Early Outbreak Detection Using an Automated Data Feed of Test Orders from a Veterinary Diagnostic Laboratory

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Abstract. Disease surveillance in animals remains inadequate to detect outbreaks resulting from novel pathogens and potential bioweapons. Mostly relying on confirmed diagnoses, another shortcoming of these systems is their ability to detect outbreaks in a timely manner. We investigated the feasibility of using veterinary laboratory test orders in a prospective system to detect outbreaks of disease earlier compared to traditional reporting methods. IDEXX Laboratories, Inc. automatically transferred daily records of laboratory test orders submitted from veterinary providers in Ohio via a secure file transfer protocol. Test products were classified to appropriate syndromic category using their unique identifying number. Counts of each category by county were analyzed to identify unexpected increases using a cumulative sums method. The results indicated that disease events can be detected through the prospective analysis of laboratory test orders and may provide indications of similar disease events in humans before traditional disease reporting.

1 Introduction

Prompt detection of outbreaks might provide for earlier intervention efforts that result in minimizing their overall impact [11], [19], [28], [32]. Some animals are susceptible to infection from many of the same pathogens as humans, sometimes showing signs of disease earlier [1], [12]. Therefore, animals might be used as sentinels and provide for earlier recognition of disease outbreaks that could affect humans. As pet animals share much of the same environment as their human owners, they especially might prove to be valuable outbreak sentinels [2].

Most of the current disease surveillance systems used for animal populations are considered inadequate for detecting outbreaks of emerging disease, potential acts of bioterrorism, or outbreaks resulting from pathogens for which the system was not

specifically designed for in a timely manner [16], [20], [21], [24]. Such functionality in animal-based systems has been considered important to our overall bioterrorism and disease outbreak preparedness capabilities [13], [14], [25], [28], [31], [32], [34]. Syndromic surveillance methods utilize population health indicators to warn of potential outbreaks earlier than reports of confirmed diagnoses. Although many sources of data have been investigated for syndromic surveillance in humans, there is paucity in the literature describing similar studies in animals [17].

Laboratories are recognized as important sources of data for disease surveillance in animals as well as humans [9]. Test orders for specimens submitted to commercial medical laboratories have been utilized as one of the data sources for syndromic surveillance in humans [5], [33]. Most of the private veterinary practitioners in the United States also submit specimens to commercial laboratories for diagnostic testing [15]. Through the utilization of data from these commercial laboratories, we might possibly achieve the benefit of the aggregation of many veterinary providers across a wide geographic area. Such centralized aggregation of data may be important in detecting certain outbreaks [11]. The results of a previous investigation conducted by us demonstrated the representation of companion animals in select veterinary diagnostic laboratory (VDL) data and indicated the potential for identifying clusters of cases through analysis of the aggregated orders [27].

Although laboratory analyses are not as frequently a part of the veterinary care of pet animals compared to the medical care of humans [31], we hypothesize that the consistency of test orders over time is such that increases in cases of disease will result in detectable increases in the number of test orders submitted by veterinarians that can be identified using prospective analysis.

2   Methods

We conducted a prospective study of laboratory orders submitted to IDEXX Laboratories, Inc. (Westbrook, Maine) for specimens originating from veterinary clinics in Ohio between September 1, 2006 and November 30, 2006. IDEXX transferred once daily to a server located at the Real-time Outbreak and Disease Surveillance (RODS) Laboratory (University of Pittsburgh, Pennsylvania), via secure file transfer protocol, an automatically generated text file containing records of laboratory orders for specimens received within the previous 24-hour period. Each record included the accession number assigned by IDEXX to the specimen, date and time that IDEXX received the specimen, 5-digit ZIP code of the clinic submitting the specimen, species of animal, and numerical code/s of the laboratory product/s ordered.

2.1   Mapping Laboratory Orders to Syndromic Category

We distributed a list of product descriptions ordered during a 2-week period to ten small and large animal veterinarians asking them to consider the diseases that they might use each product to confirm or rule out during the diagnostic process. The veterinarians then assigned each product to syndromic categories based on the expected

presentation of these diseases. Eight categories were considered initially: respiratory, gastrointestinal, neurologic, behavioral, dermal, reproductive, non-specific, and sudden death. Seven of the ten surveyed veterinarians returned the categorized lists (Table 1). The behavioral and sudden death categories were subsequently removed based on zero responses from the surveyed veterinarians for these categories.

In addition to the surveyed veterinarians, two IDEXX laboratorians also reviewed the list of products. Based on their input and advice, five categories were added to further describe many of those products that had been classified into the non-specific category. These additional categories were endocrine, hepatic, infectious, febrile, and renal. Records were mapped to syndromic category based on the identifying number for the laboratory product ordered and appropriately classified as the server received them.

