Global Foot-and-Mouth Disease Surveillance using BioPortal

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Abstract. The paper presents a description of the FMD BioPortal biosurveillance system (http://fmd.ucdavis.edu/bioportal/) that is currently operating to capture, analyze, and disseminate global data on foot-and-mouth (FMD) disease. The FMD BioPortal makes available to users world-wide FMD-related data from the Institute for Animal Health at Pirbright, England. The system's tools include those for tabulating and graphing data, performing spatio-temporal cluster analysis of outbreak cases of FMD, and analyzing genomic changes in FMD viruses. The FMD BioPortal also includes the FMD News (http://fmd.ucdavis.edu/index.php?id=1), which is a near real time web search to identify and capture FMD-related news items appearing worldwide. Major systems components include a communication backbone for secure, real-time data transfer, a data analysis module that can run analytical programs to assess spatial-temporal clustering, and an interactive visualization tool for integrated analysis and display of epidemiological and genomic data.

Key words: Foot-and-mouth disease, BioPortal, surveillance

1 Introduction

Foot-and-mouth disease (FMD) is a highly contagious disease that imposes severe and far-reaching economic consequences for countries that acquire the disease. The disease is caused by the FMD virus (FMDV), which is considered to be one of the most infectious disease agents known for cloven-hoofed mammals. Major economic and social impacts of the disease occur world wide as a result of inefficient animal production and restrictions on trade, which can manifest in limiting national development and socio-economic growth. The disease is spread by transmission of exhaled or excreted virus through direct physical contact between animals, such as cattle, pigs, sheep, and goats, and by indirect contact with fomites containing infectious virus, such as contaminated vehicles, feed, or clothing of livestock personnel. As a consequence, increased contact among animals, such as would occur at markets or following transportation of animals to

new areas, increases the rate of transmission. Disease spread in endemic regions of the world tends to follow animal and human movement patterns, where the rate of new outbreaks can be expected to increase at times of increased transportation or movement of animals or animal products. Programs for control and prevention of FMD generally apply strategies of diagnostic screening, vaccination, movement restriction, quarantine, and the killing of infected and in-contact animals.

There are a number of disparate factors, however, that can influence the extent to which a country is able to control or eradicate FMD. These factors include technical problems with vaccine efficacy and with diagnostic test accuracy, the absence of political will or economic capacity to provide critical animal health infrastructures necessary to control disease, the geographic proximity of FMD in neighboring countries, and religious and cultural practices and philosophies that prevent application of certain animal control measures. In addition, the nature and biology of the virus imposes other constraints to control. FMD viruses are immunologically diverse, with seven distinct serotypes (A, O, C, SAT1, SAT2, SAT3, Asia1), which can make diagnosis and vaccination problematic. The high mutation rate and massive replication of the virus in infected animals contribute to the extensive genetic diversity of the virus throughout the world. Such diversity can be an impediment to control and eradication of the disease because vaccine strains can become less effective, or ineffective, against newly emerging field strains and because new strains may evade detection if mutations occur at sites of the genome being targeted by diagnostic assays.

A problem faced by all countries, regardless of their FMD status, is that in order for them to be able to prevent or control FMD, they require an awareness and information about the global situation of FMD. Such information would address such questions as where can we expect to find FMD today, and where will it likely be this time next year; what are the conditions necessary for FMD to move from one country to another; what are the new or emerging strains of virus that might not be protected by current vaccine strains or that might not be detected by current PCR assays; what changes have taken place in the projected risk of our country acquiring FMD; what countries or regions should be targeted for additional resources in efforts to stave off predicted new outbreaks and spread.

Increasingly, there is a recognized need for countries and agencies to have situational awareness for FMD and to be able to anticipate new incursions of FMD, of new FMD viruses, or new or elevated risks of FMD so that appropriate measures can be taken in advance to prevent or mitigate disease and its impact. One of the strategies for early detection of and response to FMD is that of surveillance, both at a national and at a global level, that would aim to seek out specific information about FMD, risks of FMD, and the FMD virus that is needed by the international community and by individual countries in planning and preparing FMD programs. A fundamental element of a surveillance system is how well the system can provide information rapidly in order to allow necessary planning and preparation to begin immediately. Thus, it will be critical that a

surveillance system route information and analysis of data in real time in order for timely changes in programs to prevent and control FMD.

