Parallel Session
Epidemiology II

PREDICTABILITY OF PREVALENCE OF SEXUALLY TRANSMITTED INFECTION ON COMPLEX NETWORK

RYOSUKE OMORI

omori@czc.hokudai.ac.jp

Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

Keywords: Sexually transmitted infections, Infectious disease epidemiology, Network.

Estimation of epidemic potential of sexually transmitted infections (STIs) is difficult due to the difficulty in quantification of sexual contact network, an alternative method is required. Prevalence of STIs can be obtained easier than sexual network, it is practical if a STI prevalence can be estimated from other STI prevalences. Prevalence of STIs propagate in same sexual contact network, prevalences can be expected to correlate each other. Using mathematical modeling describing STI transmission on sexual network, we aimed to quantify effects of key network statistics on prevalences, and extent to which prevalences of a STIs can be a proxy of another STI prevalence. To this end, an individual-based model was constructed to describe sex partnering and transmission of STI, and was parameterized with representative natural history, transmission, and sexual behavior data. Correlations were assessed on model outcomes (STI prevalences) and multiple linear regressions were conducted to estimate adjusted associations. We observed that variation in the association between STI prevalences and network statistics. We also observed that network statistics explained most of the variation in STI prevalences. This implies that prevalence of STIs can predict another STI epidemic potential.

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HYBRID STOCHASTIC FRAMEWORK PREDICTS THE PROPHYLACTIC EFFICACY OF ANTIVIRALS AGAINST HIV-INFECTION

MAX VON KLEIST

vkleist@zedat.fu-berlin.de

Freie Universität Berlin

Joint work with Sulav Duwal (Freie Universität Berlin), Laura Dickinson (University Liverpool) and Saye Khoo (University Liverpool).

HIV continuous to spread globally. Currently, there is no cure, nor an effective vaccine in sight. In light of this situation, pre-exposure prophylaxis (PrEP) with the drug combination 'Truvada' has been proposed by UNAIDS as one of the 'five pillars' to drastically reduce HIV transmission. Despite its many advantages, Truvada is costly and requires individuals to adhere to a once-daily regimen. Next-generation PrEP compounds, including long-acting formulations, are currently developed to improve PrEP. However, clinical trials using next-PrEP often fail. Since they involve many (> 1000) individuals and long durations, the current practice in clinical testing incurs unacceptable costs, apart from individual tragedies. While animal- and *ex vivo/in vitro* experiments poorly translate into human efficacy, predictive tools are urgently needed that allow for PrEP candidate prioritization.

Mathematically, HIV infection denotes an intrinsically stochastic event: After virus exposure, there is a trade-off between virus elimination and irreversible infection. This trade-off depends on exposure-related factors, such as the virus inoculum, and pathogen- and host-specific factors like the rate of virus clearance and -replication. Prophylactic drugs inhibit virus replication, thereby shifting the aforementioned trade-off in favor of virus clearance.

We developed a mechanistic approach to predict the prophylactic efficacy for any antiviral drug [1, 2]. Foremost, we compute a drug- and dose-specific 'extinction simplex', which we use to classify hybrid stochastic-deterministic trajectories as infection events. A unique advantage of our approach is the ability to incorporate pharmacokinetic profiles, which allows testing different dosing/adherence schemes.

Foremost, we use the model to screen treatment approved drugs for their pharmacological potential in prophylaxis. We predict that the currently neglected drugs darunavir, efavirenz, nevirapine, etravirine and rilpivirine may provide complete protection at clinically relevant concentrations against wildtype HIV after sexual exposure. Of the NRTIs, we found that FTC, followed by 3TC and then TDF have the highest PrEP efficacy at clinically relevant concentrations. We predicted that Truvada (FTC+TDF) prevents infection with 96% probability in fully adherent individuals, largely resembling the efficacy of FTC alone. However,

TDF has a lower propensity to select for transmitted drug resistance than FTC or 3TC and retains some efficacy of the regimen in case of sporadic dosing [3]. After integrating plasma and cellular pharmacokinetics, we predicted PrEP efficacy in case of dose reductions, for inadequate adherence, 'PrEP on demand' or post-exposure prophylaxis (PEP) exemplarily for oral dolutegravir, TDF, FTC, 3TC, TDF+3TC and Truvada. We found that 50mg oral dolutegravir is non-inferior to Truvada in all aforementioned prophylaxis schemes.

The presented framework can be used to assess factors determining PrEP efficacy, is useful to pre-select PrEP candidates and test drug administration schemes. Computed concentrations-prophylaxis profiles can guide kinetics of extended release formulations and help assess risks for adverse events. Moreover, the work can extent epidemiological modelling efforts assessing the population-wide impact of PrEP.

References

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FEEDBACK CONTROL OF AN HBV MODEL BASED ON A NONLINEAR KALMAN FILTER

HEE-DAE KWON

hdkwon@inha.ac.kr

Department of Mathematics, Inha University, Incheon, South Korea

Keywords: Feedback control, HBV, Model predictive control, Kalman filter.

