Mathematical Epidemiology

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1 Background

Population growth and spread, global climate change, and the emergence and reemergence of novel and deadly forms of infectious diseases have increased the need for sound quantitative methods to guide disease intervention practice [1, 15, 18]. In the 20th century, influenza was pandemic several times and new diseases such as Lyme disease, Legionnaire's disease, toxic-shock syndrome, hepatitis C, hepatitis E, and hantavirus were encountered. The human immunodeficiency virus (HIV), which is the etiologic agent for acquired immunodeficiency syndrome (AIDS), was identified in 1981 and now causes over 3 million deaths per year in the world. Drug and antibiotic resistance have become serious issues for diseases such as tuberculosis, malaria, and gonorrhea. Prions have been identified as the infectious agents for bovine spongiform encephalopathy (BSE or mad-cow disease), Creutzfeldt-Jacob disease, kuru, and scrapie in sheep. Changing patterns of social behavior and travel present new classes of disease transmission problems. For example, West Nile virus has spread to North America. Biological terrorism with diseases such as smallpox or plague has become a new threat. In the 21st century, we have already encountered severe acute respiratory syndrome (SARS) and will undoubtedly face more new infectious disease challenges.

The epidemiological modeling of infectious disease transmission has a long history in mathematical biology, but in recent years it has had an increasing influence on the theory and practice of disease management and control [15]. Mathematical modeling of the spread of infectious diseases has become part of epidemiology policy decision making in several countries, including the United Kingdom, Netherlands, Canada, and the United States. Epidemiological modeling studies of diseases such as gonorrhea, HIV/AIDS, BSE, foot and mouth disease, measles, rubella, and pertussis have had an impact on public health policy in these countries. Thus modeling approaches have become very important for decision-making about infectious disease intervention programs. Recent approaches include deterministic models, computer simulations, Markov Chain Monte Carlo models, small world and other network models, stochastic simulation models, and microsimulations of individuals in a community. These techniques are often implemented computationally and use data on disease incidence and population demographics. Sometimes the epidemiology, immunology, and evolution of a disease must all be considered. For example, some recent research has studied the rational design of influenza vaccines by considering the effects on the immunology of influenza immunity in individuals of the yearly epidemics of influenza A variants, the vaccine composition each year, and the yearly evolutionary drift of influenza A virus variants.

One barrier to effective modeling of infectious diseases and intervention policies has been the lack of communication between the modelers and the policy makers. A primary objective of the BIRS Mathematical Epidemiology workshop was to encourage communication among internationally-recognized applied

mathematicians, statisticians, and epidemiologists. To promote communication, 50 minute lectures were followed by 30 minute discussion periods on specific diseases, epidemiological problems, public health policies, comparisons of disease intervention strategies, recent advances, open questions, new approaches, and future directions for research. The formal lectures and discussions in the mornings and evenings were supplemented by more informal discussions and special sessions in the afternoons. The topics included Compound Matrices, Incidence Functions, Modelling Rubella Vaccination, and Wildlife Diseases.

Partcipants in this BIRS workshop (August 20-25, 2005) presented the latest results on the theory and applications of mathematical modeling of infectious disease epidemiology and control. Mathematicians, statisticians, and epidemiologists presented successful examples of mathematical modeling studies. They also described current epidemiological problems and questions about strategies for vaccination and other prevention methods that could be studied using mathematical modeling approaches. The variety of approaches included not only deterministic and stochastic modeling, but also network and agent-based modeling. Some talks emphasized new methods in dynamical modeling of infectious diseases, while others considered new applications of modeling approaches and new methods for parameter estimation from data. The participants included many young scientists including assistant professors, postdoctoral fellows, and graduate students.

Both mathematical modelers and public health policy decision makers will ultimately benefit from this workshop on modeling as a decision making tool for the epidemiology and control of infectious diseases. Epidemiologists and public health policy makers have much to learn about successful and potential applications of modeling approaches to understanding disease transmission and using interventions to reduce disease incidence. It was the consensus of the participants that workshops should be organized by modelers for public health officials, in which they would work on epidemiology modeling and computer simulations of infectious disease transmission and control. Applied mathematicians and statisticians learned about new and challenging problems in modeling the spread and prevention of diseases. This workshop may lead to new projects and collaborations involving the applications of modeling approaches to problems in understanding infectious disease transmission and intervention strategies.

