Summary

The goal of this project is to understand the epidemiology of infectious diseases in the ecological context of networks of host movements. Specifically, the goal is to understand transmission and maintenance of Foot and Mouth Disease Viruses (FMDV) in networks of livestock movements in the Far North Region of Cameroon. Because FMD is endemic and vaccinations are not used, the region provides an unprecedented opportunity to examine how different networks of livestock movements affect disease epidemiology. In addition, fundamental questions about the nature of the FMD virus (FMDV) can be examined in this natural laboratory. Data on disease incidence and prevalence will be collected for four years in overlapping networks of livestock movement including daily foraging, annual transhumance, regional markets, and transboundary trade. The data will be used to develop coupled models including a Susceptible-Infected-Recovered (SIR) model of infections within herds, an Agent-Based Model (ABM) of movement and connectivity between herds within and across networks, and molecular modeling to provide additional data and to validate the other models.

Intellectual merit. These models will improve on former models' ability to capture extensive host movement, simulate epidemiology of a pathogen that varies over time, and incorporate newly observed data. An interdisciplinary approach using molecular, spatial, ethnographic, and epidemiological data sets will be ideal to develop and validate these coupled models of livestock movements and disease transmission. The project will use FMD in the Chad Basin for model development, but the resulting models could be used to understand and predict the transmission patterns of infectious diseases in other contexts in which hosts move in overlapping networks.

In addition, this study will examine a number of fundamental questions about the nature of FMDV, including evolution of the virus when subject to varying degrees of natural immunity, characteristics of the virus in carrier animals, and roles of carriers and imported hosts in maintenance of transmission. Because FMDV is a typical RNA virus, information gleaned from this project might be applied to other RNA viruses such as the causative agents of the common cold and hand-foot-and-mouth disease.

Broader impacts. The main goal is to develop coupled models of epidemiology of infectious diseases in the ecological context of networks of host movements. The models will be extremely useful for researchers who study other infectious diseases with networks of host movements, for example, diseases in pastoral systems elsewhere in the world; avian flu and the interaction among migratory and non-migratory birds; and spread of HIV along trucker routes in Africa. These disease ecologies involve mobile hosts and require the integration of spatial, epidemiological, and evolutionary models.

A web-based database and model will be developed that can be manipulated and managed by veterinary and human health services in Cameroon and other nations in the Chad Basin to monitor disease and explore possible interventions for many diseases. The project will also include training Cameroonian veterinary students and researchers in the use of the model and in epidemiology and modeling in general. In addition, local herders will be trained to assist in data collection and surveillance of disease outbreaks using a cell-phone reporting system. The combination of local surveillance system that is embedded in the pastoral system and a regional monitoring system that can analyze epidemiological trends, can improve disease interventions.

Introduction and Significance

Due to the limited ability of researchers to experiment with transmission of infectious diseases in large, naturally occurring populations, *in silico* models of infectious diseases provide powerful tools to understand the mechanisms behind disease spread and maintenance of infections in populations. In addition, models are essential for predicting the outcomes of possible interventions intended to halt disease spread.

The goal of our project is to understand the epidemiology of infectious diseases in the ecological context of networks of host movements. Specifically, we want to know how livestock movements affect the epidemiology of Foot-and-Mouth Disease (FMD) in the Chad Basin and how the FMD virus (FMDV) behaves in this endemic setting. We will develop a coupled model to understand the epidemiology and test possible interventions that will reduce disease transmission without limiting the mobility of livestock, which is critical to sustainable development of pastoral systems.

To pursue this line of inquiry, we will develop a new coupled model. Past epidemiological studies, for the most part, have either summarized existing data providing little in the way of prediction or modeled the spread of brief epidemics of diseases in contexts in which hosts were stationary; though, individuals moved between herds (Bates 2003; Ferguson 2001; Green 2006; Keeling 2001). However, in African pastoral systems entire herds of livestock move seasonally in search of forage and water, and livestock move between markets within and across nations. These livestock movements in pastoral and trade systems, within and across national boundaries have implications for the spread and control of infectious diseases. In addition, disease transmission models have generally treated pathogens as consistent entities (Anderson 1991), though they are known to evolve over time.

We propose to develop linked spatial, epidemiological, and evolutionary models to understand these dynamic systems. We will use an interdisciplinary approach collecting linked molecular, spatial, ethnographic, and epidemiological data sets to develop and validate these models. Our project will focus on FMDV and livestock movements in the Chad Basin, but the model will be used to predict the transmission patterns of other diseases with similar spatio-temporal host dynamics and could be applied to other settings. We focus on FMD because multiple serotypes are endemic in the Chad Basin, FMD is not targeted in vaccination campaigns, and the disease is not treated or avoided by pastoralists; providing a natural laboratory in which we can examine how livestock mobility affects the transmission and evolution of infectious diseases.

Background

FMD is a viral infection of even-toed ungulates and is one of the most popular diseases in the literature on animal disease modeling. This is likely due to the availability of data from experimental studies (Eble 2006) and brief epidemics (DEFRA 2001) for model fitting, the high transmissibility of the virus (Alexandersen 2003), and the interest of countries with available funding for research in controlling outbreaks (Kitching 2004). However, due to the available data and funding, nearly all models of FMD simulate brief epidemics and control strategies in naïve populations with fixed herd locations and exposure from movements of subsets of herds, fomites, and airborne virus (Bates 2003; Ferguson 2001; Green 2006; Keeling 2001). An exception to this trend in modeling would be the studies by several groups modeling infections in wildlife in Australia who allowed their models of epidemics to proceed to an endemic state (Dexter 2003; Doran & Laffan 2005; Fleming 2006). Though these studies looked at free-roaming animal populations, these models still only generally

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modeled contact between "herds" in the environment (Dexter 2003; Doran & Laffan 2005; Fleming 2006). Even in the modeling of other diseases, like influenza (which is endemic in human and bird populations across the world), researchers model the epidemic situation rather than the underlying endemic problem (Ferguson 2005).

