Parallel Session

Epidemiology VI

QUANTIFYING ANTIVIRAL ACTIVITY OPTIMIZES DRUG COMBINATIONS AGAINST HEPATITIS C VIRUS INFECTION

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Keywords: Multi-drug combination, Mathematical model, Hepatitis C virus.

With the introduction of direct-acting antivirals (DAAs), treatment against hepatitis C virus (HCV) has significantly improved. To better manage and control this worldwide infectious disease, the "best" multidrug treatment is demanded based on scientific evidence. However, there is no method available that systematically quantifies and compares the antiviral efficacy and drug-resistance profiles of drug combinations. Based on experimental anti-HCV profiles in a cell culture system, we quantified the instantaneous inhibitory potential (IIP), which is the logarithm of the reduction in viral replication events, for both single- and multiple-drug combinations. From the calculated IIP of 15 anti-HCV drugs from different classes (telaprevir, danoprevir, asunaprevir, simeprevir, sofosbuvir, VX-222, dasabuvir, nesbuvir, tegobuvir, daclatasvir, ledipasvir, interferon-α, interferon-λ1, cyclosporin A, SCY-635), we found that the nucleoside polymerase inhibitor, sofosbuvir, had one of the largest potentials to inhibit viral replication events. We also compared intrinsic antiviral activities of a panel of drug combinations. Our quantification analysis clearly indicated an advantage of triple-DAA treatments over double-DAAs, with triple-DAAs showing enhanced antiviral activity and a significantly lower probability for drug resistance to emerge at clinically relevant drug concentrations. Our novel framework provides quantitative information to consider in designing multidrug strategies prior to costly clinical trials [1, 2].

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CONCURRENCY OF PARTNERSHIPS, CONSISTENCY WITH DATA, AND CONTROL OF SEXUALLY TRANSMITTED INFECTIONS

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Keywords: Concurrency, Vaccination, Pair Formation Model, Sexual Networks.

Sexually transmitted diseases are a globally increasing public health problem. Mathematical models, carefully matched to available epidemiological and behavioural data, have an important role to play in predicting the action of control measures. We explore the effect of concurrent sexual partnerships on the control of a generic sexually transmitted infection with susceptible-infected-susceptible dynamics. To do this we develop three nested pair-formation models: one where infection can only be transmitted via stable sexual partnerships, one where infection can also be transmitted via casual partnerships between single individuals, and one where those individuals in stable partnerships can also acquire infection from casual partnerships. While our first two models describe situations where individuals are serially monogamous, our third model introduces *concurrency* into the population by allowing those in stable partnerships to form additional casual partnerships.

For each model, we include the action of vaccination before sexual debut to inform about the ability to control. As expected for a fixed transmission rate, concurrency increases both the population prevalence and critical level of vaccination required to eliminate the disease significantly. However, when the transmission rate is scaled to maintain a constant prevalence across models, concurrency has a far smaller impact upon the critical level of vaccination required. Further, when we also adjust partnership parameters to maintain a constant number of new partnerships over time, including concurrency can slightly decrease the critical level of vaccination. These results highlight that while increases in concurrency are likely to generate public-health problems, the inclusion of concurrency has limited impact in models that are constrained to match epidemiological and behavioural data.

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POPULATION-BASED AND INDIVIDUAL-BASED MODELLING OF *OPISTHORCHIS VIVERRINI*

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Keywords: Population-based model, Individual-based model, Modelling, Opisthorchis, Transmission dynamics.

The liver fluke, *Opisthorchis viverrini*, is highly endemic in Southeast Asia, particularly in Lao PDR, Thailand, Cambodia and Vietnam. An estimated 10 million people are currently infected. Chronic infection may lead to severe morbidity including the fatal bile duct cancer (cholangiocarcinoma). The life cycle of *O. viverrini* includes two intermediate hosts, snails and Cyprinoid fish; and definitive mammalian hosts including humans and reservoir hosts, such as cats and dogs, who acquire infection by consuming raw or undercooked infected fish. Public health interventions focus on regular treatment of infected individuals, improved sanitation and behavioural change communication campaigns. The importance of the reservoir hosts for the transmission of *O. viverrini* is poorly understood.

We developed deterministic population-based and stochastic individual-based models of the transmission dynamics of *O. viverrini*, calibrated to data from southern Lao PDR, to assess the importance of the reservoir hosts in maintaining transmission and the impact of different intervention strategies on the transmission of *O. viverrini*.