2 Challenges in modeling influenza and antigenic variation

Viggo Andreasen opened the conference with a detailed presentation of the biology of influenza viruses, and of mathematical models used to understand influenza's evolutionary ecology. As Andreasen discussed, influenza's biology is complicated, even though the disease is caused by a relatively small RNA virus. The virus consists of eight separate RNA segments encoding a total of 10 genes. In temperate regions of the globe, the virus causes regular, annual epidemics. In the years 1918, 1957, and 1968, however, the virus caused major pandemics worldwide. As Andreasen described, pandemics are associated with antigenic "shifts" – that is, reassortment of entire viral RNA segments between avian and human forms of the virus. In non-pandemic years, by contrast, annual epidemics are possible because of antigenic "drift" – that is, the gradual accumulation of point mutations in hemagglutinin, the gene encoding the primary surface antigen of influenza. The phylogeny of drifting influenza viruses is very unusual when compared to all other known RNA viruses (such as HIV).

Influenza drift is the result of selection for novel antigenic viral strains, selected because of "cross-reactivity" between related strains. The processes of influenza transmission and drift can be modeled by generalizing the standard SIR framework in one of several ways:

1) Assume a fixed set, K, of n distinct strains. Instead of using only three classes of individuals ($S(t)$ $I(t)$ and $R(t)$), we introduce more classes (order 2^n) of individuals, which indicate the set of strains, $J \subset K$, from which an individual has previously recovered, or the strain with which an individual is currently infected. The resulting model requires a very large number of ODEs, but it has been thoroughly analyzed in the case of $n = 4$ strains. 2) Assume of a one-dimensional continuum of strains, and index susceptible individuals according to the strain of their most recent infection. This results in a PDE version of the SIR model, and the steady-state evolutionary rate depends upon the kernel of cross-immunity between strains. The phylogenetic structure of viral strains cannot be studied in such a model. 3) Employ individual-based stochastic simulations that keep track of the full infection history of each individual, transmission events between individuals, and mutational events to viral strains.

Although individual-based simulations have successfully reproduced the empirical patterns of influenza

drift evolution [13, 26], such simulations are very complicated and do not easily reveal the underlying principles that govern the structure of influenza drift. Dr. Andreasen introduced new work based on an earlier framework he has developed with colleagues [19, 2]. Andreasen and Sasaki have recently analyzed simplified 2-strain "annualized" models which attempt to determine the conditions under which a mutant viral lineage will co-exist with its parent strain (phylogenetic branching), and under what conditions a mutant viral lineage will extinguish earlier lineages (phylogenetic pruning). This modeling approach helps to identify generic principles that govern the structure of drifting influenza viruses.

In the second session, Junling Ma presented another model intended to help gain analytic understanding of the complex process of influenza drift. Ma's approach synthesized a variety of data about drift to support the development of a simple modeling framework that captures key aspects of influenza drift. He presented an argument beginning from a Poisson process of random mutations arising and showed that a few simple assumptions allow construction of a novel modeling framework similar to the earlier models of Andreasen et al. [3, 19, 2].

Junling Ma thereby provided a rationale for the "linear" strain-evolution framework of Andreasen, Levin and others. He showed that his model leads naturally to cycles of about one year, with explicit evolution, tying in to an earlier theory by Dushoff and others [9] that strong annual cycles in influenza arise from resonance between a natural tendency to cycle and exogenous seasonal forcing. This earlier theory was developed in part at a 2003 BIRS workshop in honor of Lee Segel.

The discussion ranged over a broad set of existing challenges in influenza modeling, including: how to how to bridge scales from cellular interactions, to individual outcomes, to population-level patterns of disease incidence and viral evolution; and how to guide choice of vaccine strains and policies of vaccine allocation. We expect that collaborations started here will lead to significant progress on these important questions.

Most of the diseases discussed at the workshop exhibit antigenic variation: the ability of the disease organism to change its surface in order to evade the immune system. Discussions focused on models incorporating multiple strains for subtypes of a virus circulating in a host population. For example, the virus responsible for Dengue Hemorrhagic Fever may appear in one of four subtypes, which has complicated the development of an effective vaccine. These subtypes co-circulate in the host population and the course of infection within a host depends on the previous history of infections with other subtypes. Subsequent infections are hypothesized to increase one's viral load, and increase one's infectiousness. This effect is called antibody dependent enhancement (ADE). Even the simplest assumptions of this phenomenon lead to large complex models, which possess very interesting dynamics, both from the mathematical and epidemiological perspective. The complexity of these models is necessary to resolve questions of outbreak patterns and development of effective vaccines and vaccination strategies.