While epidemics of FMD in developed countries are important and costly (Serecon 2002; Ekboir 1999), the true problem with FMD (as with many other infectious diseases) is the endemic reservoir of disease. Epidemics of FMD in developed nations are caused by occasional long-distance spread of disease from countries where the disease is common and endemic (Samuel 2001). Controlling the disease in these endemic reservoirs is thought to be essential to preventing epidemics in developed countries and to improving livestock health in endemic regions. A recent study, which used extensive data from Africa, found that FMD was one of the top ten diseases constraining poverty alleviation in developing countries (Perry 2002). While the cost of the disease is believed to be high in developing countries due to loss of meat and milk production, loss of draft power, and opportunity cost for exports due to trade restrictions against countries with FMD, the disease often is not of concern to local livestock producers (Perry 2007; Garabed in preparation). The disease affects livestock species including cattle, buffalo, swine, sheep and goats but the clinical signs of this disease, though recognizable as blisters in the mouth and along the line where the hoof meets the leg, are often not severe (Alexandersen 2003; Kitching 2002).

Bronsvoort et al. (2003, 2004a, 2004b) have studied FMD extensively in the Adamawa Region of Cameroon, which is south of the Chad Basin. They found a prevalence of 58% and that herdsmen reported changing their behaviors to prevent outbreaks of disease in their herds (Bronsvoort 2003). However, these behaviors were not reported in a pilot study in the Far North province of Cameroon though herders reported an FMD prevalence of 68%: 64% in stationary herds (n=11) and 70% in mobile herds (n=27) (Garabed in preparation). Several herders reported that they liked to have FMD in their herds because, after recovery, cows that had had FMD seemed to produce better than other cows (Garabed in preparation). It is unclear whether this view is true or if it is based improved immunity to future infections, misdiagnosis of sub-clinical infections, or unobserved production losses. However, the view that FMD has either no effect or a beneficial effect on cattle would bolster the argument that no control efforts are practiced in this setting. The lack of interventions for FMD control, the likely presence of at least three circulating serotypes (A, SAT 2, and O) of FMDV (Bronsvoort 2004b), and the high prevalence of the disease make this an ideal setting to study how FMDV behaves in an endemic setting.

In the absence of prediction models to provide justification for one control strategy over another, conventional wisdom has driven disease control efforts in developing countries. This conventional wisdom, based on centuries of FMD control efforts in (now) developed countries (Blancou 2002), has suggested that livestock should be settled in confined areas to prevent contact between infected and susceptible animals (Vosloo 2002). Though this strategy has been somewhat successful in South Africa, Namibia and Botswana (Vosloo 2002), it has not proved to be sustainable in the face of changing political, economic and environmental conditions (Letshwenyo personal communication 2007).

Moreover, in mobile pastoral systems, in which herd animals have economic and cultural importance, the transhumance or seasonal movement of livestock is a critical environmental adaptation. Studies conducted within the paradigm of new rangeland ecology have shown that grazing ecosystems are much more complex and dynamic than was previously assumed and that opportunistic grazing strategies that closely track resources are highly appropriate and effective ways to cope with the variable, unpredictable, and heterogeneous environments of Africa's drylands (Behnke 1993; Ellis & Swift 1988; Oba 2000; Sullivan & Rode 2002). This means that the mobility patterns of African pastoralists are highly sustainable adaptations that should be supported (Galvin 2009; Niamir-Fuller 1999). Ethnographic studies have shown how pastoralists adaptively change

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their transhumance movements in response to changes in rainfall, forage availability, epidemics and insecurity (McCabe 2004; Stenning 1957). However, how livestock movements in pastoral systems influence the epidemiology of infectious diseases is less clear (Macpherson 1995).
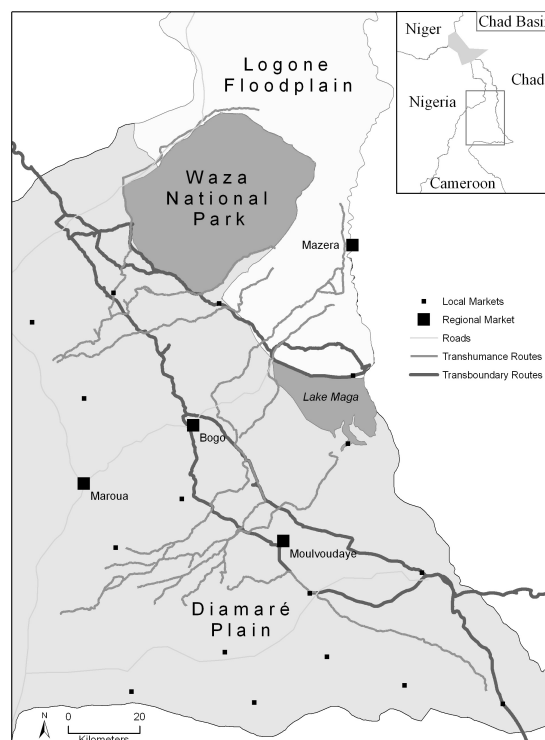
Previous research

Our research project builds on considerable expertise in of the study of pastoral mobility in the Far North Region of Cameroon and FMD modeling.

Moritz has studied different communities of pastoralists in the Far North Region of Cameroon since 1993. One project compared agro-pastoralists, peri-urban pastoralists, and mobile pastoralists (The market and the moral economy of Fulani pastoralists in northern Cameroon, 1999, BCS-9910557) and documented the general patterns in livestock movements between local and regional markets and transboundary trade (Moritz 2003). Moritz has found that mobility continues to be extremely important in pastoral systems that are pursuing more intensive strategies (2008; 2010).

In an ongoing study in collaboration with *Centre d'Appui a la Recherche et au Pastoralism* (CARPA), Moritz is documenting the mobility patterns of FulBe and Arab pastoralists that go on an annual transhumance to the Logone floodplain (CAREER: Pastoral Management of Open Access: The Emergence of a Complex Adaptive System, 2008, BCS-0748594). They have currently collected two years of mobility data for 300 camps incorporating approximately 1,500 households and 150,000 animals (2008-2009). They have used GPS technology to map the transhumance routes that connect rainy and dry season pastures and the transit routes that transboundary traders use to transport cattle from Chad to Nigeria (see Map 1). They have developed a spatial database that includes terrain information and satellite images that can be used to derive land use and cover data.

Map 1: Networks of livestock movements and cattle markets in the Far North region of Cameroon.

Garabed has studied the factors relating to global FMD presence and evolution since 2003. An initial study focusing on trade status designations used Bayesian statistical models to explore the political and economic factors associated with persistence or absence of FMD in 210 countries (Garabed 2008a). Additional studies then explored the risks associated with disease occurrence at a sub-national level (Garabed 2008b) and with variation in the FMDV genome (Garabed 2009).

