Innovative Mathematical Modeling For The Analysis Of Infectious Disease Data (IMAID2018)

Abstract

Sponsored by:
Japan Science and Technology Agency CREST project (on the application of big data technique to infectious disease modeling, PI: Hiroshi Nishiura)

From 17 January -18 January 2019

Hanabishi Hotel, Hakodate, Hokkaido, Japan

1-16-18 Yunokawacho Hakodateshi Hokkaido, 042-0932,

JAPAN

PROGRAM

Invited talk: 40 min (=30 min talk + 10 min discussions)
Invited lecture: 20 min (=15 min talk + 5 min Q&A)
Individual talk: 6 min (=4 slides in 4 min + 1 min Q&A + 1 min to switch presenter)

DAY1: 17 January 2019 Thursday

SESSION 1: Chaired by Shinji Nakaoka

13:00 Introduction to IMAID, Hiroshi Nishiura
13:10 Invited talk, Sungmok Jung
13:50 Break (10 min)
14:00 Individual talk
- Asami Anzai, Hokkaido University
- Nao Yamamoto, Hokkaido University
- Kosaku Kitagawa, Kyushu University
- Natalie Linton, Hokkaido University
- Hyojung Lee, Hokkaido University
- Andrei Akhmetzhanov, Hokkaido University
- Kiyeon Kim, Hokkaido University
- Baoyin Yuan, Hokkaido University

15:00 Invited talk, Saki Takahashi
15:40 Break (10 min)

SESSION 2: Chaired by Shingo Iwami

15:50 Invited lecture, Mitsuaki Takaki
16:10 Invited lecture, Toshikazu Kuniya
16:30 Individual talk
- Yichi Yang, Hokkaido University
- Tetsuro Kobayashi, Hokkaido University
- Shoya Iwanami, Kyushu University
- Yusuke Ito, Kyushu University
- Masa Saitoh, The Institute of Statistical Mathematics
- Toru Takada, Kyushu University
- Keita Yoshii, Hokkaido University
- Yusuke Asai, Hokkaido University

17:30 Closing first day
17:40 Conference dinner (faculty invitation)

DAY2: 18 January 2019 Friday

SESSION 3: Chaired by Hiroshi Nishiura

09:10 Invited talk, Jess Metcalf

09:50 Invited talk, Taishi Kayano

10:30 Break (10 min)

10:40 Individual talk

Takayuki Yamaguchi, Hokkaido University

Kwangsu Kim, Kyushu University

Ki-deok Lee, Hokkaido University

Ryohei Saitoi, Hokkaido University

11:00 Invited lecture, Yusuke Kakizoe

11:20 Invited lecture, Hisashi Inaba

11:40 Closing remark

ABSTRACT

Invited talk 1: Sungmok Jung, Hokkaido University
Title: The impact of pneumococcal vaccination on pneumonia mortality among the elderly in Japan: A difference-indifference study

Individual talk 1: Asami Anzai, Hokkaido University
Title: Estimating the risk of tuberculosis among foreign residents by nationality in Japan

Individual talk 2: Nao Yamamoto, Hokkaido University
Title: Quantifying the impact of public concern on the acceptance of human papilloma virus vaccine

Individual talk 3: Kosaku Kitagawa, Kyushu University
Title: Stability analysis of a multiscale model for hepatitis C virus infection

Individual talk 4: Natalie Linton, Hokkaido University
Title: Estimation of the effective reproduction number of a measles outbreak in Guinea, 2017

Individual talk 5: Hyojung Lee, Hokkaido University
Title: Probability of the end of an Ebola virus disease epidemic in West Africa accounting for the impact of sexual transmission

Individual talk 6: Andrei Akhmetzhanov, Hokkaido University
Title: On occurrence of hemorrhagic fever with renal syndrome in Russia

Individual talk 7: Kiyeon Kim, Hokkaido University
Title: Application of Tajima's D value to predict next prevailed clade of an influenza A (H3N2) epidemic in northern hemisphere

Individual talk 8: Baoyin Yuan, Hokkaido University
Title: Transmission dynamics and control of Dengue outbreak in Tokyo in 2014