Lora Billings presented a dynamical system model of co-circulating subtypes in diseases such as dengue, with both autonomous and seasonally driven outbreaks [7]. She showed that for sufficiently small ADE, the number of infectives of each subtype synchronizes, with outbreaks occurring in phase. When the ADE increases past a threshold, the system becomes chaotic, and outbreaks from differing subtypes become desynchronized. However, windows of synchronization can persist. This drives down the number of susceptibles, and can threaten persistence of the virus. She concluded that increased number of subtypes and ADE effect may provide a competitive advantage to a virus, but there are limits.

The current state of the art in both the epidemiological data and the analysis of the models falls short of answering the questions of vaccine strategies, but desynchronized outbreaks of different subtypes can be partially understood. There are several clear directions for research: one, the further development of analytical techniques for these types of dynamical systems, particularly, bifurcation analysis and integration methods, and two, further study of immunological mechanisms and within-host modeling of immune response to both understand the details of susceptibility and immunity and to properly model the spread of subtypes within the host population. The challenges surrounding within-host aspects of antigenic variations, such as drug resistance and its consequences for treatment and vaccination programs, were not discussed at the meeting and should be addressed in a future workshop.

3 New approaches: Network modeling

Mark Newman's talk on Disease Dynamics on Contact Networks provided an introduction to the use of network approaches in epidemiology, together with a number of examples of their application to real-world problems. The spread of an infection on a network can be mapped onto a percolation problem, where the probability of there being a connection between two nodes is given by the transmissibility of infection. This quantity is simply the probability of transmission between an infective and a susceptible, over the entire infectious period of the infective. With this mapping, the well-developed machinery of percolation theory (most notably, generating function methods) can be brought to bear on the problem. Epidemic thresholds, probabilities of disease invasion and epidemic sizes can then be calculated. A number of examples of networks were presented, together with a discussion of the problems and issues that accompany attempts to capture the structure of real-world networks. The central point is that a network consists of both nodes (individuals) and edges (connections between individuals). The statistics of sampling individuals from a population is a well-studied problem, but appropriate techniques for sampling edges are less well understood. Many techniques, such as contact tracing, may introduce biases into the sample of the network obtained. The network structure is highly dependent on the infection setting, as witnessed by the impact of increased long-range travel: the spread of Black Death in medieval Europe involved mainly local spread of infection whereas the SARS outbreak rapidly jumped between countries and even continents.

For many rapidly spreading infections, the contact network can be treated as being fixed, but such an assumption would be quite inappropriate for sexually transmitted infections. In many settings, transmission is enhanced by superspreaders: individuals who give rise to many more secondary infections than the average person. The percolation analysis highlights this phenomenon, with the basic reproductive number depending not only on the average number of contacts made (i.e. the mean of the degree distribution) but also on the second moment of the degree distribution. This result echoes the familiar "mean + variance over mean" result from mathematical epidemiology. A hospital-based network model was presented, depicting hospital wards, patients and caregivers. Fitting the model to data on an outbreak of Mycoplasma pneumonia suggested that the probability of transmission between patients and caregivers was highly asymmetric, with a much higher transmission probability from caregivers to patients than from patients to caregivers. As a consequence, the model makes a strong prediction regarding control: each caregiver should be limited to one ward, and caregivers should be given antibiotics. These recommendations are in stark contrast with conventional public health wisdom, which states that patients should be confined to wards and patients should be treated. In the resulting discussion, it was pointed out that the standard policy might be more concerned with mitigating the effects of infection (i.e. preventing patient deaths) rather than preventing transmission.