We have recently begun an extension of this work in studying pastoral systems and global statistical modeling with funding from two internal grant competitions at The Ohio State University (the Public health Preparedness for Infectious Diseases and Initiative in Population Research Targeted Investments in Excellence). This funding allowed Garabed to spend over a month in the Far North of Cameroon working with a team from CARPA to interview pastoralists concerning cattle and human diseases and cattle management practices (Garabed in preparation). In addition, the team collected biological samples from cattle for Brucella and FMD serology and microscopy to diagnose trypanosomiasis (Garabed in preparation).

This proposed work is a logical combination of ethnographic and movement modeling (Moritz), molecular and statistical modeling (Garabed), and field sampling of disease occurrence (Garabed). To complete this team, Xiao brings extensive experience in network and spatial modeling as well as web-based applications, Liang has both experience modeling environmental effects on disease transmission and modeling of zoonotic diseases (which will be included in the broader impacts of the model), and Pomeroy adds extensive experience in ecological and evolutionary modeling.

Objectives

The goal of our project is to understand the epidemiology of infectious diseases in the ecological context of networks of host movements. Specifically, we aim to understand the transmission and maintenance of FMDV in the different networks of livestock movements in the Far North Region of Cameroon. Because no interventions for FMD are practiced, multiple FMD serotypes circulate, and multiple mobile networks of pastoralists overlap in this region we are able to collect and analyze data from an ideal natural experiment, which will allow us to understand the dynamics of viral pathogens like FMDV in an endemic setting. We will examine four hypotheses that may explain the maintenance of FMD in the Far North Region of Cameroon and expect that gained knowledge will inform targets for intervention. These hypotheses are not mutually exclusive and all three processes may contribute to the transmission and maintenance of FMDV in local herds. In addition we will examine whether pastoralists' perception of FMD as non-threatening disease is accurate, since their perceptions and management decisions play a major role in the transmission and maintenance of FMDV in the Chad Basin.

H1: New introductions of virus from transboundary trade cattle initiate repeated epidemics of disease in the local herds. Transboundary trade of cattle in Africa has been held responsible for the dissemination of new strains of FMD from Somalia into Cameroon (Fèvre 2006). In the Chad Basin, FMD may be self-limiting in local cattle populations and observed clinical disease may be due to regular epidemics of strains carried by cattle in the transboundary trade network.

H2: Genetic drift of the virus in carrier animals in local herds is sufficient to overcome natural immunity periodically producing renewed clinical disease. FMDV has been show in some cases to produce a persistent carrier state in cattle in which the virus continues to survive for up to 3.5 years and possibly results in continued infectiousness (Alexandersen 2002). The virus continues to reproduce in this state and FMD (like other RNA viruses) has been shown to be highly variable (Alexanderson 2002; Cottam 2009). Thus, small mutations over time in carrier animals could produce genetic drift in the overall profile of the viruses infecting the animal. If these new viruses were sufficiently different from prior circulating strains, the natural immunity of the carrier's herdmates might not protect them from infection with the new "home grown" strain and clinical disease might be observed in the herd.

H3: Annual transhumance provides new exposure of recovered herds to old viral strains which, coinciding with waning maternal immunity result in clinical disease. After an outbreak of FMD, cattle generally develop immunity to the strain with which they were infected and to closely related strains (Doel 1999). Calves born to previously infected dams also become immune to the virus for a short time due to FMDV antibodies passed in the dam's first milk (called colostrum) (Kitching 2002). Though this maternal immunity will protect calves for a brief period of time, it wanes to the point of providing little to no protection after 3 months of age (Kitching 2002; Doel 1999). In the Far North Region, calves are generally born at the start of the rainy season (approximately June-July)

and would, thus, be immune until September or October. Transhumance generally begins at this time with animals congregating in the dry-season pastures of the floodplain in November through January. With the congregation of animals in the floodplain coinciding with waning immunity in calves, annual outbreaks of clinical disease may be confined to these immunologically naïve animals.

H4: There is a measurable economic advantage provided by FMD in terms of cattle production and reproduction. In interviews with pastoralists in the Far North Region of Cameroon we have consistently found that they do not consider FMD a major threat to animal production. This is contrary to what other researchers have found among African pastoralists (Rufael 2008) and warrants a systematic investigation. We can think of several possible explanations for this phenomenon. Cattle infected with FMD in one season may be immune to later infections and, thus, produce better than their non-infected counterparts. This was the principle behind the practice of exposing herds to infected material (aphtisation) to "get the disease over with" (Blancou 2002). An other explanation might be that the cattle raised in this region are adapted to the virus and at least show no lasting ill effects of disease due to damage of the thyroid and udder as seen in other breeds of cattle (Kitching 2002).

Research Design

In order to test the four hypotheses we will use an interdisciplinary approach that consists of two overlapping and integrated phases: a data collection and a modeling phase. We will collect movement and disease prevalence data in the first four years of our study and start building models after the first year of data collection. In subsequent years we will use the cumulative data to get more accurate parameters and build more realistic models. The main research activities are the following:

    A.   Document the movement of livestock in the different networks.
    B.   Estimate the prevalence of diseases among multiple host species in different networks.
    C.   Measure costs and benefits of FMD for cattle production and reproduction.
    D.   Develop and validate models of disease transmission within herds Susceptible-Infected-Recovered (SIR) and across herds in different networks Agent-Based-Model (ABM).
    E.   Describe the interplay of viral evolution and epidemiological dynamics on the same time scale.
    F.   Couple the three models.

Study Area and Population

The Far North Region of Cameroon, located in the Chad Basin, is an ideal site for modeling livestock movements and disease transmission because the area is a microcosm of multiple and overlapping networks of livestock movements that can be found throughout Africa. The Far North Region is an important pastoral area with large populations and high densities of livestock (FAO 2007). The Cameroonian Ministry of Livestock, Fisheries and Animal Industries (MINEPIA) estimated the number of cattle at 650,000 and sheep and goats at 1,700,000 in the Far North Region in 1991 (Seignobos 2000).

      The types of networks of livestock movements are the following: sedentary agro-pastoral (geographically delineated farms where animals remain within a designated area most of the time), mobile pastoral (geographically unbounded herds of animals that are moved daily and seasonally in search of food and water), local and regional markets (animals being moved in a network of buyers, sellers, and transporters), and transboundary trade (animals that are moved long distances across

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borders for sale). In the Chad Basin, these networks overlap in that livestock share routes, pastures, watering points and markets (Jamin 2003; Magrin 2003).

