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Evaluation of Microbiology Orders from a Veterinary Diagnostic Laboratory as a Potential Data Source for Early Outbreak Detection

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Animals continue to be recognized as a potential source of surveillance data for detecting emerging infectious diseases, bioterrorism preparedness, pandemic influenza preparedness, and detection of other zoonotic diseases. Detection of disease outbreaks in animals remains mostly dependent upon systems that are disease specific and not very timely. Most zoonotic disease outbreaks are detected only after they have spread to humans. The use of syndromic surveillance methods (outbreak surveillance using prediagnostic data) in animals is a possible solution to these limitations. The authors examine microbiology orders from a veterinary diagnostics laboratory (VDL) as a possible data source for early outbreak detection. They establish the species representation in the data, quantify the potential gain in timeliness, and use a CUSUM method to study counts of microorganisms, animal species, and specimen collection sites as potential early indicators of disease outbreaks. The results indicate that VDL microbiology orders might be a useful source of data for a surveillance system designed to detect outbreaks of disease in animals earlier than traditional reporting systems.

Medical Subject Headings: Animal Diseases; Bioterrorism; Communicable Diseases, Emerging; Disease Outbreaks; Epidemiology; Sentinel Surveillance; Zoonoses.

Abbreviations: VDL, veterinary diagnostics laboratory.

INTRODUCTION

Emerging infectious diseases are newly recognized, clinically distinct, or known diseases that are increasing in incidence in a given place or specific population (1). More than 35 such diseases have been reported in humans between 1980 and 2003 (2). Many emerging pathogens are zoonotic (capable of infecting both humans and one or more species of lesser animal) (3–5). Indeed, organisms that can infect multiple species are 2 to 4 times more likely of being associated with an emerging infectious disease than those that are specific to a single host (3,4,6).

Although humans serve as the main reservoir for only 3% of all zoonotic pathogens (3), discovery of zoonotic disease outbreaks has often relied on the identification of human cases rather than surveillance in animals (5,7). Detection of a zoonotic disease outbreak in an animal population first

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could possibly result in control efforts that prevent or greatly reduce human morbidity such as postexposure prophylaxis of contacts or quarantine of animals (7,8). Improved surveillance systems and methods in animals might specifically benefit pandemic influenza preparedness (9–11), bioterrorism defense (12–15), and response to other public health threats (16,17).

Disease surveillance continues to develop as a core veterinary activity (18); however, regulatory programs and efforts to eradicate specific diseases have typically directed disease surveillance in animals (19). Therefore, these activities tend to be very disease specific and limited in their ability to detect other diseases, especially those that present with nonspecific signs (20–22). Analysis of prediagnostic data (ie, syndromic surveillance) may provide a solution to the disease-specific limitations of current surveillance systems used for animals. Systems using such analytic methods do not focus on any specific disease, but rather capture incidence of nonspecific, health-related events that may be indicators of disease. A key feature of many of these systems is the use of preexisting electronic data such as found in databases of registration, accounting, or inventory records.

Although scarcer in the veterinary community, sources of data exist that appear to be similar to those used by early outbreak detection systems for humans. We considered VDLs one of those sources. Veterinary diagnostic laboratories exist in three sectors: public laboratories usually associated with government agriculture departments, schools of veterinary medicine, and commercial laboratories. These facilities typically maintain electronic records of test orders and results that include animal species, date, and geographical references (eg, ZIP code). We hypothesized that the following:

1. Microbiology order records of VDLs would possess the qualities of representativeness and timeliness required for use in an early outbreak detection system. Representativeness and timeliness establish, in part, the quality of the data, one of the criteria important to building a successful system. Representativeness is a determination of how well records in the system describe the target population and indicates the potential to accurately determine the distribution of cases by time and place. The presence of a species may be a more important measure of representativeness for early outbreak surveillance (23). For example, if detecting emerging diseases in pets is the goal of the system, then it follows that the data need to include information for companion animals.