The spread of SARS in a city such as Vancouver was studied using a simulated contact network, based on demographic data. Properties of the network were discussed, together with epidemiological questions (such as the probability of invasion) that can be addressed using the percolation approach. Interestingly, despite all of the structure that was included in the network, it appeared, in many ways, to behave very similarly to a random graph model. Sexual partnership networks have a quite different structure to the social networks that govern the spread of respiratory infections. The dynamic structure of the network, as sexual partnerships are formed and break up, is an important feature, as is the degree to which partnerships overlap (concurrency). If the infectious period of sexually transmitted infections is short, then most transmission events must be associated with partnerships that are either concurrent or that closely follow other partnerships. "Gap dynamics" are, therefore, an important determinant of transmission, in addition to concurrency. Survey data that examines partnership dynamics, including concurrency and gap dynamics, were presented. There was considerable discussion of biases in such data. The talk concluded with the question of whether network models are really appropriate for sexually transmitted infections, despite their long history of use in this area.

A lively discussion followed. Questions of different network structures were raised. Bipartite graphs have been used in some instances, such as the EpiSims model for spread of smallpox in Portland, Oregon, that describes people and places, such as offices, schools and stores. In such models, places can be considered as being infected, so that people visiting those places can acquire infection. Vector borne diseases may be more appropriately described using random graphs, if it is assumed that the vector (e.g. mosquito) does not distinguish strongly between different people. On the other hand, such networks may exhibit aggregation if the vector shows preference for biting certain classes of people.

The usefulness of the basic reproductive number concept in network settings was questioned. In reply,

it was pointed out that different network structures (and hence R_0) may explain the different patterns of spread of HIV in different settings. Control measures can also be explored using the analytic approach. The difficulties in applying network approaches to the real-world were a recurring theme in the talk and discussion. Important issues remain regarding how we can gain insights into the structure of networks on which infection spreads. There are only a small number of instances (such as SARS, for which intensive contact tracing was carried out, or the hospital study presented, whose small scale enabled a complete description of the network to be obtained) in which detailed network data is available. In other settings, we only have a sample of the network or a sample of the individuals involved in the network.

Mercedes Pascual spoke about her joint work with Juan Aparicio on translating from networks to populations using modified mean-field models of disease dynamics. Such models ignore network structure and assume homogeneous mixing. At the opposite extreme, high-dimensional models that are both individual-based and stochastic incorporate the distributed nature of transmission. In between, moment approximations have been proposed that incorporate the effect of correlations on the dynamics of mean quantities of interest. As an alternative closer to traditional epidemiological models, she presented results on 'modified mean-field equations' for disease dynamics, in which only mean quantities are followed and the effect of heterogeneous mixing is incorporated implicitly. She illustrated the idea of formulating these equations from the basic reproductive number of the disease (R_0), and illustrated the approach with SIR dynamics in random and small world networks. She asked how much detail is needed on the transmission network to predict the population course of disease dynamics. She derived an expression for R_0 in small networks and showed that in spite of high levels of clustering, the resulting system of differential equations are able to capture the initial transients and the long-term equilibrium of the more complex network simulations. Pascual argued, however, that modified mean field equations will be most useful when the network is not known, and therefore, when the analytical expression for R_0 is not know. Thus, she addressed how much information is needed on the network to parameterize the model using only the initial transients (i.e. the beginning of an epidemic). From initial data on incidence vs. time, she estimated R_0 and used it as a parameter in the modified mean field equations. This exercise showed that no information on the network is required to parameterize the system and predict the course of the disease. Limitations of the approach were discussed.

A second method relies on power-law relationships between global and local densities. Pascual specifically investigated the previously proposed empirical parameterization of heterogeneous mixing in which the bilinear incidence rate kSI is replaced by a nonlinear term kS^qI^p [25, 21], for the case of stochastic SIRS dynamics on different contact networks, from a regular lattice to a random structure via small world configurations. She showed that, for two distinct dynamical regimes involving a stable equilibrium and a noisy endemic steady-state, the modified mean field model approximates successfully the long term dynamics and short term transients of decaying cycles. A regime of coherent cycles in the small world regime is not well-approximated by this simple model. Pascual argued that future work should couple aspects of the two proposed approximations to better capture the effects of heterogeneous mixing.