The spatial and temporal overlaps of these networks take place through the following networks of livestock movements:

1. Annual transhumance of mobile pastoralists between the rainy season pastures in the Diamaré and the dry season pastures of the Logone floodplain (transhumance routes).
2. Weekly transport of transboundary trade cattle from Chad through Cameroon to Nigeria (international trade routes). The number of trade cattle has been estimated at 155,000 annually (Seignobos 2000).
3. Weekly transport of trade cattle between local and regional markets in the Far North Region (regional trade routes).
4. Daily movements of cattle from sedentary and mobile pastoral systems to shared pastures and watering points (areas around villages and mobile camps).

The Far North Region, thus, provides an ideal place to test methods for 1) modeling networks of livestock movements, 2) modeling transmission of foot-and-mouth disease among livestock, 3) exploring the relationships between viral isolates, and 4) identifying cost-effective and minimally disruptive targets for intervention to reduce disease transmission. In each of these networks, herders raise cattle alongside sheep and goats that are susceptible to infection with FMDV and can spread the virus. In addition, a relatively small number of pigs (also susceptible to infection and capable of transmitting the virus) are kept in some villages and have the potential to contaminate pasture, water sources, and fomites such as people's shoes and vehicle tires.

Data Collection and Analysis

Activity A. Document the movements and numbers of livestock in different networks

To document the movements and numbers of livestock in the different networks throughout the year, we use a combination of GPS technologies and surveys.

Mobile pastoralists. We will record mobility data for all mobile pastoralists in the study area for four consecutive years using a combination of transhumance surveys and GPS tracking. In previous studies we have successfully used surveys to record pastoralists' transhumance patterns – pastoralists could recall with ease how many days they had camped on each site in the preceding year (Scholte et al. 2006). We will also collect information about how pastoralists decide to move from one location to another. We are using GPS devices to collect geo-coordinates four times during the year (February, May, August, and November) to check and validate the data from the transhumance surveys. We are currently using GPS technology to map all the campsites and transhumance routes in the study area. Because location of the campsites and transhumance routes are relatively fixed we can analyze the data from the transhumance surveys in ArcGIS (ESRI 2009). We are using vaccination data from the veterinary services to estimate the number of livestock in the different transhumance networks.

Sedentary agro-pastoralists. Using GPS devices we will track the daily herd movements of sedentary agro-pastoralists in three different seasons – rainy (August), cold dry (October), hot dry (March) – to document the herding radius (maximum distance from the village) and document watering points (Moritz in preparation; see also Adriansen 2005; Bassett 2006; Coppolillo 2000). We will select villages that are directly connected to the transhumance and transboundary networks and villages that are indirectly connected through shared pastures and watering points with connected villages.

Regional livestock trade. In collaboration with veterinary services we will document the origin and destination of livestock sold and bought at local livestock markets during one week (markets are held on different days of the week). The veterinary services keep records of all the

animals bought and sold and their destination. We will do this four times a year at all the 25 livestock markets in the study area in order to estimate the number of cattle that moves through this network. In an earlier study we collected data from mobile pastoralists and sedentary agro-pastoralists about the sales and purchases of livestock at regional markets (Moritz 2003), this allows us to estimate the linkages between these pastoral systems and the market systems.

 Transboundary livestock trade. Livestock trade, mainly cattle, from Chad and Sudan travels through the Far North Region of Cameroon to Nigeria following established trade routes, with overnight stops, grazing zones, and watering points. We will be using GPS technology to map all these routes, points and zones. We will use observations (by local villagers along the routes), interviews with herders and traders, and local veterinary services to document the volume of the transboundary livestock trade in the study area.

Activity B. Estimate the prevalence of diseases among multiple host species in different networks

Mobile pastoralists. In previous studies we have found that mobile pastoralists move in one of two transhumance networks to the Logone floodplain: the East network and the West network (see Map 1). Using previously collected data on movement of different pastoralists, we will randomly select fifteen mobile pastoralist herds for biological sampling. We will select five herds from the West network and ten herds from the larger East network. The pastoralists whose herds are selected will be invited to participate in the study. If they decline or are lost to follow-up after the first sampling, the herds will be replaced by another randomly chosen herd.

 For those herds participating in the study, the owner and/or herder will be interviewed extensively to identify all animals in the herd and their disease history, general management, and approximate dates and locations of transhumance in the previous year. The herds will be visited at least twice a year (once during the rainy season and once during the dry season) for four years to provide updates of this information and to collect biological samples to estimate FMD prevalence.

 Three types of biological samples will be taken from each animal: 1) historic exposure to FMD and some information about immunity will be assessed by taking serum samples for ELISA testing (Bronsvoort 2004c), 2) samples of pharyngeal fluid (probang samples) will be collected and tested using virus isolation and PCR to identify animals carrying FMDV (Alexandersen 2002), and 3) samples of epithelial tissue will be taken from animals displaying clinical signs of FMD and they will be tested using virus isolation and PCR (Kitching 2002). All samples will be prepared and frozen as soon after collection as possible — serum will be separated from whole blood using centrifugation and will be frozen at -20 C and tissue and probang samples will be mixed with transport medium and frozen at -80 C. Serum samples will be stored and tested in Cameroon under a collaborative agreement with LANAVET national veterinary laboratory in Garoua, and virus isolation, PCR testing and sequencing will be conducted on tissue and probang samples under a collaborative agreement with USDA-ARS's vesicular diseases laboratory at Plum Island Foreign Animal Disease Laboratory, New York (see supporting documents for letters of support).

 Five animals in each herd will be selected at random during the first visit and these will be sampled at each subsequent visit. All additions to the herd will be sampled in subsequent visits along with the original five animals and any animals identified as carriers will be sampled at every visit after the first identification. Twice during the study period, the entire herd including any small ruminants will be sampled. In addition, any animals with clinical signs of FMD will be sampled when they are identified.

 Some of these animals showing clinical signs of FMD will be identified during regular sampling visits; however, to increase the sampling of incident cases of FMD, we will rely on reports of disease from herders. Each herder enrolled in the study will be given a cellular telephone and an allocation of pre-paid minutes. Research assistants from CARPA (see letter of support in supporting

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documents) in Cameroon will phone these herders regularly to ask about the health of the herd and will ask the herders to phone them if they identify any signs of FMD. Upon notification of clinical signs of FMD in a study herd, the research assistants will go to the location of the herd and take survey data and biological samples from animals showing clinical signs of disease.

