Schedule

NIMBioS Investigative Workshop: Malaria-Leishmania Co-infection

May 26-28, 2015

Tuesday May 26

Workshop Moderator (AM): Christopher Kribs

8:00 - 9:00 Breakfast and Registration at NIMBioS

9:00 - 9:30 Welcome: NIMBioS

Introduction of Participants

9:30 – 11:00 AM Session

9:30-10:00 **Workshop Talk: Erika van den Bogaart.**
Title: Epidemiology of visceral leishmaniasis-malaria co-infection in East Africa

10:05-10:30 **Workshop Talk: Olivia Prosper**
Title: Mathematical modeling of malaria-leishmaniasis co-infection

10:30-10:45 **Coffee break**

10:45-11:10 **Workshop Talk: Joshua Yukich**
Title: Economics in malaria and leishmaniasis control: results from economic evaluations coupled with control trials

11:10-12:00 **Discussion:** Identifying gaps and posing research questions

12:00-1:00 **Lunch at NIMBioS**

Workshop Moderator (PM): **Folashade Agusto**

1:00-2:00 **Topic selection & group formation**

2:00-4:00 **PM Session**

2:00-2:20 **Workshop Talk: Nakul Chitnis**
Title: Mathematical Modeling to Support Malaria Control and Elimination

2:25-2:45 **Workshop Talk: Lisa Sattenspiel**

Title: Social and cultural influences on the transmission and spread of leishmaniasis and malaria: implications for modeling

2:50-3:10 **Group photograph**

3:10-3:30 **Workshop Talk: Christopher Kribs**
Title: Invasion reproductive numbers for multistrain infections

3:35-3:55 **Workshop Talk: Luis Fernando Chaves Sanabria**
Title: Leishmaniasis sand fly vector density reduction is less marked in destitute housing after insecticide thermal fogging

4:00-6:00 **Working session 1**

The new groups meet to develop their goals and sketch out their broad approach.

5:45 **Reception at NimBioS**

Wednesday, May 27

Workshop Moderator (AM): **Anuj Mubayi**

8:00-9:00 **Breakfast at NIMBioS**

9:00-10:15 **AM Session**

9:00-9:20 **Workshop Talk:** **Carlos Castillo-Chavez**
Title: **Preliminary multiple risk and co-infection models within heterogenous populations**

9:25-9:45 **Workshop Talk:** **Ephantus J. Muturi**
Title: **Biology and control of malaria vectors in Africa**

9:50-10:10 **Workshop Talk:** **Zachary Brown**

Title: **Economic Evaluation and Decision Analysis in Malaria Control Programs**

10:15-10:30 **Coffee break**

10:30-12:00 **Working session 2**

12:00-1:00 **Lunch at NIMBioS**

Workshop Moderator (PM): **Ephantus J. Muturi**

1:00-2:15 **PM Session**

1:00-1:20 **Workshop Talk:** **Katia Vogt Geisse**
Title: **A vaccine-age structured model to study the effect of a pre-erythrocytic vaccine on malaria prevalence**

1:25-1:45 **Workshop Talk:** **Malay Banerjee**
Title: **Visceral Leishmaniasis and HIV co-infection in Bihar, India-Identification of important factors through mathematical modelling**

1:50-2:10 **Workshop Talk:** **Ibrahim Elmojtaba**
Title: **Mathematical model for the dynamics of visceral leishmaniasis-malaria co-infection**

2:15-2:30 **Coffee break**

2:30-6:00 **Working session 3**

6:00 **Dinner**

Thursday, May 28

Workshop Moderator: ***TBA***

8:00-9:00	**Breakfast at NIMBioS**
9:00-9:30	**Final Session**
	working groups prepare to give presentations & submit documents
9:30-12:30	30-minute reporting/feedback sessions
12:30	Closing Remarks

Abstracts

Visceral Leishmaniasis and HIV co-infection in Bihar, India-Identification of important factors through mathematical modelling

Malay Banerjee

Abstract:

Visceral Leishmaniasis (VL) and HIV co-infection recently has seen a surge in number of cases. India, which constitute 50% of worldwide cases of VL, also is the third largest contributor to the HIV/AIDS total cases and deaths in the world. The majority of the VL cases in India are reported from state of Bihar. Even though low number of HIV cases in Bihar, the coinfected cases of the HIV-VL are thus considered as the reservoirs of the VL and may be providing obstacle in reaching target goals of eradication of the disease. We develop and analyze a mathematical model to study the impact of the confection prevalence of HIV-VL on the elimination target. The model incorporates various co-infection initiated mechanisms, in particularly, relapse after initial cure from treatment. The delay, defined as, average constant initial cure period, is incorporated in the model. The goal of the study is to understand the dynamics of the VL in the presence of small number of HIV cases and to identify factors that may be critical in destabilizing the high endemicity of the VL infection in Bihar.