Pascual asked whether the demographic noise introduced by finite populations in individual-based models must be kept. That is, do we need the noise even when network structure is only implicitly incorporated? She presented some recent results on the dynamics of a stochastic SIR models for infectious diseases with immigration. In particular, she derived the power spectra of both infective and susceptible numbers and gave conditions under which large and sustained cyclic stochastic fluctuations are expected. This analytical result formalizes the well-known observation that demographic noise sustains persistent oscillations when the corresponding deterministic system approaches an equilibrium with decaying cycles [4, 22]. These results show that the dominant period of the deterministic and stochastic system do not necessarily coincide. More importantly, they suggest a complementary explanation for the major dynamical transitions observed in epidemics of childhood infectious diseases after vaccination, from regular to irregular cycles [11, 5]. Seasonal forcing does not appear to change the basic character of the power spectra, other than adding an annual peak. They also show that childhood diseases fall in regions of parameter space prone to high noise amplification, an observation that raises interesting evolutionary questions. Discussion of the interplay of seasonality, stochasticity and nonlinear disease dynamics clearly shows that this is an important area in need of further study.

4 Modeling emerging/reemerging diseases such as HIV, SARS and West Nile Virus

The presentation by Brandy Rapatski and James Yorke [23] dealt with the epidemiology of HIV. There have been only a few attempts in the literature to estimate the probability of HIV transmission per sexual contact. A number of years ago J. Jacquez and J. Koopman at the University of Michigan analyzed a data set dealing with gay men in San Francisco that were part of a hepatitis B vaccine trial for which multiple blood samples were taken during the early years of the HIV epidemic. From analysis of the data from 1978-1984, before the introduction of antiretroviral therapy, Jacques and Koopman concluded that the highest probability of transmission occurred during the first few months after infection, a period called primary infection. Rapatski and Yorke reanalyzed the same data with a model that incorporated three stages of disease, primary infection, asymptomatic infection (lasting on average 7 years), and symptomatic infection (lasting on average 3 years). Using data on the fraction of gay men that were HIV positive vs time during the years 1978-1984, they concluded that to sustain the rapid increase in the number of infected gay men into the later years of the San Francisco epidemic that the probability of transmission must be highest during the third stage, the symptomatic stage of disease, rather than during primary infection. Their conclusion, given the data, seemed very surprising given the adoption by the field that HIV is mainly spread during primary infection. This talk, which was supported by rigorous modeling and data analysis, presented an important change in the view of HIV spread. Much discussion followed both about the methods used and the conclusion, but no one identified any flaws. In fact, all approximations seemed to be conservative and adding more realistic features to the model only appeared to increase the probability of transmission in the third stage.

Zhien Ma spoke about the work of his group on modeling the SARS outbreak in China during November 2002 to June 2003 [29, 28]. A compartmental model is proposed that mimics the SARS control strategies implemented by the Chinese government after the middle of April 2003: the division of the whole population into two parallel blocks corresponding to the so-called free environment and the isolated environment and the partition of these blocks further into the compartments of susceptible, exposed, infective, suspected SARS, diagnosed, removed and health care workers. A novel approach was introduced to calculate the transfer rate from the free environment to the isolated environment. This approach incorporated undiagnosed suspected SARS individuals that were put into isolation because fast SARS tests were not available. Methods were developed for parameter identification using the daily reported data from the Ministry of Health of China. Simulations based on these parameters agree with the accurate data well, thus providing additional validation of the model. Finally some parameters were varied to assess the effectiveness of different control measures: these new parameters correspond to the situation when the quarantine measures in the free-environment were prematurely relaxed (thus the observation that the second outbreak with the maximal number of daily SARS patients is much higher than the first outbreak) or when the quarantine time of SARS patients is postponed (noting the delayed peak time but with much higher number of SARS patients at the peak). The basic reproductive number and the basic adequate contact rate were also calculated.

Interestingly, the modeling work was carried out in 12 days by Zhien Ma and his group in May of 2003, before the SARS infections had subsided in China. Yet, their results came very close to predicting the real SARS case data in China that accumulated almost a month later. This demonstrates the need for modelers to consider approaches to real-time modeling and prediction on an ongoing outbreak, as opposed to the traditional prediction of future outbreaks or retrospective analysis, which are abundant in the literature.

Zhilan Feng presented work done together with John Glasser (CDC) in which they investigated potential public health response strategies for an emergent infectious disease. They constructed a general compartmental ODE model incorporating the possibility of infectiousness during clinically distinguishable stages, during which patients could be quarantined or isolated with varying efficiencies. They tested their model by application to SARS data in Hong Kong. Analysis of this model with increasingly accurate and complete information indicates that recommended public health interventions may change during the course of an epidemic. This led into a more general discussion of how mathematicians can best help public health decision-makers who are planning for or responding to epidemics.