Although there has been considerable discussion about the needs and prospects for a global surveillance system for foot-and-mouth disease, little in the way of formal action has taken place to create such a system. In this report we describe a new system, referred to as the FMD BioPortal, which is currently operational and aimed at providing real time information, analysis, and visualization of FMD data. We describe new developments in the FMD BioPortal, including key features, its IT design and functionality, and thoughts on future needs for real time surveillance and use of the BioPortal. We also offer some concepts, definitions, and considerations for global FMD surveillance function and operation, which hopefully will encourage advancement of surveillance research and initiation of political will and dialogue necessary to move forward in formalizing international surveillance efforts.

2 Elements and Concepts of Surveillance

2.1 A Working Definition of Surveillance and Other Competing Terms

The definition applied here for surveillance is "an active, ongoing, formal, and systematic process aimed at early detection of a specific disease or agent in a population or at the early prediction of an elevated risk of a population acquiring an infection or disease, with a pre-specified action that would follow detection of the disease, agent, or elevated risk" [1]. A surveillance system can be considered analogous to a diagnostic assay, in which surveillance is applied to a population for the purpose of detecting the targeted agent or disease, if it is truly present (surveillance sensitivity), and of verifying freedom from disease or infection, if it is truly absent (surveillance specificity). The term 'monitoring' is considered here to be a process undertaken to obtain an ongoing assessment of disease trends, and not intended to seek out and find disease. Quite often, programs referred to as surveillance are actually a type of monitoring system. The term 'survey', as used in the context of disease studies, refers to the process followed to identify possible causal factors of disease or to estimate disease prevalence.

2.2 Surveillance System Design and Architecture

Local or regional FMD surveillance design and architecture, particularly that related to sampling schemes, should be directed by the biology and epidemiology underlying FMD in the area, the population dynamics of species susceptible to FMDV infection, and the cultural and social features of the region or country that could influence risk or transmission of infection. The strain-and-host-specific pathogenesis, for example, influences duration of disease transition states, amount of virus shed, severity of clinical signs, and likelihood of transmission to other animals and should be considered in defining sampling schemes.

Herd and flock management and husbandry practices can alter the chances for contact between infectious and susceptible animals and some animal trade networks can, more than others, promote spread of FMD to other regions or countries. Cultural or religious practices and events that involve animals also can affect transmission of the virus by bringing together infected and susceptible animals. Surveillance sampling schemes will need to vary depending on the likely location and timing of infected animals, in which high risk animals may be targeted for aggressive, frequent sampling. The design of local or regional surveillance, therefore, should take into account the biology of prevailing serotypes in the host species, as well as the cultural and husbandry practices that will affect changing geographical and temporal distributions of infected animals. Design of a global system also should consider all local, regional, and country-specific systems in a way that would interconnect and support one another, and that would identify in real time the FMD distributions and risk prevailing in the world.

2.3 Surveillance Strategies

We will not discuss the numerous surveillance strategies envisioned for various surveillance objectives, suffice it to say that depending on a country's needs and resources and on the epidemiology of FMD in the region, surveillance objectives and operation would be expected to differ for each country. One possible approach to a global FMD surveillance system could involve a network of surveillance systems, whereby local or regional systems would be nested within a country or sub-continental system, which in turn would be nested within a global framework. The framework would provide the connectivity among the various layers of surveillance; the type or nature of surveillance for each subsystem would depend on whether FMD is epidemic or endemic, or if the area is considered free without vaccination or free with vaccination. An overarching network connecting subsystems would necessarily have to be able to communicate among the dissimilar aspects of each system, including disparate data and reporting formats, different assays and language, and unique aspects of other international animal health agencies, such as those for the Office International des Epizooties (OIE) and the Food and Agriculture Organization (FAO). Thus, design of a global system will need to address methodologies for standardization and translation in order to maximize communication compatibility with previously existing programs and systems.

For many countries that lack adequate infrastructure to detect FMD, let alone develop a surveillance system, international agencies could use surveillance of correlated surrogates for FMD or FMD risk as a proxy for actual disease surveillance. For countries that do not report FMD, but that are known to have the disease, some predictors of FMD presence can include political will and voice and economic capacity [3]. Other information, including OIE data and expert opinion, can be applied in prediction models to obtain estimates of FMD risk in various regions and countries, particularly those where no diagnostic or reporting systems exist [Rebecca Garabed, unpublished data].

