Porcine reproductive and respiratory syndrome virus is a positive-stranded, enveloped RNA virus that is 50 to 65 nm in diameter with a smooth surface and cuboidal nucleocapsid core that has a diameter of 25 to 35 nm. Similar to other members of the Arteriviridae family, PRRSV is species specific (infects only swine) and highly variable. It is transmitted through all bodily secretions, including urine, feces, colostrum, milk, saliva, semen, and nasal secretions. The infectious dose appears to be low and variable and is dependent on the virus strain, route of entry, concurrent health conditions, and age of the pig.

Clinical manifestation of PRRSV infection was first documented in the United States in North Carolina during the 1980s. Since then, PRRSV has rapidly spread throughout the US swine population and is now considered the most economically important disease of modern swine production, with annual production losses estimated at $560 million in 2005 and increasing to $664 million in 2011. Direct production losses associated with PRRSV infection are far-reaching. In sows, PRRSV infection causes abortions, stillborn piglets, mummified fetuses, irregular returns to estrus, and death. In suckling and growing pigs, PRRSV causes preweaning death, lethargy, respiratory tract disease, anorexia, and a decrease in daily weight gain. In boars of reproductive age, PRRSV causes acute respiratory tract disease, anorexia, lethargy, lack of libido, and a reduction in semen quality.

Several studies have been conducted to determine the relationships between the probability of a herd developing a new PRRSV infection and various risk factors such as herd size, biosecurity score, season in which a herd was established as uninfected with PRRSV, and PRRSV status of neighboring farms. The Production Animal Disease Risk Assessment Program is a commonly used survey in the swine industry that allows herds to compute internal (practices done within farm) and external (conditions outside the farm) biosecurity scores, which can then be benchmarked against herds in a national database.
study identified a correlation between a new PRRSV infection and the season during which a herd was established as uninfected with PRRSV (PRRSV negative), with herds established as PRRSV negative in the winter having a greater risk of developing a new PRRSV infection than herds established as PRRSV negative in the summer. Additionally, results of that study indicates that herds with low overall external biosecurity risk scores as determined by the Production Animal Disease Risk Assessment Program survey have a significantly higher probability of remaining PRRSV negative longer than do herds with high overall external biosecurity risk scores. Other risk factors for PRRSV infection include the size of the sow herd as well as the distance to, size of, and duration of PRRSV infection on neighboring swine herds.

Certain critical aspects of PRRSV epidemiology have yet to be elucidated. For example, to our knowledge, the nature and extent of temporal and spatial clustering of PRRSV-infected herds in the United States have not been evaluated. The goal of the project reported here was to provide metrics that describe the apparent repeatability of the temporal and spatial patterns of PRRSV epidemics on US sow herds.

Materials and Methods

STUDY POPULATION

This project was approved by the University of Minnesota Institutional Animal Care and Use Committee and was initiated in 2011. The target population was sow herds in the United States, and a convenience sample of herds was enrolled on the basis of project awareness subsequent to presentations at meetings such as the annual conference of the American Association of Swine Veterinarians and follow-up contact. Participation was voluntary and anonymous, and production companies (which breed and raise pigs for marketing purposes) provided retrospective data from July 2009 to the date of enrollment and then prospective data thereafter through June 2013. Thus, data were available for 4 full years (from July 2009 through June 2013). Within each production company, eligible sow herds weaned piglets into off-site locations, and at the time of enrollment, those herds were requested to begin testing at least 30 piglets of weaning age monthly for PRRSV by means of a PCR assay on the sow farm. Because some production companies have large multisite breeding operations where pigs live in multiple barns during different life stages, the World Organization for Animal Health (OIE) definition of an epidemiological unit was used to define a herd to avoid counting a new PRRSV infection twice. Therefore, sites that shared pig or personnel movement without isolation or biosecurity practices were considered a single unit, regardless of the geographic distance between them. All participants were required to sign participation and confidentiality agreements.