Economic Evaluation and Decision Analysis in Malaria Control Programs

Zachary S. Brown

Abstract:

In recent years, government aid agencies and international organizations have increased their financial commitments to controlling and eliminating malaria from the planet. This renewed emphasis on elimination is reminiscent of a previous worldwide campaign to eradicate malaria in the 1960s, a campaign which ultimately failed. To avoid a repeat of the past, mechanisms must be developed to sustain effective malaria control programs.

Several sociobehavioral, economic, and biophysical challenges exist for sustainable malaria control, particularly in high-burden areas such as sub-Saharan Africa. Sociobehavioral challenges include maintaining high long-term levels of support for and participation in malaria control programs, at all levels of society. Biophysical challenges for the sustainability of national malaria control programs encompass evolutionary challenges in controlling the protozoan parasite and the mosquito vector, as well as volatile transmission dynamics which can lead to epidemics. Economics has proven useful for addressing these challenges, but policies can be improved through more careful, detailed, and timely integration of economics with the natural sciences to maximize and sustain the impact of renewed donor commitments for malaria control.

This talk will focus on two aspects of economic evaluation and decision analysis in the control of malaria. First, I present a framework for the economic evaluation of different control programs, using biomathematical models of disease transmission, and provide some intuition on how nonconvexities in disease transmission often lead to optimal policies characterized by ‘all-or-nothing’ levels of disease prevention. I build on this basic observation in a model-based cost-benefit analysis of malaria control portfolios. I then present a framework for evaluating potential externalities resulting from individuals’ disease prevention decisions, and demonstrate application of this framework considering individuals’ decisions whether or not to participate in an IRS program in northern

Uganda. Using data from a stated preference discrete choice experiment, I show that efficient economic incentives for correcting the positive externality associated with IRS may reduce malaria by around 10%.

Preliminary multiple risk and co-infection models within heterogenous populations
Carlos Castillo-Chavez

Abstract

In this presentation, I will discuss potential approaches to model co-infections-particularly those involving debilitating diseases and vector-borne diseases. The talk will try to initiate a dialog that may lead to further discussions during this meeting.

Mathematical Modeling to Support Malaria Control and Elimination
Nakul Chitnis

Abstract

Increased funding and a scale up of effective control interventions have resulted in significant reductions in malaria transmission and disease burden in large parts of the world over the last decade. To further reduce transmission and potentially eliminate malaria, the global malaria community needs to (i) improve deployment of current interventions to populations with low coverage; (ii) develop new interventions to drive down residual transmission where the current interventions are not as effective; and (iii) prevent the re-establishment of transmission where malaria has been eliminated; while facing the threats of decreased funding for malaria control and the development of resistance to interventions (physiological and behavioral) in mosquitoes and to drugs in parasites.

Mathematical models can help to answer all of these questions. Here we briefly survey mathematical models of malaria, from simple population-based compartmental models that provide qualitative comparisons of control interventions to detailed stochastic individual-based simulation models that provide quantitative predictions of current and new interventions and statistical models that estimate the global distribution of humans, mosquitoes and parasites.

Mathematical model for the dynamics of visceral leishmaniasis-malaria co-infection
Ibrahim M. ELMojtaba

Abstract:

A mathematical model to understand the dynamics of malaria-visceral leishmaniasis co-infection is proposed and analyzed. Results show that both diseases can be eliminated if R0, the basic reproduction number of the co-infection is less than unity, and the system undergoes a backward bifurcation where an endemic equilibrium co-exists with the disease-free equilibrium when one of Rm or Rl, the basic reproduction numbers of malaria-only and visceral leishmaniasis-only, is precisely less than unity. Results also show that in the case of maximum protection against visceral leishmaniasis (VL), the disease-free equilibrium is globally asymptotically stable if malaria patients are protected from VL infection, similarly, in the case of maximum protection against malaria the disease-free equilibrium is globally asymptotically stable if VL and post kala-azar dermal leishmaniasis (PKDL) patients and the recovered humans after VL are protected from malaria infection. Numerical results

show that if Rm and Rl are greater than unity, then we have co-existence of both disease at an endemic equilibrium, and malaria incidence is higher than visceral leishmaniasis incidence at steady state.