   The availability of data reflects the potential gain in terms of timeliness (24), the time from the disease event to the time the event is discovered (25). Timeliness has become a major objective of surveillance systems that are used to detect outbreaks of infectious disease (26). This potential gain establishes the value of data for earlier detection of disease outbreaks compared to traditional disease reporting and detection systems.
2. Baselines for microbiology orders and isolated microorganisms could be determined from historic records. The Centers for Disease Control and Prevention have identified the ability to provide baseline information on incidence trends and geographic distribution as a prerequisite to detecting new or reemerging infectious-disease threats (27). The baseline becomes especially important to determining whether counts are abnormally elevated. Making accurate interpretations from the results of detection analyses is difficult without first establishing what is normal (28,29). Baselines help to determine the noise in the data and to provide for establishing expected values required for the analyses. Such indices are important to validate the statistical models used by detection systems in order to to determine abnormal patterns of distribution or counts (30,31).
3. Examination of microbiology order counts using detection algorithms could identify pattern changes in the order time series resulting from increased counts of microorganisms, animal species, and/or specimen-collection sites that might indicate a possible outbreak.

MATERIALS AND METHODS

We conducted a retrospective study of a dataset obtained from IDEXX Laboratories, Inc. (Westbrook, Maine) that contained microbiology orders that had been submitted by veterinary providers in a 7-county area of central Ohio from January 2001 through December 2003. IDEXX Laboratories receive, on average, about 11,500 specimens daily from clients throughout the United States, either by courier or by express parcel service (eg, FedEx) (Bill Davis, IDEXX Laboratories, Inc., personal communication, 2006). Upon receipt of specimens, IDEXX personnel enter the date and time of arrival into a laboratory information system. These and other data populate data repositories at the IDEXX corporate office at the time of record creation. Other information included in the dataset provided were a specimen-unique accession number, animal species, the anatomical collection site of the specimen, date of test result, and species of microorganism isolated.

To evaluate the quality of the data, we studied the dataset with descriptive statistics using EpiInfo v3.3.2 (Centers for Disease Control and Prevention, http://www.cdc.gov/epiinfo/). We determined the frequency of animal species in the dataset to evaluate representativeness. Turnaround time (the time between the laboratory's receiving a specimen and recording the test results) was used to measure the potential gain in timeliness by averaging the difference between the dates for each record.

We used a tool developed by Burkom (32) in Excel 2003 (Microsoft Corporation), to study the weekly time series of microbiology orders with a modified CUSUM method, commonly identified as C3 and used in the Early Aberration Reporting System, that combines the current period CUSUM

value with previous ones to obtain a statistical value (33). We used a baseline equal to 5 weeks, with a buffer of 1 week, and an alert threshold equal to a statistical value of 1. Weeks consisted of 7 days beginning on Sunday. Week 1 was the 7-day period that included January 1. The statistical value was calculated as

$$S_t = \max\{0, S_{t-1} + (X_t - (\mu_n + \sigma_n))/\sigma_n\}, \quad [1]$$

where X_t is the actual count for week t; μ_n the mean of the baseline counts $((t-2 + t-3 + \ldots t-6)/5)$; and σ_n the standard deviation of the baseline counts.

We developed weekly time series of isolate counts of specific microorganisms by grouping the records according to genus and studied the baseline occurrence with Serfling's regression method using Excel 2003. Weeks consisted of 7 days beginning on Sunday. Weeks 1, 53, and 105 were the 7-day periods that included January 1. Data from 2001 and 2002 (weeks 1–104) were used to determine expected weekly counts for 2003 (weeks 105–156). We chose the Serfling method because of the seasonal variance in counts that we expected for many enteric organisms such as *Escherichia coli* and *Staphylococcus*. As the frequency of observed counts in the time series approach zero, the accuracy of the Serfling model becomes more unreliable (Garrick Wallstrom, University of Pittsburgh, personal communication, 2006) so we examined only the more frequently occurring microorganisms. The Serfling method combines a linear term with sine and cosine terms to describe any seasonal change (34),

$$\hat{Y}_t = \alpha + \beta_t t + \beta_s \sin(2\pi t/52) + \beta_c \cos(2\pi t/52), \quad [2]$$

where a is the intercept value, β_t is the linear coefficient, and β_s and β_c are the model coefficients for the sine and cosine terms, respectively, that describe any seasonal effect at week t. The Serfling method requires data from nonepidemic periods to develop a base model. Information was not available to distinguish epidemic from nonepidemic weeks so we used a procedure similar to the one described by Tsui et al (35) to remove counts that possibly represented epidemic weeks. The first 104 weeks of data (January 2001–December 2002) were used to build the regression model that was applied to weeks 105–156 (January–December 2003). The procedure involved three steps.