Invited talk 2: Saki Takahashi, Princeton University
TBA

Invited talk 3: Mitsuaki Takaki, Kyushu University
Title: Development of a quantitative simulator of HTLV-1 proviral integration sites

Invited talk 4: Toshikazu Kuniya, Kobe University
Title: Stability analysis of the endemic equilibrium of an age-structured SIR epidemic model

Individual talk 9: Yichi Yang, Hokkaido University
Title: Estimating the transmission potential of influenza using distributions of serial cross-sectional seroepidemiological surveys

Individual talk 10: Tetsuro Kobayashi, Hokkaido University
Title: Reconstructing the epidemic dynamics of measles in Yamagata, Japan, 2017

Individual talk 11: Shoya Iwanami, Kyushu University
Title: A comparison between HCV JFH-1 and Jc1 strains by quantitative analysis of infection dynamics.

Individual talk 12: Yusuke Ito, Kyushu University
Title: Prediction of antagonism/synergistic effect of multidrugs against hepatitis C virus considering drug interactions

Individual talk 13: Masa Saitoh, The Institute of Statistical Mathematics
Estimation of reporting ratio of sentinel influenza surveillance using seroprevalence data

Individual talk 14: Toru Takada, Kyushu University
Title: Evolutionary selection of HIV-1 mutant among specific immune-background populations

Individual talk 15: Keita Yoshii, Hokkaido University
Title: Simulation-based assessment of model selection criteria during the application of benchmark dose method to quantal response data

Individual talk 16: Yusuke Asai, Hokkaido University
Title: Estimation of the basic reproduction number using viral sequence data and the number of reported cases per sentinel

Invited talk 5: Jess Metcalf, Princeton University
TBA

Invited talk 6: Taishi Kayano, Hokkaido University
Title: Estimating the force of infection with Helicobacter pylori in Japan

Individual talk 17: Takayuki Yamaguchi, Hokkaido University
Title: Model of lung cancer considering smoking status and prediction of future trend of lung cancer

Individual talk 18: Kwangsu Kim, Kyushu University
Title: Modeling of cell to cell infection in a growing plaque

Individual talk 19: Ki-deok Lee, Hokkaido University
Title: Population attributable fraction of Helicobacter pylori for gastric cancer in Japan

Individual talk 20: Ryohei Saito, Hokkaido University
Title: Infectious Disease Modeling with Infectious-Age Dependency for Parameter Estimation of the Dynamics of Human Papillomavirus and Cervical Cancer

Invited talk 7: Yusuke Kakizoe, Kyushu University
Title: Quantifying the intracellular dynamics of hepatitis B virus using Primary Human Hepatocyte system

Invited talk 8: Hisashi Inaba, The University of Tokyo
Title: Age-structured SIS epidemic model in a periodic environment

The impact of pneumococcal vaccination on pneumonia mortality among the elderly in Japan: A difference-indifference study

Sung-mok Jung[1], Hyojung Lee[1], Hiroshi Nishiura[1]
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Abstract

Background: It is plausible that the routine immunization among infants using pneumococcal conjugate vaccine 13 (PCV13) from 2013 and among the elderly using pneumococcal polysaccharide vaccine 23 (PPV23) from 2014 contributed to reducing the pneumonia mortality among the elderly in Japan. The aim of present study is to estimate the causal effect of these vaccination on pneumonia mortality, analyzing the cause-of-death data and applying a difference-in-difference (DID) design to this context.

Methods: Two types of mortality data, i.e., prefecture-dependent and age- and gender-specific mortality data, from 2003–2017 were retrieved. We used mortality due to malignant neoplasm and heart disease as control groups and employed a DID design with an assumed parallel mortality trend between pneumonia and control group mortality since 2013 to estimate the causal effect of pneumococcal vaccination from 2014.

Results: Our estimation based on malignant neoplasm and heart disease as controls indicated that the reduced pneumonia mortality in 2017 owing to pneumococcal vaccination was as large as 41.9 (33.2, 50.6) and 31.2 (23.8, 38.6) per 100,000 individuals, respectively. The largest mortality reduction was observed for the oldest group aged 90 years and older.

Conclusions: The pneumococcal vaccination program, perhaps mainly represented by high vaccination coverage of PCV13 among children and partly by PPV23 administration with low coverage among the elderly in Japan, was shown to have reduced the pneumonia mortality by 20–40 per 100,000 individuals in the elderly at the population level.

