Neglected infectious diseases

organized by
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Workshop Summary

This workshop focused on identifying risk factors for neglected tropical diseases (NTD) and developing and extending mathematical and computational methods to understand their complex dynamics. The emphasis was also on problems of partially available data and on evaluation of control strategies in light of limited resources.

NTD continue to be a serious threat to the health and well-being of the people who live in developing countries. WHO defines NTD based on the local frequency and level of infection despite globally available preventive measures. Naturally, NTDs are typically problems in developing countries and strongly linked to poverty.

For example, for visceral leishmaniasis (VL) in rural India, infection in low-income laborers restricts their ability to provide for their families. Moreover, the cost of treatment and the duration of reduced income pushes them into a vicious cycle of further hardship and irrecoverable financial deprivation. Although, local government authorities and the WHO have devised control programs to lower the burden of VL in these regions, VL frequently creeps back after a brief period of relief. Major blame for this ultimate ineffectiveness has been attributed to severe under-reporting of cases and death, a lack of clarity in the causes of the disease, and an under-estimation of the role of asymptomatic individuals and other reservoirs of infection.

Participants represented a truly global research community, spanning both developing and developed countries. Participants were from Brazil, Canada, China, Ecuador, England, India, Indonesia, Mexico, Nigeria, South Africa, and the USA. Some were from primarily teaching institutions whereas others from primarily research institutions. Participants also varied on their focused discipline: biological sciences, mathematics, statistics, public health, epidemiology, entomology, medicine, and computational science. The participants were interested in the mathematical modeling of NTD, understanding the epidemiology and ecology of the pathogens, mathematical analysis of NTD models, and linking data to models.

The speakers during the morning sessions of the first two days of the workshop were Profs. Priscilla Greenwood (stochastic modeling of NTD), Helen Wearing (ecological and evolutionary processes that determine the maintenance of vector-borne disease), Pauline van den Driessche (transmission dynamics of cholera), and Claudio Struchiner (genetic diversity in mosquito populations). During the other days, there were short talks by Profs. Malay Banerjee (mechanisms that can generate complex and conflicting dynamics), Daozhou Gao (global stability and the reproduction number), Brajendra Singh (parameter estimation in neglected diseases), and Winfred Just (mathematical modeling and the use of computational software).

The initial discussion during the first day started with clarification and identification of appropriate topics for projects. The discussion included questions like:

- What is the meaning of neglected tropical disease?
- What are WHO's NTD?
- What factors are commonly found in developing countries that can drive NTD?
- Do we know of models that have critically addressed neglected components? If so how?
- What mathematical analysis will be relevant some models?
- What data are needed to estimate model parameters?
- How to quantify the effects of climate changes, globalization, urbanization and habitat loss on infectious disease patterns in human and animal populations?
- Socio-demographic and economic factors are know to influence populations. How can we evaluate their impact on the distribution and prevalence of infectious diseases?
- How to design effective policies and mechanisms of intervention to prevent or reduce the spread of infectious diseases related to environmental change?

These questions were very general, so during the second day, these questions further discussed leading to relatively precise questions:

- What aspects of urbanization favor epidemics?
- Develop criteria for deciding when to include genetic heterogeneity in terms of R_0.
- How to find a threshold of treatment level needed for site-specific elimination (or of mosquito population to sample)?
- Should we aim to eradicate a disease or keep it below a threshold? (under-reporting, reservoir of infection)
- How to construct models from scanty information? Estimating uncertainty.
- Coinfection is the major issue in many of the region. The co-infection mechanism is guided by either facilitation or competition. How to can we incorporate these two factors?
- How can we study optimal allocation of limited resources?
- How does climate change affect the vector species distribution?

On the third day, the participants divided into three primary research groups. These groups were very active and lasted the remainder of the week-long workshop. Given the level of interest in each group, we expect that each will produce one or more journal articles from the topics. Moreover, each group was entirely new collaborations for all involved.

1 Controlling the ongoing Ebola outbreak

At the time of the workshop (August 2014) an Ebola outbreak of unprecedented size and intensity was raging in West Africa, and the international community was scrambling to provide the affected countries with resources to combat the epidemic. Ebola virus is spread through direct contact with body fluids of either the living ill, or recently deceased. Symptoms appear after 2–21 days, and the disease quickly progresses and kills most infected patients (up to 60% or even 80% case mortality) within a few days. The current epidemic—particularly its rapid spread, its high mortality, and the absence of available treatments—has heightened the need for effective control measures.