In this talk, we consider a guideline for efficient drug treatment strategies for hepatitis B virus (HBV) infection. We introduce and analyze a mathematical model that describes the HBV infection during antiviral therapy. The reproduction number R_0 is determined. The local/global stability of virus-free steady state is investigated. We formulate a control problem which minimizes the viral load as well as treatment costs. In order to reflect the status of patients not only at the initial time but also at the follow-up visits, we consider the model predictive control based on ensemble Kalman filter and differential evolution. The ensemble Kalman filter is employed to estimate full information of the state from incomplete observation data [1]. We derive piecewise constant drug schedule applying techniques of differential evolution algorithm [2]. Numerical simulations are performed using various weights in the objective functional to suggest optimal treatment strategies in different situations.

References

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IMPACT OF PRE-EXPOSURE PROPHYLAXIS ON THE DUTCH HIV EPIDEMIC AMONG MEN WHO HAVE SEX WITH MEN

GANNA ROZHNOVA

g.rozhnova@umcutrecht.nl

Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, 3584CX, Utrecht, The Netherlands

Joint work with Daniela Bezemer (Stichting HIV Monitoring, Amsterdam, The Netherlands), Ard van Sighem (Stichting HIV Monitoring, Amsterdam, The Netherlands), Janneke Heijne (National Institute for Public Health and the Environment, Bilthoven, The Netherlands), Anne Presanis (Cambridge University, Cambridge, UK), Daniela De Angelis (Cambridge University, Cambridge, UK) and Mirjam Kretzschmar (University Medical Center Utrecht, Utrecht, Netherlands).

Keywords: HIV elimination, Men who have sex with men, Pre-exposure prophylaxis coverage, HIV prevalence.

Background: At present pre-exposure prophylaxis (PrEP) is considered to be one of the most promising interventions to help end HIV epidemic among men who have sex with men (MSM) in the Netherlands. National PrEP guidelines recommend PrEP use by MSM at high risk of HIV acquisition. PrEP coverage in this population is still below 10%, but changes in PrEP uptake are expected to occur after the rollout of this intervention. We aimed to assess the potential impact of PrEP on HIV prevalence among MSM and to determine the levels of PrEP coverage necessary for HIV elimination.

Methods: We developed a mathematical model of HIV transmission in a population stratified by sexual risk behavior with universal antiretroviral treatment (ART) and daily PrEP use depending on an individual's risk behavior. We computed HIV prevalence, ART and PrEP coverage for increasing ART and PrEP uptake levels and examined how these were affected by the reduction in PrEP effectiveness and the duration of taking PrEP.

Results: At current level of ART coverage, PrEP effectiveness of 86% and PrEP duration of 5 years, HIV elimination required 82% PrEP coverage in the high risk group (5.7% of all MSM or 12500 individuals with more than 18 partners per year). When PrEP was taken in two groups with highest risk behavior, HIV elimination was not feasible but prevalence dropped from the current 8% to 4.6%. If ART coverage increased by 9%, HIV elimination threshold was at 70% PrEP coverage. For a shorter duration of taking PrEP and lower PrEP effectiveness elimination prospects were less favorable. At 75% effectiveness, the elimination threshold was at 92% PrEP coverage. If PrEP was taken for 1 year HIV elimination was achieved at 84% coverage. In all cases, the time to elimination exceeded 80 years, but HIV prevalence was reduced by half within 40 years.

Conclusion: PrEP for HIV prevention among MSM could, in principle, eliminate HIV from this population in the Netherlands. To achieve elimination, public health services should target PrEP to 70%-92% of individuals with more than 18 sexual partners per year. The highest impact of PrEP on HIV prevalence was predicted if ART coverage in the Netherlands continued to increase. The current level of PrEP uptake by the Dutch MSM may reduce HIV transmission but is insufficient to make a significant impact on the epidemic.

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HOPF BIFURCATION AND OPTIMAL CONTROL OF A DELAYED HIV MODEL

CRISTIANA J. SILVA

cjoaosilva@ua.pt

Center for Research & Development in Mathematics and Applications (CIDMA), Department of Mathematics, University of Aveiro, 3810-193 Aveiro, Portugal

Joint work with Delfim F. M. Torres (CIDMA, Department of Mathematics, University of Aveiro).

Keywords: HIV model, Time delays, Stability, Hopf bifurcation, Optimal control.

We propose and analyze a delayed HIV infection model based in [1, 2] where the time-delay represents the incubation period, that is, the time between the new infection of a $CD4^+$ T cell and the time it becomes infectious. The stability of the equilibrium points is analyzed. Using the time delay as a bifurcation parameter, we derive necessary and sufficient conditions for the occurrence of Hopf bifurcation. This results are illustrated through numerical simulations.

Due to the importance of the pharmacological delay in the HIV treatment, we introduce a control variable into the previous model and a discrete time-delay in the control, which represents the delay that occurs between the administration of drug and its appearance within cells, due to the time required for drug absorption, distribution, and penetration into the target cells. We formulate and solve an optimal control problem with delays in the state and control variables where the objective is to find a treatment strategy that maximizes the number of $CD4^+$ T cells as well as the number of CTL immune response cells, keeping the cost, measured in terms of chemotherapy strength and a combination of duration and intensity, as low as possible. The delayed optimal control problem is solved analytical and numerically and optimal strategies are derived.

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