1. Calculate an initial regression model for the first 104–week series using equation [2].
2. Remove those counts with standardized residual values greater than 1.645, representing a one-tailed upper 95% CI.
3. Calculate a second regression model using equation [2] for the remaining data to obtain a predicted value curve for the third year's data series.

Alerts produced by the CUSUM analysis were studied using the results of the Serfling analysis to determine greater-than-expected isolate-specific counts and counts of specimens that were stratified by animal species and specimen collection site. Mean weekly counts of orders for these groups were determined using microbiology order data from 2001 and 2002. The number of standard deviations from the mean, determined by dividing the difference between the 2003 week-specific count and the mean for that week by the standard deviation of the mean, was used to quantify the significance of change.

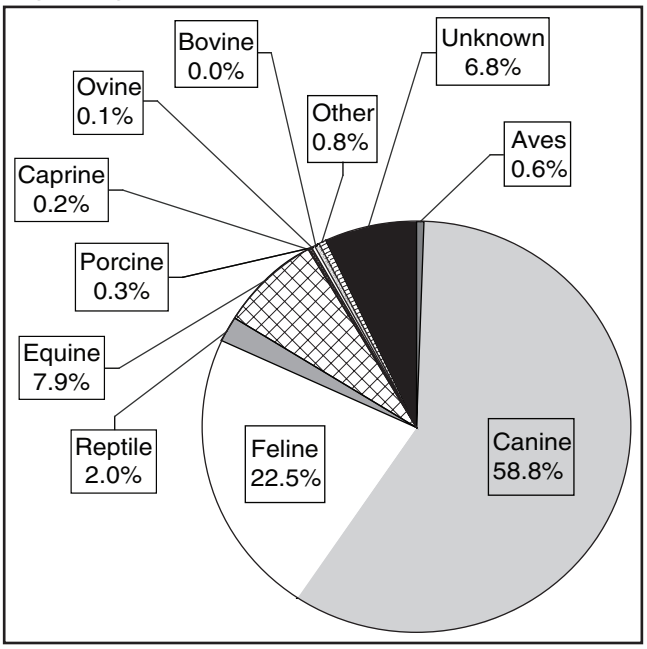
RESULTS

From January through December 2003, the total number of accessions was 3,290. The median turnaround time (time between specimen receipt and test result) was 3 days (range, 0–42 days). The data were representative mainly of specimens from companion animal species (58.8% canine, 22.5% feline, 2.0% reptile, and 0.6% birds) and equine (7.9%) (Figure 1). Agricultural species comprised only 0.6% of the total accessions.

Specimens represented in the 2003 IDEXX dataset were most frequently collected from urine (32.8%); ear (16.4%); feces (6.8%); nose (5.4%); uterus/cervix (3.6%); trachea (2.2%); abscess (1.8%); skin (1.5%); vagina (1.1%); and bladder (0.7%). Microorganisms most frequently isolated by IDEXX in 2003 included *E. coli* (28.2%); *Staphylococcus* (21.4%); *Enterococcus* (9.2%); *Pseudomonas* (8.7%); *Proteus* (8.6%); *Streptococcus* (6.8%); *Bacillus* (3.7%); *Enterobacter* (2.3%); *Klebsiella* (1.5%); and *Corynebacterium* (0.9%).

Analysis of the microbiology order time series with the C3 method identified 5 weeks (weeks 10, 20, 32, 33, and

FIGURE 1 Representation of animal species by microbiology orders submitted to IDEXX during 2003, originating from animals in central Ohio.



46) where observed counts exceeded expected (ie, alerts) (Figure 2). Comparison with microorganism-, animal species–, and collection site–specific time series indicated that each of these alerts could be associated with increased counts of specific microorganisms, animal species, and specimen collection sites (Table 1).