Spatial aspects are important in infectious disease transmission, but are often taken into account implicitly in models. Throughout the workshop, the spatio-temporal component of disease spread was often alluded to, for example during discussions on network models, but seldom discussed explicitly. Of the various modeling techniques at hand to address spatial aspects, the one that involves integro-differential equations is at the same

time the most accurate and the hardest to use. Shigui Ruan gave a presentation entitled Nonlocal Epidemic Models, in which he presented models employing this approach. He first introduced a host-vector model for a disease without immunity, with the specificity that the current density of infectious vectors is related to the number of infectious hosts at earlier times. This results in an integro-differential equation model, in which a diffusion term is used to model the spatial spread in a region. Examples of these host-vector diseases include West Nile Virus and malaria.

Ruan showed how, for the general model, the stability of the steady states can be studied using the contracting convex sets technique. When the spatial variable is one-dimensional and the delay kernel assumes some special form, the existence of traveling wave solutions is established using the linear chain trick and the geometric singular perturbation method. In a second part, Shigui used a multi-compartment model to describe the nonlocal spread of SARS, discussing in particular the effect of global travel on the transmission of the disease.

5 Recent advances in modeling disease transmission and vaccination

David Greenhalgh spoke on estimation of R_0 and evaluation of vaccination programs from age-structured serological data. There were questions on whether or not age structured bootstrap samples were used in these kinds of studies. It is likely that when the infection process is independent of the age and the age specific samples are good, then the age specific bootstrap method is applicable. In rubella, children may be infected by the adults and vice-versa, so the samples are age-dependent. However, many people have the opinion that it is not easy to validate the model. One reason for this could be changes in the behaviour of the individuals who are vaccinated. There was also discussion on general difficulties on validating the given mathematical model which predicts the proportions of newborns to be vaccinated.

John Glasser gave a talk entitled “Mathematical Epidemiology of Varicella and Herpes Zoster”. The United States has recently begun to recommend children be vaccinated against varicella (chickenpox); however, there is a complex process by which the varicella-zoster virus reactivates resulting in herpes zoster (shingles). Previous work has considered this reactivation, but this work includes the effect of boosting of immunity to herpes zoster due to either the periodic reactivation of the virus within a person or contact with a varicella-infected person.

Previous studies had cast doubt on the varicella vaccination policy of the United States because of a predicted temporary increase in herpes zoster infections in adults who are no longer boosted by exposures to children with chickenpox. Other considerations, including possible evolutionary changes in the virus caused by vaccination, might provide further evidence for or against the policy.

Chris Bauch spoke on the behavior-incidence dynamics in childhood disease vaccination. The interplay between disease prevalence, population behavior and vaccine coverage is explored in a game theoretical setting for the case of pertussis in England and Wales during the 1970’s. A model that considers imitation dynamics is able to give a good fit to the time-series data of pertussis vaccine uptake. The model is able to recover the oscillatory dynamics characteristic of some childhood diseases. The model also predicts that the probability and amplitude in oscillations increase with the intensity of imitation behavior in the population or with increases in disease prevalence. It is suggested that game theoretical approaches could aid in predicting the population behavior towards vaccination and therefore facilitate public health decision making.

In this session, we also briefly discussed issues related to parameter estimation, uncertainty and sensitivity analysis. The capability of the model to uniquely identify model parameters needs to be addressed. Parameter estimation can be achieved using maximum likelihood methods, least squares fitting, etc. Uncertainty in parameter estimates can be quantified under different assumptions in the data (e.g., heterogeneity in variance, correlated errors, etc.). Sampling techniques (e.g., latin hypercube, simple random sampling) are useful to explore the parameter space and assess the uncertainty of epidemiological quantities of interest. Sensitivity analysis (e.g., partial derivatives, partial rank correlation coefficients) of parameters on the model solution of interest are useful not only in determining the sensitivity on parameters, but also in constructing asymptotic variance-covariance matrices from which parameter variance and correlation information can be obtained.