This research group developed and analyzed a mathematical model to assess the efficacy of quarantine and isolation on the spread of Ebola. The novelty of their work was the evaluation of irregular and partial quarantine and isolation measures in West Africa for the current Ebola outbreak. Their model included the possibility that individuals may escape from quarantine, that susceptible people may be accidentally quarantined and that the bodies of recently deceased Ebola victims are highly infectious until properly buried or burned. With this model, the group assessed the efficacy of improving isolation rates, of tightening quarantine (and also ensuring good hygiene in quarantine), and of rapid burying or disinfection of the dead. In their initial analysis, they found that quick isolation of the ill in combination with disinfection of the dead are highly efficacious in reducing outbreak size, whereas quarantine only provides modest reduction in cases.

Because of the timely nature and potential critical importance of this work to public health, they prepared a rapid communications manuscript to submit to *Eurosurveillance*. They were also preparing a longer manuscript, likely to be submitted to the *Journal of Theoretical Biology* with a more thorough presentation of the analysis of the model. We expect that this newly formed group will continue past this project with a long and fruitful collaboration.

2 The effect of heterogeneity on R_0

Much work has been done in epidemiology looking at different forms heterogeneity. There was the suggestion to consider looking at the problem in a more general way such as the basic reproduction number, the number of secondary cases caused by one primary case, be a general function of the heterogeneity parameters: $R_0 = f(\text{parameters})$. For example, for dengue or malaria, this R_0 also depends on the rate of infection from various species or genotypes of mosquito vector that are present at a location. The group considered the joint distribution of the model parameters and focused on representing this heterogeneity in R_0. Using the classic Ross–McDonald R_0 for a vector–host model, the group tried to obtained an expression for the expected values of R_0 under certain conditions.

A central question in epidemiology is how heterogeneity, in its different manifestations influence the dynamics and intensity of infections. The individual differences have been named frailty in the statistical literature. In epidemic theory, the main problem in dealing with a systematic treatment of heterogeneity in the host, vector, and pathogen populations has been the empirical estimation of frailty distributions associated to each of these model components. The group proposed an epidemic model, taking into account the heterogeneities expressed as frailties in the various transition rates, and analyses its effect on the observable rates. The approach benefits from the imminent availability of a set of various genome sequences of *Anopheles* mosquitoes, vectors and non-vectors, which provides a useful resource for approaching the concept of vectorial capacity from a genetic/evolutionary perspective. The potential insights generated by the analyses of these data might prove useful in guiding new control strategies based on the genetic manipulation of these vectors.

2 HIV–VL Coinfection

Visceral leishmaniasis (VL) has also been recognized as an opportunistic infection associated with the human immuno-deficiency virus (HIV). Epidemiological changes, including increased population density, high migration, and interruptions in treatment have facilitated

an increasing overlap region of VL and HIV. VL–HIV co-infection has its own challenges for control and management. HIV-infected people are immunosuppressed and hence are significantly sensitive to acquiring VL. On the other hand, VL increases the progression rate of HIV disease and the risk of treatment failure within HIV-VL co-infected individual is high, with many fold increments in the rates of relapse and disease mortality. It is also believed that co-infected patients may act as reservoirs for VL, harboring large number of parasites in their blood.

HIV infection of VL-exposed people dramatically increases the risk of progression from asymptomatic VL infection to full VL disease; conversely, VL accelerates HIV disease progression. There are no recent and exact estimates of the absolute number of VL–HIV co-infection cases at the global level. However, a high or increasing burden has been reported from several regions. In North Ethiopia, 20–30% of VL cases are co-infected with HIV. Recent data from Bihar, India demonstrated co-infection rates of 3–4%. On the other hand, with the introduction of highly active antiretroviral treatment for HIV, the case load has decreased dramatically in the Mediterranean region. In India, VL–HIV co-infection is typically found in migrant workers. VL–HIV co-infection is characterized by high mortality, increased drug toxicity and overall poor treatment response. Moreover, even with initiation of antiretroviral treatment, multiple VL relapses remain common. There are also concerns that VL–HIV co-infected people could serve as a source and reservoir of drug-resistant parasites.

VL and HIV co-infection recently has seen a surge in number of cases. India, which has 50% of worldwide cases of VL, also has the third largest number of HIV/AIDS cases and deaths in the world. The majority of the VL cases in India are reported from the state of Bihar. Even though there are low number of HIV cases in Bihar, the co-infected cases of HIV–VL are considered as reservoirs of VL and may be providing an obstacle in reaching target goals of VL elimination.

This research group developed and analyzed a mathematical model to study the impact of the co-infection prevalence of HIV–VL on the VL elimination target. The model incorporates various co-infection initiated mechanisms, particularly, relapse with VL after initial cure by treatment. The delay, defined as the mean duration of the initial cure period, was explicitly incorporated in the model. The goal of the study was to understand the dynamics of VL in the presence of small number of HIV cases and to identify factors that may be critical in destabilizing the high endemicity of VL infection in Bihar.