Sedentary agro-pastoralists. Using the same sampling protocols as for the mobile pastoralists, we will sample fifteen sedentary pastoralist herds. These herds will be selected randomly: two in Musgum East and two in Musgum West (dry season pastures in the Logone floodplain), two in Pétté and two in Mindif (wet season pastures), two along the transhumance routes to the floodplain from Pétté, two along the routes from Mindif to the floodplain, and three along the international trade routes. In each of the villages where we sample cattle herds, we will also attempt to sample any pigs that are present to determine the contribution of pigs to FMD transmission in the area.

Regional livestock trade. To estimate the exposure of market cattle to FMD, we will sample twelve market herds at each semi-annual visit. Market herds are cattle assembled by a trader for the purposed of sale at regional markets. The market herds are transported between markets through different routes. We will sample three herds each from the largest cattle markets in the region: Mazera, Bogo, Moulvoudaye, and Maroua markets. To document the incidence and prevalence of FMD in the regional livestock trade we will survey incoming and outgoing animals. For example, at the largest livestock market in the Region, Bogo, trade herds from other markets arrive the day before (Wednesday) and newly formed herds leave the day after (Friday) to go to other regional or international markets. This sampling method allows us to estimate the FMD rates of incoming herds, locally sold animals, and outgoing herds.

Transboundary livestock trade. Informants living near stops along transboundary trade routes will be recruited and given cellular telephones so that they can report the presence of trade cattle. When trade cattle arrive at these stops, a research assistant will come and ask permission to take survey information and samples from up to five herds in the group moving through the area. As these tend to be larger herds than those of local pastoralists, ten animals will be sampled in each herd with emphasis on animals that have clinical signs of FMD or have shown signs in the recent past.

Using these methods, we will survey the prevalence and incidence of disease and the circulating viruses associated with different pastoral and trade systems in the Far North Region of Cameroon.

Activity C. Measure costs and benefits of FMD for cattle production and reproduction
To evaluate the claim of pastoralists in the Far North Region that FMD is not a problem and actually may improve the health and production of cattle in subsequent years, we will examine more rigorously the etiological and epidemiological theories about FMD and other similar diseases in this group of herdsmen. If the claim that effects of FMD are neutral or beneficial is found to be consistent, we will quantify the costs or benefits of FMD in herds by conducting progeny history analyses (Mariner 2000) of the herds enrolled in our study and update these histories twice a year during the study period. Using this method, herdsmen will recount the productivity and losses in their herds by tracing the progeny of each member of their herds (Moritz 2003). When these data are compared with the results of biological testing for FMD exposures and reported incidents of clinical FMD, we will be able to estimate the effects of the disease on production and losses. This will allow us to test hypothesis four mentioned above.

Though herders also receive income and sustenance from milk, quantifying losses from reduced milk production is not feasible in this system. Quantities of milk generally are not measured with great accuracy, and the decision of which cows to milk and how much milk to take from each is based on a variety of factors that will not be measured and may confound the data.

Model Building and Coupling

Modeling the ecology and evolution of the FMD in context of networks of host movements will require the linking of three different kinds of models: 1) a Susceptible-Infected-Recovered (SIR) model detailing the dynamics of the disease within livestock herds; 2) an Agent-Based Model (ABM) detailing animal movement and connectivity within and across different networks; and 3) and Evolutionary Models (EMs) to identify origins of FMD strains circulating in Cameroon and to predict future evolution in this system.

We conceptualize the system in Figure 1 that illustrates the networks formed by the main components of our models: pastoralists, traders, cattle, geographic locations, and FMD. To fully capture the epidemiology of FMDV in this system, the models will need to be coupled with each other (activity F). Movement and ethnographic data will be used to produce decision rules for the ABM model to simulate herder movements and connections. For example the movement of the infected herd in place C to place A and its connection to the mobile pastoralists there, in other locations, and to other types of herds. These simulated locations and levels of connectivity will then be included in the SIR model. In addition, data from the prevalence studies and estimates of viral changes from the EMs will be used to estimate transmission parameters and levels of infectivity at given time points in the SIR simulations. The SIR models (with input from the ABM and EMs at each time step) will estimate the number of infected, susceptible, immune, and carrier animals in each herd as well as population dynamics. This would be represented by the final branches (cattle) in Figure 1. Each of the three models can be validated independently, to some extent. Then, the predictions of the coupled AMB and SIR models can be compared with the results of the EM model to validate the modeling.
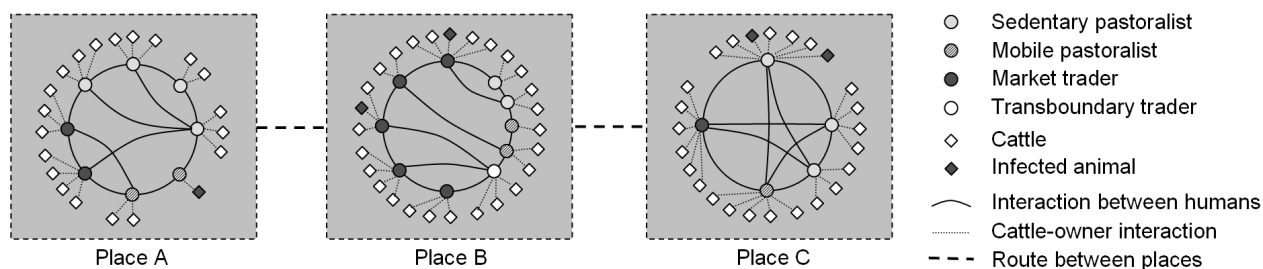

Figure 1: The networks in the proposed models. Here, solid lines represent the relationships between humans (pastoralists and traders), and the thin (dashed) lines show the relationships between cattle and humans. The routes between places are represented as thick dashed lines. The locations of each node in the network are only for illustration purposes. This figure represents the system at a particular time; mobile pastoralists, market and transboundary traders may move to different places (with their cattle) at different time.

Activity D. Develop and validate models of disease transmission within and across livestock networks

Modeling of disease dynamics within herds. To capture the endemicity of FMD in livestock, each cattle herd will be modeled with a stochastic Susceptible-Infected-Recovered (SIR) model, adjusted for the multiple infectious states observed among infected cattle. We have chosen to use a stochastic model to appropriately model the inherent variation in cattle herds and in viral epidemiology as well as to be consistent with a Bayesian estimation procedure. In this model cattle are divided into five categories: those who are susceptible to the virus (S), those who are acutely infected with the virus and show signs of infection (I_1), those who harbor subclinical infections (I_2), long-term infected carriers (I_3), and those who are recovered from the virus (R).