References

1. Chidiac C, Ader F. 2009. Pneumococcal vaccine in the elderly: a useful but forgotten vaccine. *Aging Clinical and Experimental Research* 21:222-228.
2. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. 2017. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. *PLoS One* 12:e0169368 DOI: 10.1371/journal.pone.0169368.
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pneumococcal diseases (IPDs) in the elderly: is it really effective? *Journal of Preventive Medicine and Hygiene* 53:101-103.

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5. Naito T, Yokokawa H, Watanabe A. 2018. Impact of the national routine vaccination program on 23-valent pneumococcal polysaccharide vaccine vaccination rates in elderly persons in Japan. *Journal of Infection and Chemotherapy* 24:496-498 DOI: 10.1016/j.jiac.2018.01.004.
6. Ministry of Health, Labour and Welfare, Japan. 2018a. Population census survey. Tokyo: Ministry of Health, Labour and Welfare. Available from: https://www.mhlw.go.jp/toukei/list/81-1a.html
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Estimating the risk of tuberculosis among foreign residents by nationality in Japan

Asami Anzai[1], Hiroshi Nishiura[1]
[1]Graduate School of Medicine, Hokkaido University

Abstract

Background: Although the notification rate of tuberculosis in Japan was as small as 13.3 per 100,000 population, the proportion of foreign-born cases has increased. A new policy to implement tuberculosis screening at the time of visa application is to start from the fiscal year 2019. Thus, it is essential to estimate the risk of tuberculosis among foreign residents. The purpose of this research is to reconstruct the demographic prevalence of foreign residents in Japan by length of stay using the migration statistics and to subsequently utilize the estimated size of foreign residents by the length of stay in Japan for estimating the tuberculosis risk by nationality.

Materials and methods: Six countries with frequent notifications, i.e. the Philippines, China, Vietnam, Nepal, Indonesia, Myanmar, were our subject, accounting for 80% of foreign TB patients in Japan. We reconstructed the number of foreign residents by length of stay using data on statistics on legal migrants. Solving the McKendrick partial differential equation along the characteristic line, we estimated the force of exit with time and the length of stay and reconstructed the number of foreign residents by length of stay of each year. Using the resulting distribution of migrants by length of stay and known information of the time from tuberculosis infection to illness onset, we estimated the risk of tuberculosis infection in the country.

Results: The number of foreign residents within 5 years of entry as of 2017 was 68,028 in the Philippines, 287,727 in China, 240,548 in Vietnam, 57,481 in Nepal, 33,486 in Indonesia, and 16,102 in Myanmar, respectively. We subsequently estimated the risk of tuberculosis by country.

Conclusions: Estimated risk profiles by country, and possibly by visa type in the future, will be considered useful for determining countermeasures.

Quantifying the impact of public concern on the acceptance of human papilloma virus vaccine

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[1] Department of Hygiene, Graduate School of Medicine, Hokkaido University, Japan

Abstract

Background: Human papilloma virus (HPV) vaccine is regarded as an appreciated option to reduce the burden of cervical cancer. However, the vaccine uptake has widely varied by country, and in particular, Denmark and Japan have experienced enormous public debate due to media coverage of suspected adverse events that were implicated to be associated with HPV-vaccination. The present study aims to quantify the dramatic decrease in HPV-vaccination coverage that is attributable to public reactions induced by mass media.

Method and Principal Findings: Datasets of HPV vaccination coverage for six Nordic countries (Denmark, Finland, Iceland, Ireland, Norway and Sweden) and three Asian countries (Japan, Korea and Taiwan) were collected from publicly available data sources. Among six Nordic countries, Denmark and Ireland experienced a rapid decrease in the vaccination coverage since birth cohort 2000 and 2002, respectively, while other four countries remained to maintain the coverage. Among Asian countries, Japan experienced the same trend as Denmark and Ireland. In case of Japan, the sudden drop has started on March 6, 2013 on which newspapers reported the possible link between adverse event of HPV vaccine and neuroparalysis. We employ a difference-in-difference design to purify the causal impact of public reaction on the acceptance of HPV vaccine.