Surveillance strategies also will need flexibility to address new or expanded (or diminished) risks and to maximize efficient and effective allocation of resources. A system that is designed to accommodate a hierarchy of surveillance intensities will permit ramping up or damping down sampling number or frequency, depending on assessment of risk [2]. Thus, surveillance activities and relative allocation of resources should be guided by ongoing risk projections to modify surveillance activities at specific times and geographic locations.

A critical strategic element in a global surveillance system will be real-time information transfer among the various operational groups, including laboratories, field units, and policy and decision makers. Web-based information systems will need to exist and applied in ways that permit easy electronic access to and retrieval of data, information, maps, models, and analyses. The real-time sharing of information will be key to connecting and communicating with operational units, as well as to the early recognition and understanding of emerging risks or changes in the global FMD picture.

2.4 The FMD BioPortal

The FMD BioPortal was developed as a collaborative effort of the Institute for Animal Health (the FMD World Reference Laboratory) at Pirbright, England, the Artificial Intelligence Laboratory at the University of Arizona, and the FMD Laboratory at the University of California, Davis. Version 1.0 was made operational in January, 2007 (see: `http://fmd.ucdavis.edu/bioportal/`). The initial goal was to create a web-based system that would make FMD-related data that is banked at the Pirbright laboratory available to the public and to those at the laboratory. A primary objective was to be able to apply to the data basic search and analytic tools, including graphic and tabular presentation of the data and cluster analysis, and to be able to download selected records. The data represent cases or outbreaks of FMD for which samples have been submitted to the laboratory in Pirbright since 1957. Generally, sample submissions to the laboratory have been from some OIE-member countries with ongoing programs to control and eradicate FMD. Data available include the outbreak location and time of onset, information about the host or host species, and the serotype of the virus involved in the outbreak. Data are pushed from the Pirbright laboratory to the FMD Lab at UC Davis, and generally the data are 3 months delayed to provide countries sufficient time to address changes in their FMD programs before the data are made available to the public. Version 2.0, which is planned for May 2007, will include two main additions: 1) access to aligned FMD virus sequence data available publicly from `GenBank` and to tools for real-time development and comparison of phylogenetic trees of virus isolates and 2) historic and current OIE FMD data and tools for graphics and analysis and for downloading the data. The OIE data cannot currently be accessed electronically.

2.5 FMD News

The FMD News is a real time web search service provided by the FMD Lab to identify and capture FMD-related news items appearing worldwide and to direct the information to those interested in global FMD events, directly via email or via the BioPortal. FMD News items represent both official news releases, such as from OIE or governments, and unofficial opinions, commentary, or reports by individuals or the press (see: `http://fmd.ucdavis.edu/index.php?id=1`). The FMD News offers an opportunity to obtain a global situational awareness of FMD using 'soft' information, as well as some official information. Incorporation of FMD News items into the BioPortal allows tracking, mapping, and management of the information for regions or countries or of specific topics, such as vaccination, trade embargoes, or specific control campaigns.

2.6 FMD BioPortal Design

The FMD BioPortal system was developed onto the previously existing BioPortal platform (see `http://www.bioportal.org`), which is a general purpose infectious disease information sharing, analysis, and visualization environment [5]. The system architecture of FMD BioPortal is shown in Figure 1. The major systems components of the FMD BioPortal are 1) a communication backbone for secure, real-time data transfer, 2) a data analysis module that can run several analytical programs to assess spatial-temporal clustering (hotspot analysis), and 3) an interactive visualization tool that allows for integrated analysis and display of epidemiological and genomic sequence data.