CASE DEFINITION FOR PRRSV INFECTION

A standard definition for a case of PRRSV infection in an individual farm was not used by all participating production companies. Typically, a new case of PRRSV infection was defined on the basis of professional veterinary judgement as described in a manner similar to that adopted by US sow herds for many years. A farm with a new case of PRRSV infection had to have positive PCR test results for pigs of weaning age, PRRSV open reading frame 5 sequence heterology from historical strains (if any) on that farm, and clinical signs consistent with PRRSV infection. The veterinarian or health manager of each participating production company reported new cases of PRRSV infection to project personnel on a weekly basis.

INCIDENCE

Beginning July 1 of each year, annual and quarterly cumulative incidences were computed as the proportion of susceptible herds (epidemiological units) with new PRRSV cases during a given year or quarter. Annual and quarterly cumulative incidences were compared among years and quarters, respectively, by means of χ tests. For each year, logistic regression was used to determine the odds that a herd would report a new PRRSV outbreak (yes or no) given its PRRSV infection status (infected or not infected) in the preceding year. For all analyses, values of P < 0.05 were considered significant.

EWMA

The weekly incidence of new PRRSV-infected herds was monitored with an EWMA. The approximated EWMA (smoothed) number of PRRSV-infected herds per week (E) at time period (t) was calculated as follows: E = λ X t + (1 - λ) X E t-1, where X is the observed number of PRRSV-infected herds and λ is a smoothing constant chosen to minimize the root mean square deviation of the residuals between E and X. The epidemic threshold was defined as the upper confidence limit (UCL) of the data on the basis of the following equation:

\[ UCL = \mu + K \times \sigma \times \frac{\bar{\lambda}}{\sqrt{2 - \bar{\lambda}}} \times \left( \frac{1}{1 - \bar{\lambda}} \right) \]

where μ and σ are the population mean and SD for the observed number of new PRRSV-infected herds during the summer months (July, August, and September) of the previous year, respectively, and K is a multiplier function that was arbitrarily chosen to minimize the false signal during the summer months without delaying the epidemic signal and is the tradeoff between the specificity and sensitivity of the algorithm. The λ was set at 0.2787, and K was set at 2.2. With this method, the week of the year during which the number of PRRSV-infected herds exceeded the epidemic threshold (ie, the onset of an epidemic) was identified.
CLUSTER ANALYSIS

The spatial scan statistic described by Kullendorff has been used to study whether processes (ie, occurrence of PRRSV infection in a cohort of US sow herds) are purely random or clustered in excess of the expected (baseline). This method applies a window of variable size across a study area and compares the number of observed cases of disease with the number of expected (baseline). This method has been used in veterinary medicine to identify clusters of bovine tuberculosis in Argentina and leptospirosis among dogs in the United States and Canada and assess the association between soil type and paratuberculosis in Indiana cattle herds.

For this project, a purely spatial analysis Bernoulli model was fitted to the data for each separate year of analysis. In that model, a herd (epidemiological unit) in which a new PRRSV case was identified during the year being analyzed was classified as infected with PRRSV; otherwise, it was classified as a control. The model scanned for areas with 50% of the swine population at risk and that had high rates of new cases of PRRSV by use of a circular spatial window and no geographic overlap. For each year, the observed pattern of clusters of PRRS-infected herds was compared with cluster patterns for 999 random scenarios generated by means of Monte Carlo simulation, and observed cluster patterns that had a value of \( P < 0.05 \) were considered significant.

Results

Fourteen production companies, representing 371 herds in 15 states with approximately 1.2 million sows (approx 21% of the US sow population), were enrolled in the project and provided data from July 2009 through June 2013 for analysis. The project began in early 2011 with 4 companies, and 5 more were added later that year. In 2012, 4 more companies were added, and in 2013, the last company was added.