2.2 Statistical Analysis

We used frequency analysis to describe the representation of species groups and distribution of accessions by day of the week. The percentage of the total daily records included in the dataset for each 24-hour period was used to describe availability of records.

2.3 Detection Method

A cumulative sums (CuSum) method was used to analyze category counts, as records were received, for each Ohio County, as determined by the ZIP code. The value of the CuSum was calculated as

$$S_t = \max\{0, S_{t-1} + (X_t - (\mu_t + 0.5\sigma_t))/\sigma_t\}. \tag{1}$$

where X_t was the observed count at time t, μ_t the expected count (baseline), and σ_t the standard deviation of the counts used to determine the baseline. Daily analysis was performed automatically using the count from the current and previous six days for the observed value. A moving 7-day period was chosen to reduce the anticipated day-of-week effect in the data. The expected value was calculated by averaging the weekly counts for the previous 4-week period. We defined alerts as instances when the CuSum value equaled or exceeded five.

An alert period was defined as at least two consecutive days where the CuSum value exceeded the threshold. By using this two-in-a-row rule we were able to somewhat reduce the impact of single-day increases on weekly counts. Using this rule has been shown to increase the robustness of CuSum methods [22]. Alerts were considered for all syndromic categories except non-specific, which was mostly comprised of general screening tests such as blood chemistries. We investigated alerts by identifying the specific laboratory product or products involved and contacting select veterinarians located in the same area as the alert asking about their impressions of disease activity. Veterinarians may or may not have been IDEXX clients.

Table 1. Syndrome category descriptions distributed to veterinarian sample for grouping laboratory products

Example Diseases	Clinical Presentation	Syndrome Category
Glanders, Bordetella, Aspergillosis	• Coughing • Dyspnea • Nasal discharge	Respiratory
Salmonellsis, Clostridia-associated enterocolitis, Campylobacter	• Diarrhea • Vomiting • Colic	Gastrointestinal
Heartwater, plant poisoning, Botulism, Tetanus	• Convulsions • Paralysis • Staggering • Disturbed vision	Neurologic
Poxvirus, allergies, Foot and Mouth Disease	• Abscesses • Rash • Hair loss • Vesiculation	Dermal
Brucellosis, chronic Leptospirosis	• Retained placenta • Abortion • Orchitis	Reproductive
Plague, Tularemia, Anemia, early Leptospirosis	• Lethargy • Malaise • Weakness • Fever without defining associated sign	Non-specific
acute swine erysipelas, Anthrax, Red Water Disease	• Rapid onset of death without apparent cause • Death occurring after brief display of illness	Sudden Death
Rabies, Listeriosis	• Change in appetite without defining associated signs • Unexplained aggression • Disorientation	Behavioral

3 Results

3.1 Data Transfer

During the pilot, the daily transfer of data from IDEXX Laboratories was interrupted twice. The first interruption began on September 7 and continued through September 28. This interruption in data transfer occurred because the workflow involved in the transfer had been unscheduled and the job was mistakenly shut down. The second interruption occurred October 6 through October 9 for unknown reasons. The interruptions affected the transfer of 10,847 (22.6%) records. IDEXX forwarded records that were created during these times of interruption once the data feed was re-established providing for a complete time-series.

The pilot system relied upon transfer of data from IDEXX that was being queued in a test environment. The reliability of this environment was knowingly not as stable as a production environment would be. The interruptions experienced during this pilot would not be expected in a more stable production platform.

3.2 Descriptive Statistics

During the study period, IDEXX transferred records for 48,086 accessions. Specimens originated throughout Ohio and appeared to correlate with the population of each area. Accessions displayed an obvious and predictable day-of-week effect (Figure 1) with Sundays, Mondays, and days following holidays representing days with the lowest volume. Species represented by the accessions included canine (70.1%), feline (25.6%), and equine (2.1%).

An important consideration for the designers of any syndromic surveillance system is the timely availability of data [6], [30]. Earlier detection being the overall goal, the system must receive records, with the appropriate information for analysis, within a period that provides for improved timeliness of detection compared to traditional reporting systems. Excluding the accessions that occurred during the interruption periods (n=10,847), on average, 95% of daily records were received with the next day's dataset (Figure 2). Almost all (99.4%) records were received by the fourth 24-hour period.