The communication infrastructure consists of several messaging adaptors that can be customized to interoperate with various messaging systems. Participating FMD surveillance data providers can link to the FMD BioPortal data repository *via* the PHINMS and an XML/HL7 compatible network. In addition to standard table-based data aggregation functions (e.g., based on time intervals and regions), BioPortal has spatio-temporal analysis capabilities to detect spatial and temporal clusters of events or disease, as appropriate for use in disease outbreak investigations. Cluster analysis programs are available to support methods for scan statistic analysis, for risk-adjusted nearest neighbor hierarchical clustering (RNNH), for risk-adjusted support vector clustering (RSVC), and for prospective support vector clustering (PSVC) [4, 6, 7]

The BioPortal platform has a general-purpose visualization environment, referred to as the Spatial-Temporal Visualizer (STV), which allows users to explore spatial and temporal patterns, based on an integrated tool set consisting of a `GIS` view, a timeline tool, and a periodic pattern tool [5]. The `GIS` view displays cases and sightings on a map and the user can select multiple datasets for viewing in different layers, using the checkboxes (e.g., disease cases, natural land features, and land-use elements). Periodic or cyclical temporal patterns of disease also can be viewed. All the functionalities of STV are available through FMD BioPortal to analyze FMD-related epidemiological datasets.

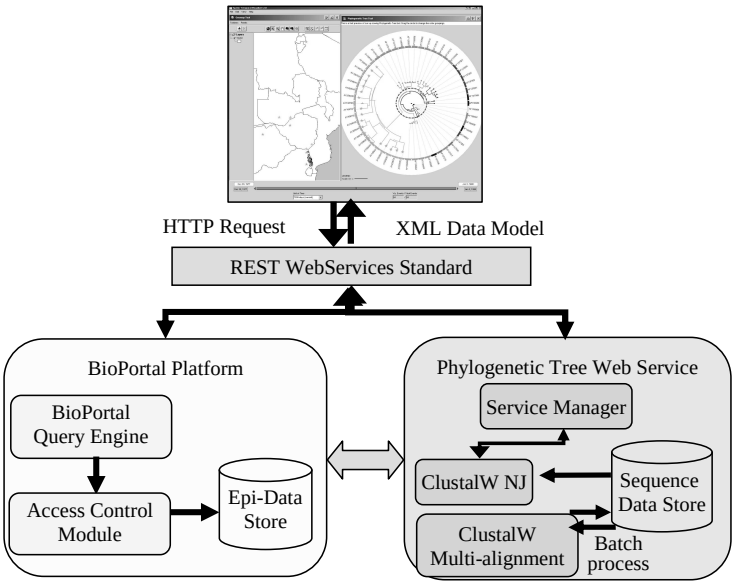

Fig. 1. FMD BioPortal system architecture based on Web Services.

In a new version, FMD BioPortal has applied the STV tool to analysis of virus gene sequence data that have been integrated with epidemiological data, such as time, place, host species, and serotype. The program allows for adjustment of the threshold genetic distance between any two isolates, as chosen by the user, to assess genetic relatedness among FMD virus strains, using a rotary phylogenetic tree display created using the neighbor-joining method. Gene sequence alignment necessary for phylogenetic tree computations is performed using open-source implementations through a web service architecture. This flexible plug-and-play `IT` architecture enables reuse of tools and leverages use of existing analysis and visualization toolsets.

2.7 Future Display and Analysis Tools

Currently the data captured and displayed by the FMD BioPortal do not represent true surveillance data in the sense that, for the most part, they were not obtained through a formal process to seek out and find the disease. Rather, the data come about as the result of investigations of known or highly suspicious cases of FMD and represent reports of cases submitted by countries with programs to control and monitor the disease. Even though these data may not represent ideal surveillance data, they do lend themselves to scrutiny and analysis that may render some insight into risk or projected risk.

Several tools are being developed or considered for inclusion in the BioPortal that will enhance the ability to detect unusual or unexpected events and to project macro changes in global risk [8–12]. Some of these tools include:

a. Various anomaly detection methods to identify outlier events or cases of FMD, using rule-based anomaly detection, which is under control of the user, and using model-based anomaly detection methods. The latter include various time series and temporal and spatio-temporal models to detect anomalous events or an unpredicted excess (or absence) of disease for a defined area, host, or time period.
b. Prediction models for identification of anomalous or unpredicted genetic variants of the virus that would not be predicted by the evolutionary history for a region and that that might represent new incursions or an 'escape' of virus from another region.
c. Molecular epidemiological models to predict severity, duration, and likelihood of transmission of disease based on molecular changes taking place in the virus over the course of an epidemic.
d. Global prediction models to project changes in risk of FMD in defined geographic grids based on changes in regional economics, trade, and political stability.
e. Models that estimate efficacy of vaccination, using genomic and immunologic information for field strains and for competing vaccine strains.
f. Models that project spread of FMD in a defined region under various control strategies and that can be used in developing disease control programs.
g. Models for surveillance sampling that identify optimal combination of sampling size, frequency, and targeting to maximize the probability of detecting FMD, given the available resources.