The increase in the number of herds (epidemiological units) from which data were obtained during the study was the result of growth of the participating production companies that had acquired or built new herds. For example, data for July 2009 were obtained from 319 herds, whereas data for May 2013 were obtained from 371 herds. The median number of herds per production company was 27 (range, 7 to 68 herds/production company), and the median herd size was 3,100 sows (range, 500 to 12,500 sows). Of the 371 participating herds, 300 (81%) were involved in commercial sow production, 48 (13%) were involved in multiplier production (herds that produce replacement gilts for commercial herds), and 23 (6%) were involved in genetic nucleus production (purebred swine herds that produce replacement gilts for multiplier herds). Seventy-eight (21%) herds used bioaerosol filtration at the end of the June 2013.

A project year was defined as July through June. The cumulative incidence pattern of PRRSV cases was similar for all 4 years of the project. The incidence of PRRSV infection was lowest in the spring and summer (February through September) and increased dramatically in the fall and winter (October through January). The annual cumulative incidence of PRRSV-infected herds was 29% for July 2009 through June 2010 (2009 to 2010), 33% for July 2010 through June 2011 (2010 to 2011), 38% for July 2011 through June 2012 (2011 to 2012), and 32% for July 2012 through June 2013 (2012 to 2013; Figure 1). Within each quarter, the cumulative incidence of PRRSV-infected herds did not differ significantly among the 4 project years (Table 1). Compared with herds that were not infected with PRRSV during the previous year, herds that were infected with PRRSV during the previous year were 2.45 (95% CI, 1.48 to 4.06) times as likely to become reinfected with PRRSV in 2010 to 2011 (\( P < 0.001 \)) and 1.88 (95% CI, 1.18 to 3.00) times as likely to become reinfected with PRRSV in 2011 to 2012 (\( P = 0.009 \)); however, the odds of a herd becoming infected with PRRSV in 2012 to 2013 (OR, 1.60; 95% CI, 1.00 to 2.57) did not differ significantly (\( P = 0.052 \)) between herds that were and were not infected with PRRSV during 2011 to 2012.

A PRRSV epidemic began during the middle 2 weeks of October in each project year (Figure 2). During those epidemics, the ratio of the observed number of PRRSV infected herds to the expected number of PRRSV infected herds was 1.97 in 2009 to 2010 (\( P < 0.001 \)), 1.34 in 2010 to 2011 (\( P = 0.039 \)), 1.88 in 2011 to 2012 (\( P < 0.001 \)), and 2.07 in 2012 to 2013 (\( P < 0.001 \); Table 2). The centroid for each epidemic cluster was located in Iowa, with radii ranging from 162.8 to 302.1 km (Figure 3).

Figure 1—Annual cumulative incidence of PRRSV-infected sow herds (epidemiological units) for project years 2009 to 2010 (solid gray line), 2010 to 2011 (dashed gray line), 2011 to 2012 (dashed black line), and 2012 to 2013 (solid black line). The project included 371 US sow herds from 14 production companies, and a project year was defined as July 1 through June 30. A PRRSV-infected herd was a herd in which at least 1 new case of PRRSV infection was diagnosed during that project year. The definition of a new case of PRRSV infection was not standardized among the participating herds, but typically included professional veterinary judgment, a positive PCR test result from a piglet on the farm as well as PRRSV open reading frame 5 sequence heterology from historical strains (if any), and clinical signs consistent with PRRSV infection.
Discussion

Results of the present project indicated that the temporal and spatial patterns of PRRSV epidemics on US sow farms were similar during the 4-year period of July 2009 through June 2013, which suggested that the PRRSV infection pattern was highly consistent and repeatable. In general, sow herds that were infected with PRRSV during the previous year were more likely to become reinfected with PRRSV during the following year than were herds that were not infected with PRRSV during the previous year. The EWMA suggested that there is a narrow window of time during which the PRRSV epidemic begins each fall, and the spatial scan statistics indicated a repeatable pattern of clustering of PRRSV-infected herds in the upper Midwest region of the United States during those epidemics.