DISCUSSION

Companion animals (eg, canine, feline, and pet birds) were the group more frequently (81.9%) represented by the IDEXX dataset. Equine species were also a frequent provider of samples (7.9%). Although sometimes labeled as agricultural (19), horses differ from most other species of agricultural animal since they generally are kept individually or in small groups for pleasure and/or show, rather than in herds for consumption (36). Veterinary care of dogs, cats, pet birds, and horses is routinely more individually based as opposed to herd animals (eg, cows, pigs, and sheep) (16), where diagnosis of disease in the unit (ie, herd) does not require testing every member (37). The number needed to detect disease is less than that needed for surveillance to estimate prevalence (38); therefore, the lower frequency of agricultural species in the datasets should not automatically preclude them as a valuable source of data for early outbreak detection in these populations. Further investigation may better evaluate the adequacy of agricultural animal representation in these data as it pertains to outbreak detection efforts.

The average turnaround time for microbiology tests (3 days) indicated the potential gain in timeliness that might be possible using microbiology order-based analysis compared to analysis using the date of test result. Based on previous models estimating the impact from outbreaks of select disease, a gain of 3 days could be substantial for reducing mortality and cost (8). This potential includes an assumption that outbreak discovery occurs at the same time results are known. This may not always be the case. Indeed, outbreak discovery is often delayed for some time until individual results from the various sample-submitting clinics are aggregated for analysis. Therefore, the actual gain in timeliness may be greater than that indicated by turnaround time. Timeliness of detection as it relates to onset of outbreak might also be affected by delays created in the process of delivery of the specimen to the laboratory. The percentage of total records received within established periods (eg, every 24 hours) might help better evaluate the impact from this potential bias.

Analysis indicated several periods of increased counts of orders (clusters) that may have resulted from disease outbreaks. The pathogens that were found to be associated with these clusters were not reportable in animals. Therefore, no registry existed to validate these instances resulting from true outbreaks of disease. While we would expect an increase in the number of specific isolates to be associated with an outbreak, periods of increased counts could have been the result of more rigorous surveillance efforts, increased veterinary visits in reaction to a public service campaign, or other causes not related to an outbreak of disease. The increase of orders by collection site and species lends support to the possibility that the clusters did result from an increase of disease in animals.

Detection systems of this type can only be expected to identify outbreaks within certain size parameters earlier

FIGURE 2 Time series of weekly counts of IDEXX microbiology orders from veterinary practitioners in central Ohio, January through December, 2003, showing alerts that were determined using C3 analysis with a 5-week baseline, 1-week buffer, and threshold statistic = 1.

