort associated with monitoring trends in diagnosis, a novel and greatly improved system and associated software application for incorporating Dx codes into ISU VDL’s tissue-based (sick pig) case records was developed (Figure 3) through a collaborative effort among ISU VDL diagnostic pathologists (K Schwartz and E Burrough) and information technology software development staff (D Patanroi and R Berghefer). This new development was incorporated into ISU LIMS Case Coordinator Cockpit application. Each Dx code is composed of 4 individual components (i.e., System, Insult type, Tissue or Lesion, and Disease or Etiology). Additionally, to accomplish this objective, there was the need to develop a tool able to summarize the information on the number of different diagnoses at ISU VDL over time. A dashboard based on the physiologic system and the etiologic assigned in the case by ISU VDL diagnosticians was developed (Figure 4).
Figure 3. A new application was developed in ISU LIMS Case Coordinator Cockpit application for incorporating Dx codes into ISU VDL’s tissue-based (sick pig) case records. Each Dx code is composed of 4 individual components (i.e., System, Insult type, Tissue or Lesion, and Disease or Etiology).
The implemented EARS-C1 algorithm was able to capture signals for different systems and agents at different weeks of the year for cases received at ISU-VDL. Examples of monitoring the number of diagnosis by the System affected are shown in Figure 5, and examples by etiological agent (pathogen) in Figure 6.

**Figure 4.** Disease diagnosis dashboards reports built utilizing a commercially available business intelligence software application (Microsoft BI®). Information filtered for respiratory diagnosis within the state of Iowa. On the top left, illustrates “System” filters. Lower left illustrates a table with the etiology. Lower right a bar chart with total number of cases within a year and season. Middle a bar chart with the proportion represented by each etiology on the total cases (lower right).

The implemented EARS-C1 algorithm was able to capture signals for different systems and agents at different weeks of the year for cases received at ISU-VDL. Examples of monitoring the number of diagnosis by the System affected are shown in Figure 5, and examples by etiological agent (pathogen) in Figure 6.

**Figure 5.** Monitoring disease diagnosis by physiological system by the EARS-C1 method. A- Respiratory cases. B – Enteric cases. X-axis year and week, y-axis number of diagnosis, bars weekly number of diagnosis, red line expect upper represent the upper boundaries of threshold of the expected number of cases, triangle shapes on the x-axis are indicative of signals for number of cases above the expected.
Discussion:
This project served to develop and assess the use of algorithms and new systems for monitoring swine diagnostic data as a means for enhancing the existing systems of monitoring the health of Iowa and US swine.

The algorithms applied to the number of porcine diagnostic case submissions and the pathogen specific detection (PRRSV, PEDV, PDCoV, and MHP) had the benefit of utilizing larger datasets, and more historical information used in their derivation. Overall, these provided a reasonable means for estimation and monitoring. However, it should be understood that the more finite increment of time used as the observational unit (day, week, month, quarter of the year), and the lower overall number of observations involved in any given point in time analysis, the more prone to variability that may not be related to a true system change. Additionally, these modelling efforts suggest that there are other sources of variability impacting the number of porcine case submissions to the VDL in a given month that go beyond an observed system change in health status.

There was a marked seasonal pattern of detection for the four agents PRRSV, PEDV, PDCoV, and MHP with a marked increase in the percentage of positive submissions during ‘cold’ months in the state of Iowa. The detected pattern of these agents within the state of Iowa was similar to the national level reported to the SDRS. However, they differ in the time and magnitude of outbreak signals. As examples, significant signals for increased detection of PRRSV were detected during the end of November and beginning of December in Iowa, whereas at a national level, this increased detection did not have such a significant increase. As an additional example, the signals for increased detection of PEDV and PDCoV during 2018 in the state of Iowa were significantly higher when compared at a national level reported by the SDRS project. Monitoring of agents at a state level is informative for veterinarians and producers within a given state, as well as for broader-scale monitoring purposes across the US.

The development of the new and improved (four component) diagnostic coding (Dx Codes) system was an expanded objective and deliverable derived during this project period. The need for an improved system for coding
out sick-pig (tissue-based) diagnostic submissions was recognized as an opportunity to create a longer-term stepwise improvement towards the overarching aim of this project that serves to develop improved systems and methodologies for utilizing VDL data to identify and monitor trends in Iowa and US swine. Going forward, this new development, coupled with the use of state of the art business intelligence (BI) software for summarizing and visualizing such data, will greatly enhance the ability to monitor historical, emerging, and remerging trends in Iowa and US swine. The consistent use of this new and improved coding system will enable the ability look at such data over longer periods of time (year over year, seasonality), than was conducted in this project and initial modeling effort.

This project developed new tools and models that allow for the scanning of diagnostic data to identify and monitor health trends in Iowa and US swine. The models and tools developed will continue to be evaluated, updated, and improved. For now, the findings have been periodically discussed with the SDRS Advisory Council, a panel of specialists, composed by field veterinarians and producers distributed across the United States and members of the participating VDLs. The major findings have been incorporated into the monthly SDRS reports, and are currently available at the Swine Health Information Center (SHIC) webpage https://www.swinehealth.org/domestic-disease-surveillance-reports/. Additionally, the written PDF, audio, and video reports can be found at the SDRS project webpage https://www.fieldepi.org/sdrs. Interested individuals can receive the monthly report pdf and audio report by email, under request to the SDRS project.

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