2.8 Prospects for International Partnerships for Global FMD BioPortal

Prospects would appear favorable for international collaboration and networking to address global sharing and surveillance for FMD. Creation of a global FMD surveillance network of countries and agencies will require long-term vision, political will, and strong leadership on the part of the U.S. and other countries to provide the best possible program for 1) early diagnosis of FMD and FMD risk, 2) identification of molecular changes in the virus and epidemiological changes in the disease, 3) projection of changes in global risk of FMD, 4) sharing of information, and 5) advancement of the science. Success will be contingent on removing barriers that currently exist for sharing the information needed to achieve common goals for controlling and eradicating FMD globally.

In recognizing that a primary objective in global surveillance will be the real time dissemination and analysis of data for the purpose of making timely decisions, careful attention will need to be given to the operational structure developed for global surveillance through the BioPortal or other web systems. Ideally, the operational organizations should be

a. dedicated primarily to providing rapid and efficient service in disease surveillance to users.
b. efficient, with minimal administrative overhead.
c. able to provide information and analyses in real-time *via* the web.
d. willing and able to foster new develop and to embrace new thinking, ideas, and initiatives.
e. open and unrestricted in that no one group can control the information, and thus can control the science.
f. able to support sustained research and development necessary to improve surveillance and efficiency of operations.

Numerous issues have been raised in discussions about developing a global FMD information system that would share and analyze data through the BioPortal, or any other web-based system. Many of these unresolved issues represent roadblocks to progress in moving forward to achieve global surveillance. Some of questions raised include:

a. Who owns the system?
b. Who owns the data?
c. Who is responsible for data integrity?
d. Who controls the data?
e. Who is responsible for maintenance and further development?
f. What agreements are necessary for data sharing?
g. Who should pay?
h. Who should administer and operate the system?

These informal discussions have revealed general agreement that a system such as the BioPortal would greatly enhance efforts globally to reduce risks of FMD and that the current operational FMD BioPortal illustrates technological barriers to development of a real time information sharing system no longer exist. However, these same discussions reveal considerable inertia yet to be overcome internationally in agreeing on how to proceed. Reasons for some of the inaction relate to wariness as to how such a system would serve special geo-political groups. For example, an EU-centric system might encourage a system that specifically addresses the critical threats the European countries face by their close proximity to FMD; whereas, such as system might not necessarily accommodate needs of countries in Southeast Asia. International agencies, such as the OIE or the FAO, may view an FMD surveillance system as falling under their own individual purview. On the other hand, the World Reference Laboratory for FMD at Pirbright has indicated an interest in directing global animal health surveillance in releasing plans develop the `ReLAIS` web-based system. Hopefully, U.S. agencies that would want to have global FMD awareness would become more engaged in these discussions.

Now that the FMD BioPortal has moved beyond proof of principle and is operational on some scale, it is time to move forward with long-term planning and development for this system on a multilateral and international level. As a next step in creation of a global network and system for FMD, including

the FMD BioPortal, it will be necessary to develop a roadmap for coordinated actions and planning. The following are suggested topics for consideration in developing such a roadmap, perhaps by a consortium of interested international partners and players:

a. Obtain views on global surveillance from the global FMD community.
b. Identify technical issues remaining for data sharing.
c. Identify political barriers for information sharing and possible solutions.
d. Obtain funding for research and development.
e. Encourage and engage stakeholders in development of a global system.
f. Design operational structure for data sharing.
g. Promote participation in the system.

In summary, there are many aspects and issues of global FMD surveillance that were not addressed here and that deserve the benefit of broad debate and discussion. Careful consideration will need to be given at various international levels, which hopefully will include the U.S., for further development of the FMD BioPortal, its tools, and linkages with other Web-based systems that will be necessary to address the needs for research and for prevention, control, and eradication of the disease globally.

The development of the FMD BioPortal represents a critical first step toward realizing a goal of global infectious disease surveillance and in recognizing that global surveillance will not be possible without a system for international real time information sharing about FMD.

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