References

1. Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health 2016; 4:e453–e463. doi:10.1016/S2214-109X (16)30099-7
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Stability analysis of a multiscale model for hepatitis C virus infection

Kosaku Kitagawa[1], Toshikazu Kuniya[2], Shinji Nakaoka[3], Yusuke Asai[4], Koichi Watashi[5,6], Shingo Iwami[7]

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[2]Graduate School of System Informatics, Kobe University

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Abstract

Mathematical modeling has revealed the quantitative dynamics during the process of viral infection and evolved into an important tool in modern virology. Coupled with analyses of clinical and experimental data, the widely used basic model of viral dynamics described by ordinary differential equations (ODEs) has been well parameterized. In recent years, age-structured models, called "multiscale model," formulated by partial differential equations (PDEs) have also been developed and become useful tools for more detailed data analysis. However, in general, PDE models are considerably more difficult to subject to mathematical and numerical analyses. In our recently reported study, we successfully derived a mathematically identical ODE model from a PDE model, which helps to overcome the limitations of the PDE model with regard to clinical data analysis. Here, we derive the basic reproduction number from the identical ODE model and provide insight on the global stability of all possible steady states of the ODE model.

References

1. Kitagawa K, Nakaoka S, Asai Y, Watashi K, Iwami S. A PDE multiscale model of hepatitis C virus infection can be transformed to a system of ODEs. Journal of theoretical biology. 2018;448:80-85.
2. Guedj J et al. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. Proceedings of the National Academy of Sciences of the United States of America 2013;110:3991-3996.

Estimation of the effective reproduction number of a measles outbreak in Guinea, 2017

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Abstract

Background: Measles is a highly contagious vaccine-preventable disease (VPD) and a major cause of child mortality in developing countries. Guinea is a low-income coastal country in West Africa where vaccine hesitancy and interruptions to routine vaccination occurred following a regional Ebola virus disease epidemic in 2014–2016. The resulting immunity gap increased the proportion of individuals susceptible to measles in Guinea and paved the way for a nationwide measles outbreak that began at the beginning of 2017.

Methods: Transmission dynamics of the 2017 measles outbreak in Guinea were assessed by prefecture using nonlinear spatial and temporal analyses for all measles cases with illness onset from the beginning of the outbreak through calendar year 2017.

Results: The impact of introducing vaccination on the resulting transmission dynamics was assessed using the estimated effective reproduction number. The model appropriately captured spatial dependence using a gravity type kernel function.

Conclusions: Calculation of reproduction numbers for VPD outbreaks can assist in understanding local transmission dynamics and timing of vaccination to reduce further spread. During this outbreak, continued transmission was affected by regional variation in response efforts. Understanding localized transmission conditions can assist responders in countering and preventing outbreaks by providing insight into population immunity and vaccination coverage, as well as necessary timings for response efforts.

Probability of the end of an Ebola virus disease epidemic in West Africa accounting for the impact of sexual transmission

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Abstract

Background: The end of an Ebola virus disease (EVD) epidemic was not explicitly defined by the World Health Organization (WHO) in West Africa from 2015-2016, partly due to the recrudescent events caused by sexual transmission [1]. WHO declared Ebola free after 42 days have passed since the last confirmed case was tested negative on two blood samples or was buried. The waiting period of 42 days is the twice the observed maximum incubation period of EVD, which was expected to identify the interruption of human-to-human transmission chains. While WHO criteria are based on a prespecified waiting time, the sexual transmission was not considered as an important factor in sustaining Ebola transmission. The purpose of this study aims to propose a more objective approach to determining the end of EVD epidemic by employing a mathematical model.

Methods: We analyzed the empirical data in Guinea, Liberia and Sierra Leone [2]. We devised a statistical model [3] by accounting for sexual transmission and under ascertainment of cases to compute the probability of the end of an EVD epidemic. The sensitivity analysis was conducted by varying the unknown parameters to identify the impact of sexual transmission and under-ascertainment of cases. Moreover, we assessed the validation of our model by means of random simulation and implemented a cost-effectiveness analysis to evaluate the economic cost of waiting time comparing to the WHO criteria.