3.3 Aberration Detection

The system identified nine alert periods during the study period using the CuSum detection method as previously described. All of the alerts involved canines and/or felines. The number of accessions generating the alerts ranged from eight to 43. No cause could be determined for three of the nine (33.3%) alert periods and two (22.2%) were possibly related to breeding operations that existed in the area (e.g. screening of litters for pathogens). Two (22.2%) others were potentially the result of provider interest. One veterinary practice located in an area where a gastrointestinal alert occurred reported being especially interested in educating clients about the risks from parasite ova. Another provider in an area where an endocrine alert occurred had recently been ordering an increased number of thyroid tests that were unrelated to increases in clinical disease. The remaining two (22.2%) alert periods were linked to verified disease activity in the pet population during the time of the alert.
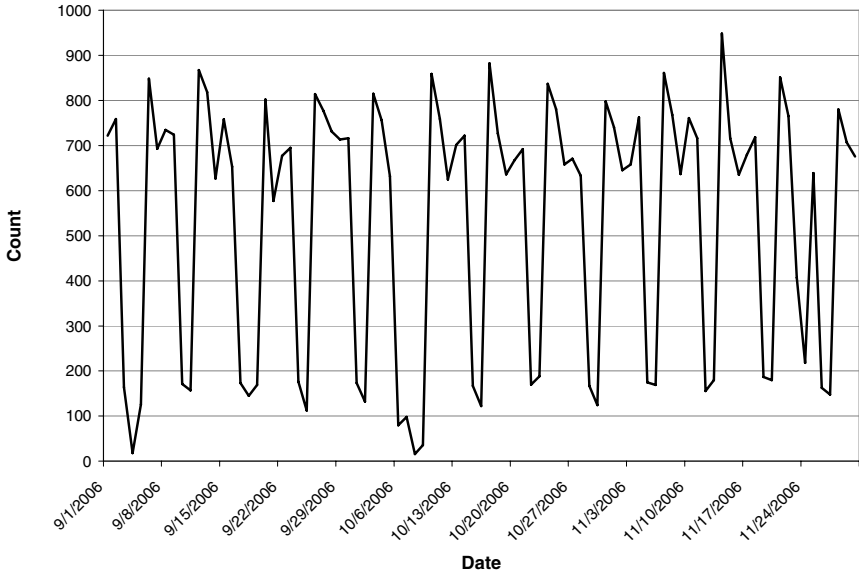
Fig. 1. Counts of specimens received by IDEXX from veterinary clinics in Ohio from September 1 through November 30, 2006

3.4 Case Reviews

On September 11, 2006, the system generated an alert in Preble County located in western Ohio. Cases (20 cats and 2 dogs) were equally distributed between two ZIP codes. Follow-up with area veterinarians confirmed that many small animal practices were treating an increased number of animals that lived or spent a significant amount time out-of-doors for unspecified gastrointestinal distress. Following consultation with the Ohio Department of Natural Resources, veterinarians suspected that the cases may have resulted from corona virus infections acquired from rodents (Melissa Howell, Preble County Health Department, personal communication). An increased number of rodents were noted in the area, coinciding with the harvesting of local grain fields. Veterinarians speculated that pets may have captured and consumed some of the rodents, resulting in the self-limiting intestinal condition. Although health authorities received no reports of human cases, the Real-time Outbreak and Disease Surveillance System used by the Ohio Department of Health indicated significant increases in both gastrointestinal-related chief complaints of emergency department patients and sales of anti-diarrheal medication in these areas during this time (L.S., unpublished data, 2006).

The pilot system generated a gastrointestinal alert for Lake County in northeastern Ohio on September 4, 2006. This alert included test orders for specimens originating from ten cats and three dogs submitted by clinics in two ZIP code areas. A local veterinarian from this county telephoned the State Public Health Veterinarian on
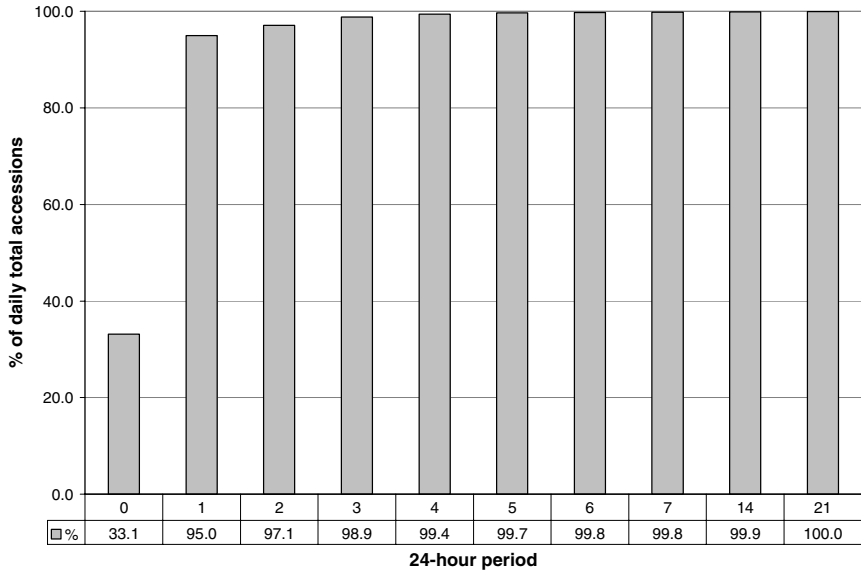
Fig. 2. Delay in receipt of daily records from IDEXX during prospective pilot