Leishmaniasis sand fly vector density reduction is less marked in destitute housing after insecticide thermal fogging.

Luis Fernando

Abstract:

Insecticide thermal fogging (ITF) is a tool to control vector borne diseases, but little is known about its potential to control Sand Flies vectors of Leishmaniasis. We conducted a 15 month insecticide control trial that included two deltamethrin [6 mg a.i.m-2] based ITF interventions in 12 of 24 monitored houses at Trinidad de Las Minas, a hyperendemic cutaneous leishmaniasis transmission village in western Panamá. During the study we followed sand fly (SF) abundance, keeping track of rainfall and quantified housing quality using an index based on architecture and construction materials. We found a 50 to 80% reduction in SF density in the fogged houses when compared with control houses, while controlling for seasonal changes in SF abundance associated with rainfall. We found heterogeneities in the reductions, as abundance changed according to SF species: Lutzomyia gomezi, Lu. panamensis, Lu. dysponeta and Lu. triramula reduced in density between 40% and 90% after ITF. In contrast, Lu. trapidoi density increased 5% after ITF. Differences in the impact of ITF were associated with housing quality, the most destitute houses, i.e., those with features that ease insect entrance, had a disproportionally larger SF abundance, in some cases with increased domiciliary SF density following the ITF. Our results suggest the potential of insecticide application to control SF density and leishmaniasis transmission could depend on housing quality beyond insecticide efficiency.

A vaccine-age structured model to study the effect of a pre-erythrocytic vaccine on malaria prevalence

Katia Vogt Geisse

Abstract:

A deterministic compartmental malaria model will be presented to study the effects of a pre-erythrocytic vaccine on malaria dynamics. A promising candidate for such a vaccine has finished phase III clinical trials and would provide a necessary addition to existing control measures in sub-Saharan Africa. In the model, the human population is divided into susceptible, infected and vaccinated individuals. Two vaccinated classes for humans are included, the first for initial vaccination dose(s) and the second for a booster dose. Each of these classes is structured by an additional temporal variable representing vaccine-age (time since vaccination). A vaccine-age dependent transition between vaccinated classes makes it possible to model a minimum vaccine-age required for receiving the booster vaccination. The mosquito population is divided into susceptible and infected compartments. The control reproduction number $\mathcal{R}$ is derived and shown to determine the local stability of the disease free equilibrium. Certain conditions for the existence of endemic equilibria are identified and backward bifurcation dynamics are shown to occur. Numerical simulations allow us to discuss how different vaccine efficacy scenarios impact malaria prevalence and to what extend minimum vaccine-ages for receiving the booster dose affect disease dynamics.

Invasion reproductive numbers for multistrain infections

Christopher M Kribs

Abstract

Reproductive numbers are well-known key threshold measures of an infection's ability to persist in a population, with measures developed to derive canonical expressions for the basic or control reproductive number. In many cases, however, multiple infections (or multiple strains of an infection) are cocirculating, with coinfections such as HIV+TB of great concern in some regions. A primary infection can make an individual more or less susceptible to secondary infections, entangling the transmission dynamics.

Invasion reproductive numbers (IRNs) measure an infection's ability to invade a population where another infection is already resident. In this talk I will show how next-generation methods developed to derive R0 can be used to derive IRNs, and apply it to two examples--one where coinfections are advantaged and one where cross-immunity precludes them.

Biology and control of malaria vectors in Africa

Ephantus J. Muturi

Abstract

Although significant progress in malaria control has been made since the beginning of the 21st century, this disease continues to be a major public health challenge particularly in Africa. Vector control by use of insecticide-treated bed nets and indoor residual spraying remains the cornerstone of national malaria control programs in Africa and has been critical in reducing the populations of the primary vectors, *Anopheles gambiae, Anopheles arabiensis* and *Anopheles funestus*. This talk will give an overview of the biology and ecology of the three vector species and how they are responding to ongoing vector control strategies. Progress towards malaria control and obstacles towards malaria elimination will also be reviewed.

Mathematical modeling of malaria-leishmaniasis co-infection

Olivia Prosper, Folashade Agusto and Erika van den Bogaart

Abstract

Malaria and Visceral Leishmaniasis (VL) both pose a significant burden around the globe. Regions where both diseases are prevalent face the additional challenge of swiftly and accurately diagnosing individuals showing symptoms. This uncertainty in correctly diagnosing a person is partly due to the overlapping symptoms caused by malaria and VL. One way to address the complexity of these diseases and their interaction is through mathematical modeling. I will present a brief introduction to mathematical modeling of infectious disease, followed by a description of our malaria-VL co-infection model, which was developed to address questions about the impact of delayed treatment and incorrect diagnosis of those infected with VL and those co-infected with VL and malaria. I will conclude with preliminary simulations and future directions.