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In Cameroon, three serotypes of FMD are expected to affect cattle: A, O, and SAT 2 (Bronsvoort 2004b). Little or no immunological cross-protection between serotypes means that each serotype will be modeled independently within each herd. Thus, three independent equations will model FMD state within each herd. Let φ be the force of infection, and $\boldsymbol{\beta}$ be a vector of the transmission probabilities between a susceptible individual and an infected individual in the same herd. We hypothesize that virus transmission routes can be categorized into three classes: transmission between livestock within the herd, transmission due to movement of livestock or humans between herds, and environmental pathogen transmission, scaled by the total number of cattle in the herd (N_t) in a frequency-dependent transmission formulation (equation 1).

$$\varphi = \boldsymbol{\beta}\,(I_{herd}+I_{movement}+I_{env})\,/\,N_t\,. \tag{1}$$

First, FMD transmission will depend on the epidemiologic status of cattle as well as sheep and goats associated with the herd. Sheep and goats can contract FMD from sources within the herd or outside the herd and transmit it to cattle within the herd (equation 2). These numbers of infected animals will be estimated based on the data collected from whole herd biological sampling.

$$I_{herd}=I_{cattle}+I_{sheep}+I_{goat}\,. \tag{2}$$

Second, transmission will depend on movement of infected and susceptible individuals with respect to the herd. From the local market, infected cattle, sheep, and goats can enter the herd and transmit FMD infection as local immigrants (equation 3). These additions to the herd will be estimated using herder interviews and biological sampling of immigrants to the herd.

$$I_{movement}=im_{cattle}+im_{sheep}+im_{goat}\,. \tag{3}$$

Lastly, transmission will depend on environmental modes of FMD transmission, including airborne transmission, transmission through fomites, and environmental pathogens encountered on migratory routes to all of which infected pigs may contribute (equation 4). Here the "Is" represent levels of infectivity rather than infected animals. These environmental exposures will depend on the current location of a herd, the previous herds residing in the area, the current area resident herds, and the connectivity among these herds. Models to estimate airborne transmission are already well developed (reviewed in Gloster 2004) and proximity to infected herds in time and space may be estimated from the output of the ABM model. Estimates of exposure due to fomites and contact with other herds via migration, thus, can be made from the output of the ABM.

$$I_{env}=I_{air}+I_{fomite}+I_{migration}\,. \tag{4}$$

The transmission model will be used in an SIR framework, where infected individuals contract the virus as a binomial draw, according the chain-binomial framework,

$$I_{t+1}\sim Bin(S_t,1-e^{-\varphi})\,, \tag{5}$$

thus, leaving the susceptible cattle as those that were originally susceptible less the number that contracted FMD. This will produce estimates of transmission of disease for every herd in the study area.

Acutely and subclinically infected individuals then move into the R category for each herd according to the known FMD generation time, while persistently infected (carrier) individuals remain in the infected category, though their infectiousness may not equal that of clinical carriers.

The overall population will vary over time due to the birth of new animals with waning maternal immunity and the death of animals from all disease states. The model will be initiated at t=0 using data on disease states estimated from the first field sample. These data will then be used to extrapolate predictions beyond the herds enlisted in the biological sample collection.

Although great care will be taken to use the most accurate data, by nature, reporting of data are often imprecise (Legendre 1992). Uncertainty in data comes from two primary sources: observation or measurement error, stemming from inaccurate reporting, and process error, which relates to the inherent natural variation in ecological systems (Harwood & Stokes, 2003; Clark & Bjørnstad, 2004). As a precursor to the full SIR model that describes FMD dynamics, we will use a state-space model that accounts for both observation and process errors. Using the observed data and

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data from literature as priors in a Bayesian framework, we will estimate initial parameters, such as the transmission coefficient (β) and the initial number of susceptible individuals (S_0), and posterior densities for the time course of infection for each affected local population as in Ferrari et al. (2006). Then, we will use the reconstructed time series for susceptible and infected individuals in the SIR model described above. By addressing uncertainty in the data through a Bayesian framework, we will be able to make inferences from data-driven dynamical disease models that more closely resemble the true endemic dynamics.

  Model validation. While some data from the field sampling will be used to create the model, a subset of the data will be reserved to compare with and validate the model predictions. Disease transmission parameters and sources of infection will be estimated from the data using a combination of data summary and phylogenetic source tracking and these numbers will be compared with those predicted by the model. Also, the general prevalence of infection for each serotype for each type of herd will be estimated from the data and from the model each time the data are collected and will be compared statistically to assess model fit.

  Model implementation. The SIR model will initially be implemented in MATLAB (Mathworks 2009). After the model is validated, we will export the MATLAB code into C and C++ that will subsequently be integrated with our agent-based model.

Modeling of animal movement and connectivity. Agent-based models (ABMs) represent a bottom-up approach to understanding the dynamics of a system where heterogeneous players (agents) interact in a networked environment (Epstein & Axtell 1996; Gilbert 2007). In an ABM, an agent represents an actor that plays an important role in the system being modeled. Human agents in this network, for example, often try to maintain a certain level of living standard within social, constraints. ABMs have been adopted widely in a variety of disciplines (Grimm 2005; Billari 2006; Auchincloss & Diez Roux 2008). A recent development in this area includes the specific use of ABMs on complex networks to study spread of diseases (Strogatz 2001; Newman 2002; Eubank 2004; Keeling & Eames 2005).

  In this research, we propose to develop an agent-based model that includes these types of agents: pastoralists (sedentary and mobile), traders (regional and transboundary), and cattle (with owners specified). We will model each of these agents in our model. The ABM runs iteratively where the agents interact with each other in the network (shown as links in Figure 1) in each iteration and may move to other places in the next iteration. An iteration in our model will be equivalent to a day. We believe that a daily temporal scale is sufficient to simulate cattle movements, though we note that it will be possible to model the movement of mobile pastoralists on a scale within a day.

  In the ABM, herds of cattle will interact with other herds through the co-residence of the herd owners (represented as the links between humans in Figure 1) and the movements of the owners and individual cattle. For example, the transboundary trader at Place B may water their animals in the same place where a mobile pastoralist has animals creating an environmental connection. Additionally, we will model the movement of herds from place to place using decision rules based on data collected in ethnographic interviews and environmental data.