Historically, spatial scan statistics have been used to identify regions of higher-than-expected disease clustering and provide a scientific basis for planning control programs. The findings of the project reported here indicated that there is a need for continu-

Table 1—Number of herds newly infected with PRRSV and cumulative count of PRRSV-infected herds during each quarter of each project year (July 1 through June 30) from 2009 to 2013.

<table>
<thead>
<tr>
<th>Quarter</th>
<th>No. of newly infected herds</th>
<th>Cumulative count</th>
<th>No. of newly infected herds</th>
<th>Cumulative count</th>
<th>No. of newly infected herds</th>
<th>Cumulative count</th>
<th>No. of newly infected herds</th>
<th>Cumulative count</th>
<th>χ² Test result</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>July–September</td>
<td>11</td>
<td>11</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>1.998</td>
<td>0.573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>October–December</td>
<td>40</td>
<td>51</td>
<td>65</td>
<td>72</td>
<td>57</td>
<td>63</td>
<td>86</td>
<td>0.162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>January–March</td>
<td>28</td>
<td>79</td>
<td>20</td>
<td>92</td>
<td>50</td>
<td>113</td>
<td>86</td>
<td>0.162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>April–June</td>
<td>12</td>
<td>91</td>
<td>14</td>
<td>106</td>
<td>22</td>
<td>135</td>
<td>117</td>
<td>0.247</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The project included 371 US sow herds (epidemiological units) from 14 production companies, which represented approximately 21% of the US sow population. The definition of a new case of PRRSV infection was not standardized among the participating herds, but typically included professional veterinary judgement, a positive PCR test result from a piglet on the farm as well as PRRSV open reading frame 5 sequence heterology from historical strains (if any), and clinical signs consistent with PRRSV infection.

Table 2—Results of spatial scan statistic to detect clusters of PRRSV-infected herds during the period of July 2009 through June 2013.

<table>
<thead>
<tr>
<th>Project year</th>
<th>Center coordinates</th>
<th>Radius (km)</th>
<th>No. of herds</th>
<th>No. of observed cases</th>
<th>No. of expected cases</th>
<th>Ratio of observed to expected cases</th>
<th>χ² Test result</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009–2010</td>
<td>42.8 N, 94.3 W</td>
<td>198.6</td>
<td>107</td>
<td>63</td>
<td>31.98</td>
<td>1.97</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>2010–2011</td>
<td>42.6 N, 91.8 W</td>
<td>302.1</td>
<td>146</td>
<td>63</td>
<td>46.86</td>
<td>1.34</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>2011–2012</td>
<td>43.4 N, 94.6 W</td>
<td>162.8</td>
<td>113</td>
<td>81</td>
<td>43.08</td>
<td>1.88</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>2012–2013</td>
<td>40.9 N, 94.4 W</td>
<td>280.8</td>
<td>77</td>
<td>45</td>
<td>21.76</td>
<td>2.07</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

See Table 1 for key.
ued efforts to elucidate why PRRSV infection occurs most frequently in the upper Midwest and determine which control practices could be implemented to mitigate the effects of PRRSV on the US swine industry. On the basis of the results of the spatial scan statistics for this project, it is possible that the upper Midwest has characteristics that favor the transmission of PRRSV such as the highest swine density or the most traffic to transport pigs to regional slaughterhouses, or that the production companies with producers in this region view PRRSV management differently than do production companies with producers in other parts of the United States. Regional PRRSV control and elimination programs have been implemented in the United States, Canada, and Mexico. Although many of the outcomes realized by those programs are beyond the realm of peer-reviewed literature, there is a growing body of empirical evidence that suggests that, with appropriate leadership and cooperation, control and elimination programs can successfully minimize the impact of PRRSV in some regions of the United States. The results of this project corroborate the need for the development of PRRSV control programs in swine-dense regions of the United States because, to our knowledge, such efforts are currently lacking.