Results: The proposed waiting time from proposed model was compared with the WHO criteria comprising a waiting time of 42 days. Our performance can offer an objectively interpretable probability of the end of epidemic which is varied depending on the impact of sexual transmission, while the 42-day waiting time did not explicitly account for it. If the proportional weight of sexual transmission was substantial, ascertaining the end requires even more than one year from the last case.

Conclusions: The end of Ebola epidemic cannot be determined by a pre-fixed 42 days of waiting time suggested from WHO criteria. Our results described the proportion of sexual transmission plays a critical role in determining the risk of recrudescence of EVD.

References

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sexual transmission to comprise control of Ebola virus outbreaks, Biology Letters, 2015;12:20151079.
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On occurrence of hemorrhagic fever with renal syndrome in Russia

Andrei R. Akhmetzhanov[1]

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Abstract

Hemorrhagic fever with renal syndrome is an acute viral infection transmitted from rodents to humans. The illness onset include ILI-like symptoms on the first stage of the disease, but complicates with severe back pain, kidney malfunction later on. Despite the majority of cases are either asymptomatic or with mild symptoms, the disease causes substantial burden in affected areas and cumulative number rises to thousands per year. The case-fatality risk constitutes about 1-2%. In the present work, we analyze an available data from Russia, and make an association with climatological factors using the empirical dynamic modeling approach. We derive their quantitative assessment if possible.

Application of Tajima's D value to predict next prevailed clade of an influenza A (H3N2) epidemic in northern hemisphere

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Abstract

During an influenza epidemics seasons, about half of million of death is estimated per year globally [1]. The rapid evolution of influenza A virus enables the virus to evade the human immune response. Influenza virus vaccine is an effective method to prevent the infection and spreading of the seasonal flu. Every February, WHO Consultation issues recommendation of the vaccine strain for next season in northern hemisphere. But sometimes there is mismatch between recommended vaccine strain and circulating strain.

Tajima's D is a statistic that can be used to test whether or not the population structures of target organisms follow the Wright-Fisher model using sampled nucleotide sequences information [2]. Previous simulation of simple infectious model with mutations in nucleotide sequences revealed that Tajima's D value decreased when the number of the infectious was increasing, and it increased when the infectious was decreasing [3].

In this study, we analyzed nucleotide sequences of HA gene segment from 2006-2007 season to 2017-2018 season were downloaded from GISAID. After phylogenetic analysis using nucleotide sequence information in each season, next prevailed clade were decided based on calculation of Tajima's D value and compared the consensus strain of clade and recommended vaccine strain. Preliminary research showed that a predicted clade from previous season was prevailed in next season in 8 out of 11 seasons. During the flu season in 17-18, two clades were selected to be prevailed in 18-19 season, of which major were 3C2.A1b and 3C2.A2, respectively. This result is consistent with a real time tracking of influenza A by Nextflu [4].

References

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3. Kiyeon K, et al. Inferring epidemiological dynamics of infectious diseases using Tajima's D statistic on nucleotide sequences of pathogens. Epidemics. 2017;21:21-29.
4. Neher R, Bedford T. nextflu: real-time tracking of seasonal influenza virus evolution in humans. Bioinformatics. 2015;31(21):3546-3548.

Transmission dynamics and control of Dengue outbreak in Tokyo in 2014

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Abstract

Background: Dengue fever is one of the most common mosquito-borne infectious diseases all over the world. *Ades.aegypti* and *Aedes. albopictus* are known as the major vector species of four serotypes of Dengue virus (DENV). Japan is not dengue endemic country, but an increasing number of imported cases are placing this country under dengue threat. In 2014, the first indigenous dengue outbreak was reported in Tokyo, finally causing 160 notified cases over the epidemic[1]. This unusual outbreak prompts researchers to analyze potential epidemic dynamics. The purpose of this study is to estimate the generation time and assess the effectiveness of various countermeasures.

Methodology: According to the notified cases data in Japan which includes the information of exposure experience to suspected parks, we classified three types of cases: (1) cases with exact exposure time of one day (type-1); (2) cases with serial exposure time of several days (type-2); (3) cases with no information of exposure time (type-3). First, for each type of cases, the model was developed accounting for the generation-dependent epidemic patterns of cases. Second, probability distribution of incubation period was estimated using explicit exposure time and illness onset time of type-1 cases. Last, the effective reproduction number was estimated by generation, assessing the impact of control intervention which were captured by the piecewise function.