  Model validation. We plan to validate the ABM by comparing the simulation results with our observed data (Activity A). This will be conducted by using approximately a half of our observed data to calibrate the model and using another half to validate the model. To demonstrate the robustness of our model performance, we will run a large number of tests using randomly selected observed data. This will help us identify the uncertainty of our model performance given different observed data.

  Implementation. During the past decade, a number of software packages and tools have been developed to help users implemented their agent-based models. Examples of these packages/tools include Repast (http://repast.sourceforge.net/) and NetLogo (http://ccl.northwestern.edu/netlogo/).

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While these tools have proved useful in developing various agent-based models in the literature (see, for example, Inchiosa & Parker, 2002; North 2006), our research will require highly efficient code because the proposed ABM will include a large number of agents and calibration and validation process described above are computationally intensive. We plan to use the high performance computers at Ohio Supercomputer Center (http://www.osc.edu) to expedite the calibration and validation process (see letter of support in supporting documents). For these reasons, we will develop our ABM using the C and C++ programming languages and parallel programming packages such as OpenMP (http://www.openmp.org).

Activity E. Describe the interplay of viral evolution and epidemiological dynamics on the same time scale

Foot and mouth disease is endemic in Cameroon, with outbreaks occurring periodically among the same livestock populations (Ekue 1990). Endemicity can stem from multiple sources, including viral genetic variation, influxes of susceptible individuals, or introduction of novel strains (Medley & Stokes 2009). Since the sources of endemicity within Cameroon are still unknown, we will investigate it in a phylodynamic framework (Grenfell 2004).

For a contemporary analysis, we will create phylogenetic trees of both the VP1 capsid proteins and full genomes, when available, to determine evolutionary relationships of viral isolates collected at the field sites in Cameroon in combination with similarly subtyped isolates collected worldwide and available from the National Center for Biotechnology Information (GenBank). Multiple methods will be used to create evolutionary trees, including maximum likelihood (Felsenstein 1981) and Bayesian (Rannala & Yang 1996), and results will be compared. By correlating data on the country of isolation with the genetic sequence, we can trace the character state evolution throughout the phylogeny, thus determining the country of origin for viruses circulating in Cameroon. If the current circulating sequences have an origin outside of Cameroon, we can investigate international trade and migration sources for novel viruses. We will perform this analysis for each of the three serotypes circulating in Cameroon. If the current circulating sequences have origins within Cameroon, we can investigate viral genetic diversity and as a reason FMD endemicity.

Introduction of novel strains is not the only possible source for the origin of reoccurring epidemics; the native circulating virus may evolve rapidly enough to evade the host immune response and cause individuals who were previously recovered with immunity to become re-susceptible. To determine the genetic variation of virus circulating in Cameroon, we will use the genetic sequences of serial isolates of virus over time to determine the evolutionary characteristics of the virus. Presence or absence of drift can be determined by visually inspecting the trees created by multiple methods for each serotype, while BEAST software (http://beast.bio.ed.ac.uk) can be used to infer substitution rates and the dates of most recent common ancestors as in Pomeroy et al., (2008). Because we will have data on infection status of specific individuals at multiple time points – both within FMD outbreaks and between FMD outbreaks – we can correlate infection status and the ordinal number of infections per individual with genetic drift and the other evolutionary parameters estimated to find correlations between infection and genetic drift. In this way, we can measure if genetic drift relates to host susceptibility. These estimated can be included in the SIR model to simulate re-infections of herds from new strains evolving in carrier animals.

Specifically, we are interested in genetic drift that occurs in carriers, or persistently infected cattle that exhibit little or no clinical signs (Alexandersen 2002). One hypothesis for endemicity is that carriers harbor FMDV over long time periods – during which the virus undergoes genetic drift – and periodically re-infects contacts with genetically diverse strains. Special effort will be made to identify and monitor carriers over time, with periodic viral sampling and phylogenetic analysis.

Evaluating Hypotheses

H1: New introductions of virus from transboundary trade cattle initiate repeated epidemics of disease in the local herds. By adding and removing the exposure of local cattle to transboundary trade cattle from the coupled ABM and SIR models, we will determine whether the trade cattle are important to maintaining disease transmission. In addition, we will use the EMs coupled with epidemiologic data as in Cottam et al. 2008 to discover the probabilities of infection from internal versus external sources and compare this with the coupled transmission models alone. This should estimate the role of transboundary trade in maintenance of endemic disease.

H2: Genetic drift of the virus in carrier animals in local herds is sufficient to overcome natural immunity periodically producing renewed clinical disease. The genetic drift in carrier animals in this setting will be estimated from genetic sequencing of repeated isolates from carrier animals. The isolates from clinical herdmates of carriers will be sequenced and compared to the carrier isolates with EMs to estimate the sources of isolates from clinical animals. This will provide a data-based estimate of the role of genetic drift in maintenance of endemic disease. In addition, a genetic drift that overcomes immunity can be estimated using EMs and then simulated using the coupled ABM and SIR models. Comparing these simulations to observed data will provide an independent assessment of the role of genetic drift in endemicity.

H3: Annual transhumance provides new exposure of recovered herds to old viral strains which, coinciding with waning maternal immunity result in clinical disease. The coupled ABM and SIR models will be able to simulate the variations in annual transhumance and in waning maternal immunity as well as infections in different clinical and carrier animals who might be proximal to susceptible animals. These simulations along with observations of which animals are infected in the herd each year will provide estimates of the role of transhumance and waning immunity in maintaining endemicity in mobile and stationary pastoralist herds.

H4: There is a measurable economic advantage provided by FMD in terms of cattle production and reproduction. The effects of FMD on cattle in this setting will be assessed through collection of health and productivity data and comparison of these measures to the FMD status of the animals. Though this hypothesis is not directly connected to the discovery of the causes of endemicity, finding the economic effects of FMD will be essential to later attempts to control the disease.

Training of students in interdisciplinary research

Studies of disease ecology require an interdisciplinary approach that integrates different kinds of data and multiple levels and methods of analysis. However, the organization of universities by disciplines does not foster the integration of research and teaching in interdisciplinary projects like the ecology of diseases. At the Ohio State University we have organized an interdisciplinary Disease Ecology and Computer Modeling Laboratory (DECML) with weekly meetings of faculty from diverse disciplinary backgrounds (anthropology, biology, geography, public health, and veterinary sciences). We have experienced first-hand the excitement, challenges, and advantages of interdisciplinary research in our laboratory. In our discussions we have to explain and make explicit the different approaches to theory development, data collection and analysis, and other assumptions of our respective disciplines. This has not only improved our knowledge and understanding of each others' fields, but also our own.