Vaccination of pigs against PRRSV has been used to manage disease; however, the heterologous strains of PRRSV used in commercial vaccines seem to produce incomplete immunity. Results of 2 studies suggest that vaccination against PRRSV reduces viral shedding at the individual pig and population levels and that simultaneous mass administration of a commercial vaccine to all pigs within a region might be beneficial in regional control programs.

Although regional PRRSV control programs have gained some early success, they likely represent only a partial solution to the problem, and additional research is necessary to quantify risk factors associated with PRRSV epidemics. Results of multiple studies suggest that the application of rigorous biosecurity measures and aerosol filtration effectively reduce the frequency with which PRRSV is introduced into

Figure 3—Results of the spatial scan statistic to detect clusters of PRRSV-infected herds during project years 2009 to 2010 (A), 2010 to 2011 (B), 2011 to 2012 (C), and 2012 to 2013 (D). Small black circles represent the location of PRRSV-infected herds, and small white circles represent the location of PRRSV-negative herds. The large circle demarcates the centroid of the epidemic cluster. See Figure 1 for remainder of key.
m any swine herds and these methods for controlling PRRSV transmission should continue to be studied. Finally, although much has been learned in the areas of vaccinology, immunology, and host genetics in regard to PRRSV infection in pigs during recent years, the role each plays in the control of PRRSV is still under investigation.

The results of the present project might have been affected by selection and recall biases. The participating herds represented a volunteer cohort and were not a random sample of US sow herds; therefore, it is possible some unmeasured factor influenced herd participation and consequently affected the project results. It is important to note that some areas of US swine production, including the swine-dense regions of Oklahoma and North Carolina, were underrepresented in the spatial scan statistic, and the results of this project may not accurately reflect the impact of PRRSV in those areas. Also, swine growing sites, which could play an important role in the lateral transmission of PRRSV, were not evaluated in the present project. Although this project was initiated in 2011, participating herds were required to provide retrospective data from July 2009 to the date of enrollment, and that data could have been subject to recall bias. Additionally, the diagnostic rigor for identification of PRRSV-infected pigs was not standardized and likely varied among production companies and participating herds as well as within individual herds between the pre- and postenrollment periods. Because of our familiarity with the participating production companies, we suspect that those variations were relatively minor; however, a formal assessment of potential differences in the identification of PRRSV-infected pigs within and among herds was not performed. The lack of a formal case definition for PRRSV-infected pigs during this project might have also caused biased results. For example, new cases of PRRSV-infected pigs might have been under-reported in herds with endemic PRRSV infections. Despite the potential sources of bias in the present project, the participating production companies and herds accounted for >20% of the US sow population, and the results for this population are important for elucidation of the transmission dynamics of PRRSV, one of most economically important diseases affecting the US swine industry.

In the present project, the onset of a PRRSV epidemic in US sow herds in the upper Midwest annually during the midpart of October was highly repeatable during the period of July 2009 through June 2013. These findings corroborate the need for ongoing support of regional PRRSV control and elimination projects and coordinated national PRRSV surveillance programs. The cooperative data-sharing process developed for this project may be beneficial for the implementation of those control and surveillance programs and better prepare the US swine industry for handling the introduction of potential emergent and foreign animal diseases.

ACKNOWLEDGMENTS

This manuscript represents a portion of a thesis submitted by Dr. Toussignant to the University of Minnesota Graduate School as partial fulfillment of the requirements for a Doctor of Philosophy degree.

Supported in part by the National Pork Board, the University of Minnesota College of Veterinary Medicine Signature Series Grants, and the PRRS Coordinated Agriculture Project II.

Drs. Lowe and Yeske provide veterinary consulting services for 2 of the production companies involved in this project.

Presented in part at the 45th Annual Meeting of the American Association of Swine Veterinarians, Dallas, March 2014.

REFERENCES

23. Yeske PA decision tree to guide to answering the question, is this a new virus or not to the farm?, in Proceedings. Allen D Leman Swine Conf 2013;71−75.