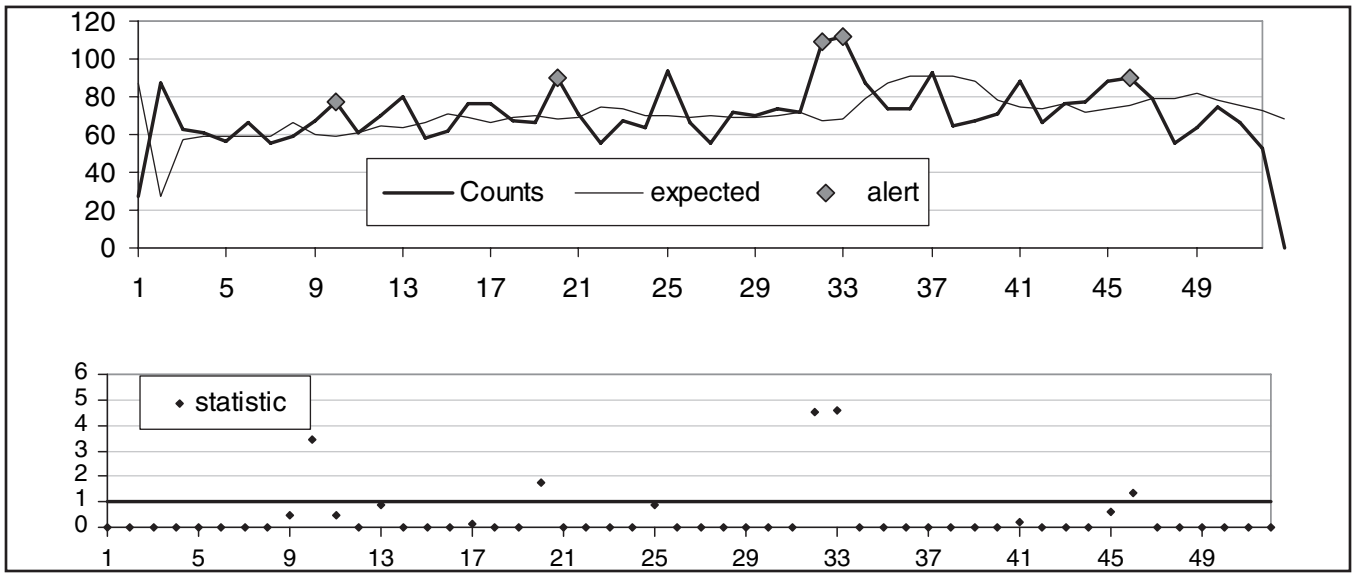


TABLE 1 Temporal clusters of microbiology orders indicated by alerts generated through C3 analysis of the IDEXX dataset compared with counts of orders stratified by microorganism, animal species, and specimen collection sites and the deviation of actual counts from expected counts

Week of Alert in Microbiology Order Time Series	Total Number of Orders	Microorganism-Specific Counts		Animal-Specific Counts		Collection Site–Specific Counts	
		Organism (count)	s's above expected	Species (count)	s's above expected	Site (count)	s's above expected
10	68	*E. coli* (22)	1.9	Canine (49)	5.5	Ear (14)	2.5
20	79	*Staphylococcus* (22)	2.8	Canine (41)	2.6	Ear (15)	9.2
				Feline (20)	2.7	Nose (8)	17.2
				Equine (11)	4.9		
32	91	*E. coli* (43)	6.1	Canine (54)	4.2	Urine (30)	4.2
		Proteus (13)	3.2	Feline (21)	4.9	Feces (11)	2.8
						Nose (5)	4.9
33	92	*E. coli* (41)	5.6	Feline (20)	2.8	Feces (16)	17.7
		Proteus (10)	1.7	Equine (9)	3.5		
46	78	*E. coli* (25)	2.6	Canine (50)	4.1	Ear (15)	2.1

than traditional methods (39,40). An astute clinician treating all or a substantial number of the patients might be better for detecting outbreaks with only a relative small number of cases. This would most likely require a situation where a rural practitioner services the majority of animal owners in an area. Outbreaks of very rare disease would most likely be detected in this way, while a large, rapidly progressing outbreak would probably not require any specialized surveillance for discovery.

A review of manual surveillance systems found decreasing motivation over time, heavy reporting load, and reporter compliance as some of the challenges in maintaining reporter participation (41–44). Early outbreak detection systems using VDL data may provide solutions for limitations encountered by other systems, especially those dependent on manual provider entries. A surveillance system that uses existing electronic data, automatically transferred from laboratories, would not be dependent on reports entered manually. Hence, motivation and reporting load of people assigned to enter data would not be factors created by the surveillance program. Another challenge of reporter driven systems, where historic data is not available, is the ability to determine baseline or reference levels (41). Electronic laboratory records provide a historical record that might provide a means to determine these baselines of occurrence.

This study indicates that microbiology order data from VDLs may have potential value for early outbreak detection in companion animal populations by alerting to increased orders that are associated with increased incidence of microorganisms. Analyzing counts of microbiology orders as they are received, rather than awaiting results, might also provide for more timely detection of disease outbreaks. Subsequent investigation of these data, including detection methods and their relation to other events, is necessary to assert their true value for any specified need.

Little is known about the potential for using these and similar veterinary data for early outbreak detection in animals. Less is known about the value of these data for providing warnings of outbreaks in humans. Certainly, consideration of results from more detailed investigations is warranted before investments are made in any large-scale surveillance system. However, further studies are justified by these initial findings and should continue to establish where these and similar data sources fit into the overall biosurveillance efforts to detect outbreaks of emerging infectious disease.

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