September 26, 2006 to inquire about a number of clients that had brought their pets presenting with vomiting and diarrhea (Nancy Niehaus, Lake County Health Department, personal communication). These clients had shared with the local veterinarian that they also were experiencing diarrhea. The Lake County Health Department reported on October 4, 2006 that they were investigating "a cluster of diarrheal illness in humans and their associated pet dogs."

4 Discussion

The primary purpose of this study was to explore the feasibility of using pre-diagnostic data from a VDL in a prospective manner to detect unexpected increases in the number of disease cases that might indicate an outbreak. We evaluated the feasibility by first determining the stability of electronic records and the success of automatically transferring them from the VDL for analysis, measured in terms of the percentage of complete records received in a timely manner. We then considered the representation of the records both by species of animal and geographic distribution. Finally, we investigated the alerts generated by the pilot system to validate if they might be associated with increases of disease.

   While no single data source provides the capability to detect all outbreaks that may occur, veterinary providers may be desirable sources to include in surveillance activities for bettering our capabilities of detecting those outbreaks that result from emerging pathogens and potential bioweapon agents [10], [12], [16], [25], [32]. The change in the number of laboratory orders submitted by veterinary providers may be a valuable proxy to measure the number of individual cases they are treating. An increase in the number of these individual cases may result from an outbreak, detection of which

may be possible through the analysis of aggregated laboratory orders counts from several providers in the outbreak area.

There are inherent biases to consider with using laboratory data. Laboratory testing in veterinary medicine is not as frequently used as in human medicine [31]. Severity of clinical disease and cost benefit are two factors that influence the use of laboratory testing for animals [26]. Severity of clinical disease as an influence on testing may provide for increased specificity since only animals with true disease/condition are included. As demonstrated in this study, the interests of the providers may also contribute to the potential biases encountered. The consistency of the veterinarians' ordering behavior may help to control some bias by recognizing the effects in the counts over time and how they contribute to the normal baseline (i.e. expected number of test orders).

The results of this study demonstrated the stability and timely availability of test order data for companion animals and how those data might be used in a prospective surveillance to detect disease outbreaks. A significant number of daily records were received within the first 24-hour period following their creation. Using pre-existing data, generated by routine workflow, minimizes any additional burden for providers. Employing an automated data transfer protocol further reduces burden and is an essential benefit to support a sustained surveillance effort [16], [17], [31]. This system also achieved the benefit of obtaining provider-level data from a wide geographic area through a single source, creating no additional work for the veterinary providers and minimal work to establish and maintain the automated transfer mechanism for records from the VDL.

The results from this study also indicated that increases in the number of test orders submitted by veterinarians can be detected in a timely manner using prospective analysis. The development of the syndrome categories and the detection method used most likely influenced the alerts generated by this pilot system. We described two alerts that linked unexpected increases in test orders to increased incidence of disease. One of these alerts may also have provided warning of human cases of disease. The number of true and verifiable outbreaks of disease that occur limits determining the performance of an outbreak detection system [18], [29]. We lacked such a gold standard in this study. Therefore, we considered attempting any estimates of sensitivity, specificity, or positive predictive value to be inappropriate. Additional investigation, following refinement of the syndrome categories, might be beneficial for better evaluating the potential of such a system to detect outbreaks of disease.

The results support the continued consideration of VDL data by demonstrating the quality of data available, the ability to transfer and analyze the data in a timely manner, and the potential for detecting real disease events in the surveillance population. The true measure of a surveillance system lies in its usefulness [7]. Additional benefits from this method of surveillance may exist that contribute intangible value to the system [4], [8]. Previous studies found that regular reports of conditions were considered beneficial by data providers [3], [23]. While prospective analysis of orders includes methods designed to detect aberrant increases, reports of area syndromic trends may be valuable to veterinarians when treating individual animals as part of their practice. The addition of test results might also provide reports beneficial for veterinarians while potentially improving the specificity of outbreak detection. Input from all potential end users should be considered when further developing the utility of this type of surveillance system to ensure its maximum benefit.

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