Social and cultural influences on the transmission and spread of leishmaniasis and malaria: implications for modeling

Lisa Sattenspiel

Abstract

The majority of mathematical models for the transmission of vector-borne diseases incorporate numerous aspects of vector biology implicated in transmission as well as aspects of human biology that influence the course of an infection within an individual. Human social activities and associated behaviors also have important impacts on transmission, but are often less important or negligible components of models of vector-borne diseases. Yet human behaviors are important at all stages of the disease transmission cycle. For example, they have direct influences on the risk of contact between humans and pathogen-carrying vectors and, in addition, alterations and reductions in risk-enhancing behaviors and activities are important strategies to assess when evaluating potential control strategies. In this presentation I compare and contrast important cultural similarities and differences between selected populations at high risk for leishmaniasis and/or malaria in Africa and South Asia. A general discussion of these aspects of human behavior will be followed by ideas on the degree to which they need to be included in epidemic models, and if so, how to effectively incorporate them into models.

Epidemiology of visceral leishmaniasis-malaria co-infection in East Africa

Erika van den Bogaart[1], Marieke Berkhout[1], Pètra Mens[1], Emily Adams[1], Koert Ritmeijer[2], Francois Chappuis[3], Bakri Nour[4], Henk Schallig[1]

[1]*KIT Biomedical Research, Amsterdam, the Netherlands,* [2]*MSF Holland, Amsterdam, the Netherlands,* [3]*MSF Switzerland, Geneva, Switzerland,* [4]*Blue Nile Institute for Communicable Diseases, University of Gezira, Wad Medani, Sudan*

Abstract:

Extensive overlap in the geographical and epidemiological distribution of visceral leishmaniasis (VL) and malaria suggests the two diseases may co-exist in the same patients. Field observations along with few medical records indicate that co-infection cases regularly occur across co-endemic areas, but data are scant, as highlighted by a systematic review of the literature. Recently, two case-control studies were undertaken to gather further evidence on the burden of the VL-malaria co-infection in East Africa. At Amudat Hospital, in the North-East of Uganda, analysis of data routinely collected by Médecins sans Frontières (MSF)-Switzerland revealed that nearly 20% of the VL-confirmed patients hospitalized between 2000 and 2006, were co-infected with malaria, with children under 10 years of age exhibiting a twofold higher risk of being co-infected as compared to VL adult patients. In East Sudan, where a second multi-center study was conducted, the prevalence of malaria co-infections amongst VL in-patients ranged from 11% to 20% during a clinical trial conducted by MSF-Holland in 1998 (Gedarif State), and from 3% to 26% (Gedarif State) and 61% (Sennar State) during the period 2005-2010. Overall, concomitant malaria resulted in clinical deterioration of VL patients, who suffered from more frequent malaise, emaciation and jaundice, despite presenting with less severe hepato- and splenomegaly. In-hospital case-fatality rates were similar in VL patients with and without co-infection, except for co-infected patients hospitalized in 1998 who were significantly more likely to die, possibly due to antimalarial treatment failure. Taken together, these data suggest that patients living in VL endemic area with stable or seasonal malaria are at high risk of developing concomitant malaria. Early diagnosis and effective case

management should be implemented to prevent disabilities and death in co-infected patients, who would also greatly benefit from an integrated approach to leishmaniasis and malaria control.

Economics in malaria and leishmaniasis control: results from economic evaluations coupled with control trials

Joshua Yukich

Abstract:
The results of two cluster randomized trials will be discussed. The first is a trial of mass testing and treatment for prevention of Plasmodium falciparum infection in southern Zambia and an accompanying economic evaluation. The second trial is a trial of several vector control approaches targeted at preventing transmission of cutaneous leishmaniasis in Morocco. In Zambia Trial results show that Mass Testing and Treatment (MTAT) can be an effective intervention for the prevention of P. falciparum. However, the overall magnitude of effect was small and while the intervention was estimated to be highly cost effective, it was much less cost-effective than existing vector control interventions. In Morocco a three armed cluster randomized trial demonstrated that Indoor Residual Spraying plus environmental management was most effective at prevention of cutaneous leishmaniasis, while insecticide treated bednets plus environmental management or environmental management alone were less effective. None of the interventions was found to be cost effective due to the relatively low burden of the disease in most of the intervention areas. IRS was however shown to be conclusively the most cost-effective of the three interventions.