6 Modeling wildlife diseases

Linda Allen spoke about modeling wildlife diseases including hantavirus infections in rodents and chytrid infection in amphibians. Hantavirus pulmonary syndrome is an emerging zoonotic disease that is carried by wild rodents. The mortality rate in humans is as high as 37%. Humans are usually exposed to the virus through geographically isolated outbreaks. Two new mathematical models for hantavirus infection in rodents were presented. The models were based on a male/female SEIR epidemic model. The first model was a system of ordinary differential equations (ODEs) while the second model was a system of stochastic differential equations (SDEs). The SDE model can be derived directly from the ODE model assuming variation with respect to the birth, death, and infection process [17]. These new models capture some of the realistic dynamics of the male/female rodent hantavirus interaction: higher seroprevalence in males and variability in seroprevalence levels.

Two diseases associated with recent amphibian declines are ranavirus infection and chytridiomycosis. Chytridiomycosis is a disease caused by the fungal pathogen *Batrachochytrium dendrobatidis*. Both pathogens causing these diseases are found throughout the world. In this presentation, models for amphibian populations infected by the fungal pathogen were discussed [12]. The amphibian host population is structured according to two developmental stages, juveniles and adults. The juvenile stage is a post-metamorphic, nonreproductive stage, whereas the adult stage is reproductive. Each developmental stage is further subdivided according to disease status, either susceptible or infected. There is no recovery from disease. Each year is divided into a fixed number of periods. The first period represents a time of births. Amphibians are generally explosive breeders, resulting in a large increase in population density during the breeding season. During the remaining time periods there are no births, only survival within a stage, transition to another stage or transmission of infection. Conditions were derived for population extinction. High transmission rates can destabilize the disease-free equilibrium and low survival probabilities can lead to population extinction.

There are several reasons for studying wildlife diseases [14, 8, 27, 16].

1) If the wildlife species is of conservation interest and there are concerns about the impact of the disease on the survival of the populations, for example, rabies in Ethiopian wolves.

2) If there is increasing worry about the possibility of either transmission from wildlife to humans or to domestic animal species. In this case we often think of wildlife as the reservoir species.

3) Wildlife diseases pose a threat to global diversity. Control of wildlife diseases is important for the preservation of our natural world.

Emerging diseases often occur because of anthropogenic changes to the environment or human encroachment. These changes result in increased contact with wildlife species which allows disease to jump between species. Wildlife diseases are often associated with diseases in humans (zoonotic disease) and domestic animals. A few examples of wildlife disease that are transmitted to humans include hantavirus pulmonary syndrome (transmitted by wild rodents such as rats and mice), influenza in birds, and plague from prairie dogs and rats. Rabies cases in humans are often due to bites by infected bats. The annual number of human deaths worldwide caused by rabies is estimated to be between 40,000 and as high as 70,000. An estimated 10 million people receive post-exposure treatments each year after being exposed to rabies suspect animals.

Vector-transmitted diseases affecting wildlife and humans include West Nile Virus and Lyme disease. Canine distemper virus is a spillover infection from domesticated dogs that has resulted in extinction of black footed ferret and African wild dog populations. A few emerging diseases are known to only impact wildlife, such as chytridmycosis, a fungal infection in amphibians, and chronic wasting disease (transmissible spongiform encephalopathy) in deer and elk.

The main differences between modelling wild life and human disease identified in the discussion are that

i) Wildlife populations do not remain constant over time; indeed, they can be highly variable due to environmental factors or the landscape. This can have a profound impact on the dynamics of the disease.

ii) Multiple species interactions are often involved. For example a reservoir for infection does not have to consist of one species, but can be made up of a number of species which interact (at least) via the pathogen and allow the disease to persist. There are many diseases which infect multiple species and we often observe “apparent competition” between these species via the pathogen.

iii) In many cases, wildlife population dynamics are believed to be controlled by pathogens. For example, red grouse and Trichostrongylus tenuis (although we can also think of examples where diseases have had a profound effect on human populations, e.g. HIV in Africa).

iv) Data can be more easily obtained from animal systems. In particular, it is often possible to do experiments on wildlife populations, or individual animals without the ethical issues involved with human disease systems.

The workshop concluded with remarks by the organizers and suggestions for follow-up activities. The organizers and participants thank BIRS and the funding agencies for their support for this excellent workshop. The following references were suggested by participants, but this list is not comprehensive.

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