The population-based model includes the mean worm burden in reservoirs host and humans (with age-dependency in humans), and the prevalence of infection in the intermediate hosts. We calculate the basic reproduction with an adapted model, where we split the humans into age groups. We show that letting the number of age groups go to infinity leads to the basic reproduction number of the original model. Previous modelling showed that reservoir hosts are not necessary to maintain transmission and interventions targeting humans would be sufficient to eliminate transmission in these regions of southern Laos. We simulate different intervention strategies focusing on specific age groups to compare the impact of the strategies to the mean worm burden. In particular, we consider the treatment of infected individuals in the different each groups with three scenarios: ideal mass drug administration (MDA)

(where coverage is independent of age), school-based treatment and realistic mass drug administration (where treatment of the young and the elderly population is higher than the middle aged adults). Results suggest that for school based-treatment to be effective, it needs a very high coverage of almost all the school-aged children. The ideal and the realistic MDA show similar results over all age groups, so targeting all age groups is much more effective than school-based treatment.

The individual-based model looks at each definitive host separately and tracks its worm burden. We used prevalence data of the hosts, data on infection intensity in humans and their eating habits from two islands in Southern Laos to estimate the likely distributions of worms burden and eating habits depending on age. Further we used data form the UN from Lao PDR to estimate the distribution of number of humans and their mortality depending on age. Running intervention scenarios as in the population-based model show us the effect of the school-based treatment with including the overdispersed distribution of *O.viverrini* as well as the possibility to eliminate this parasite with different interventions in a certain time range. This model allows us to capture both intensity of infection and prevalence simultaneously and this enables us to model disease progression.

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EVALUATING THE DRUG COMBINATION THERAPY AGAINST HEPATITIS C VIRUS

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Keywords: Hepatitis C Virus, Quantitative virology, Drug combination therapy.

Because of improvements of drug development, so many anti viral drugs against Hepatitis C Virus which are called direct-acting antivirals (DAA) were developed. Using these DAAs, patients obtained significantly improved outcomes, however, one cannot choose which drugs are optimal for each patient. Koizumi et al [1] quantified antiviral activity of 15 different drugs in the case of single drug therapy, double- and triple-drug combination therapy. Besides these quantitative understandings, in this study, we tried to develop a new practical index to evaluate which drug combination therapy is more cost-effective. Using this index, we evaluated all drug combination therapies which are reported in [1] and ranked them according to this index. This evaluating method will be helpful when patients have some drug resistance or need to minimize side effects against some particular drugs.

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MATHEMATICAL MODELING OF THE INTERACTION BETWEEN WILDS AND WOLBACHIA-INFECTED MOSQUITOES

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Keywords: Population dynamics, Aedes aegypti, Wolbachia.

Population dynamics is an important area of research in mathematical biology and even more when it concerns species which are disease vectors and threating the public health, such as the mosquito Aedes aegypti. We propose a mathematical model to study the population dynamics between wild and Wolbachia-infected mosquitoes Aedes aegypti. The model is based on a system of nonlinear ordinary differential equations, describing the interaction between wilds and Wolbachia-infected mosquitoes, assuming that both species are in a specific location and they compete for the same vital resources, like: food, breeding sites, among others.

The use of the bacterium Wolbachia is a new strategy designed to control the population of wild Aedes Aegypti mosquitoes. Wolbachia is intracellular bacteria that can be introduced into Aedes aegypti with different effects: cytoplasmic incompatibility (CI), mosquitoes' lifespan and dengue transmission are decreased. This model takes into account some of the phenotypes, specifically: the CI, maternal inheritance and shortening of lifespan.

A mathematical analysis of the system is performed, presenting the important features of the model. According to the demographic theory, we determine and discuss the threshold basic offspring number, defined as the average number of secondary female insects produced by a single female insect.

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STOCHASTIC MODELLING OF VECTOR-BORNE DISEASES

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Keywords: Epidemiology, Vector-borne diseases, Dengue, Stochastic models, Asymptotic stability.

Vector-borne diseases are among the most serious health problems in the world. Recently, World Health Organization reports that every year there are more than one bilion cases and over one milion deaths from vector-borne diseases. Vector-borne diseases are illnesses caused by pathogens and parasites, which are transmitted by vectors from one infected individual to another. Vectors are usually bloodsucking insects including mosquitoes, ticks, flies, sandflies, fleas, bugs. Taking into account climate change, migration and human mobility, we observe that spreading of vector borne disease happens not only in tropical and sub-tropical regions, but also in new areas. Therefore more than half the world's population is at risk from vector borne diseases such as dengue, malaria, zika, Lyme disease, chikungunya and yellow fever.

The epidemiology of vector-borne diseases can be described by stochastic models given by a system of stochastic differential equations. We study the long time-behaviour of the solutions and prove the asymptoptic stability of the system.

Acknowledgements: This work has been supported by the European Union in the framework of the COST Action: CA16227 - "Investigation and Mathematical Analysis of Avant-garde Disease Control via Mosquito Nano-Tech-Repellents"(IMAAC).

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