The primary educational goal of our project is to infuse students with the excitement of interdisciplinary research by training and educating them to work innovatively, collaboratively, and

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productively in interdisciplinary projects on the ecology of infectious diseases. The training will focus on the integration of theoretical and empirical research, different modeling approaches, and interdisciplinary collaboration.

We plan to support two graduate students per year with different disciplinary backgrounds at the Ohio State University. They will assist with data collection and analysis, ethnographic research, GIS analysis, SIR modeling, ABM modeling, and the evolutionary model. To aid these students in their exploration of international infectious disease research, we will create interdisciplinary courses in research methods and modeling directed towards graduate students interested in modeling infectious disease dynamics and collecting data in developing countries. Courses that members of the DECML are currently developing are: *Modeling Infectious Diseases*, *Public Health in Developing Countries*, and *Participatory Methods in Public Health Research*.

Undergraduate students will also be involved in our study of Livestock Movements and Disease Epidemiology in the Chad Basin. Undergraduate research is well supported by the Ohio State University, but most of it is conducted within the framework of a single discipline; our efforts will focus on undergraduate research within interdisciplinary projects. Students will be trained in all aspects of scientific research, including design, grant writing, IRB review, fieldwork, data analysis, writing, presenting at professional meetings, and communicating with policy makers. This intensive mentoring of students is critical for their professional development as researchers. We are already have successfully mentored undergraduate students who conducted independent research in the Far North Region of Cameroon.

Graduate and undergraduate students will participate in our laboratory (DECML) where we will discuss epistemological, theoretical, methodological, ethical, and practical issues in interdisciplinary research. The lab is a place where we discuss faculty and student work, e.g., grant proposals, research reports, posters, and where "expert" students learn to mentor "novice" students (Lave & Wenger 1991).

We will collaborate with the Veterinary School of the University in Ngaoundére (Cameroon) and support and hire two graduate students each year. The students will design and conduct their own independent research within the framework of our study of Livestock Movements and Disease Epidemiology in Chad Basin and assist in the data collection and analysis. We will also bring these students to OSU for participation in our DECML laboratory and further training in disease epidemiology and modeling. The Ohio State University already has a program in Veterinary Public Health that is designed for Masters of Public Health students and that provides an existing structure for these visiting students from Cameroon.

Broader impact

One of our main goals is to develop an integrated model of epidemiology of infectious diseases in the ecological context of networks of host movements. The model will be useful to researchers that study other infectious diseases with networks of host movements, for example, zoonotic diseases in pastoral systems elsewhere in Africa and the world; avian flu and the interaction among migratory and non-migratory bird; and the spread of HIV along trucker routes in Africa and UN peace keeping forces that are redeployed. All these disease ecologies involve mobile host that move in overlapping networks and require the integration of spatial and epidemiological models.

We also plan to make the model accessible to veterinary and human health services in Cameroon and other nations in the Chad Basin to aid in effective interventions and control of infectious diseases in the context of overlapping networks of pastoral and trade livestock movements. We will develop a web-based database and mapping application that can be used by veterinary and human health services in the Chad Basin. We will train Cameroonian veterinary students and researchers who are collaborating in this research in relatively simple but effective modeling of

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disease epidemiology in order to effectively intervene to control the spread of diseases. We will organize workshops in Cameroon and invite researchers and policy makers from other nations in the Chad Basin. The goal is to develop regional monitoring systems in the different nations that can quickly analyze epidemiological trends in the Chad Basin.

As part of our research program will train a team of local herders from different Arab and FulBe groups in assisting with the handling of the animals and the collection of biological samples. Working with local herders who are respected in the community will greatly facilitate our data collection. We will provide them with mobile phones and pre-paid minutes so that they can contact our Cameroonian collaborators when there is an outbreak of FMD during our study. This will allow us to collect samples of the active virus and track the outbreaks throughout the study area. In addition, we will train the herders in primary veterinary care and so develop "barefoot veterinary assistants" that are embedded in mobile pastoral societies and can act as liaisons between veterinary services and mobile pastoralists. The combination of local surveillance system that is embedded in the pastoral system and a regional monitoring system that can analyze epidemiological trends, can greatly improve the interventions when there are epizootic or zoonotic outbreaks.

Intellectual merit

In the context of this project, we will develop a new integrated spatial, epidemiological, and molecular model to simulate the dynamic systems of mobile pastoral herds. Our model will improve on former models' limited ability to capture the extensive movement of hosts in multiple and overlapping networks, to simulate epidemiology of a pathogen that itself varies over time, and to incorporate newly observed data.

When populations of host animals are mobile rather than stationary the model must capture additional possibilities for disease transmission through a contaminated environment and increased mixing of animals that changes from day to day. Former FMD models have not modeled this situation (Bates 2003, for example) or have represented animals as a density to avoid looking at individual contacts (Dexter 2003, for example). In addition, these models do not capture differences in human behavior over time that may affect the transmission of disease. By linking a traditional susceptible-infected-recovered (SIR) model to and underlying spatially explicit agent-based model (ABM), we can incorporate aspects of animal movement and human decisions in the simulation of FMD transmission.

In addition, we intend to model variation in viruses by treating each serotype of FMDV as a separate model rather than looking only at one virus strain as has been done in previously. Our model will also be able to incorporate changes in the epidemiology of the virus that develop over time by using simultaneous Bayesian estimation of the model parameters as data are observed during simulation runs. Also, we will be monitoring the evolution of viruses over time with phylogenetic models so that we may be able to predict when changes in epidemiology may occur and add this information into the Bayesian parameter estimation in the form of prior distributions.

In the endemic situation we have chosen to examine, the lack of intervention from humans creates a natural laboratory in which to explore a number of fundamental questions about the nature of FMDV. As we examine exposure to different FMDV strains over time, we will be able to model waning natural immunity to as well as waning maternal immunity in calves to provide estimates of how the virus will evolve over time under immune pressure. In addition we will be able to identify and follow carrier animals to look at their role in maintenance of endemic disease and the possible adaptation of the virus to endure in this state. Because FMDV is a typical RNA virus in many respects, the information gleaned from this project might be applied to other RNA viruses including influenza and the causative agents of the common cold and hand-foot-and-mouth disease.

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