Results: The different models by generation were compared based on Akaike Information Criterion (AIC). The best-fit model with the minimal value of AIC was determined. The course of outbreak was well identified by using the model of three generations of transmission. Moreover, the unknown first infection time was also estimated as around two weeks prior to the first day of illness onset of all cases.

References

1. Kutsuna S, kato Y, Moi ML, Kotaki A, Ota M, Shinohara K, et al. Autochthonous dengue fever, Tokyo, Japan, 2014. Emerg Infect Dis. 2015;21(3).

Development of a quantitative simulator of HTLV-1 proviral integration sites

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Abstract

Background: Human T-cell leukemia virus type 1 (HTLV-1) is a persistent CD4 T-lymphotropic retrovirus. Most HTLV-1 infected individuals remain asymptomatic, but a proportion develop adult T cell leukemia (i.e., ATL) or inflammatory disease, such as HTLV-1-associated myelopathy (i.e., HAM). Interestingly, the clonality of proviral integration sites are different between ATL and HAM (monoclonal vs. polyclonal). Therefore, if we understand a mechanism of the future clonality based on HTLV-1 infection dynamics, we can predict disease progression at asymptomatic phase.

Materials and Method: In order to establish a model predicting the clonality, we focused on two properties of HTLV-1; cell population dynamics and gene expression[1]. We developed a simulator which could describe changes of the clonality dependent on the multiscale dynamics.

Results and Conclusions: By performing the simulations in several conditions, we could know which condition lead to different type of the clonality. This simulator enables us to predict the clonality, and therefore the disease progression.

References

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Stability analysis of the endemic equilibrium of an age-structured SIR epidemic model

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[1]Graduate School of System Informatics, Kobe University

Abstract

The endemic equilibrium of an age-structured SIR epidemic model can be unstable even if it uniquely exists. To clarify the stability and instability regions of it is important both from the theoretical and application points of view. In this talk, we study the stability and instability of the endemic equilibrium of an age-structured SIR epidemic model. Specifically, we show that under an assumption on the transmission rate, the model can be transformed into a system of ordinary differential equations, and the endemic equilibrium is asymptotically stable in some biologically relevant parameter regions[1]. On the other hand, under an assumption that the transmission rate is concentrated in a specific age, we show that the model can be transformed into an integral equation of Fredholm type, and a sustained periodic solution can emerge due to the destabilization of the endemic equilibrium through the Hopf bifurcation[2].

References

1. Kuniya T. Stability analysis of an age-structured SIR epidemic model with a reduction method to ODEs. Mathematics 2018, 6(9), 147.
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Estimating the transmission potential of influenza using distributions of serial cross-sectional seroepidemiological surveys

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[1]Graduate School of Medicine, Hokkaido University

Abstract

Background: Using seroepidemiological surveillance data has been demonstrated to be useful for estimating the cumulative incidence of influenza, measuring the difference of pre and post epidemic seropositive fractions. Nevertheless, such studies relied on almost arbitrarily chosen cut-off value of seropositivity[1,2].

Objective: We aimed to analyze distributions of serial cross-sectional seroepidemiological surveillance data using an epidemiological model, so that the transmission potential can be estimated without imposing cut-off value.

Methods: A mathematical model of influenza transmission with antibody titer level was constructed. The final size equation for pre and post epidemic titer levels was derived. Subsequently, using the estimated distribution of the dilution increase due to infection and measurement error distribution, we optimized the model parameters using the maximum likelihood estimation method.

Results: Without imposing the cut-off level, the cumulative incidence was quantified, yielding an estimate of the basic reproduction number. For the purpose of exposition, the proposed method was applied to A/Victoria/3/75 (H3N2) epidemic data collected from Houston, Texas[3], comparing serological data between 1975 and 1976.

Conclusion: Proposed method without cut-off yields better predictive performance than that using the cut-off value of hemgagglutination inhibition level.

References

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3. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974-76. N Engl J Med 1978; 298:587-592.

Reconstructing the epidemic dynamics of measles in Yamagata, Japan, 2017

Tetsuro Kobayashi[1], Hiroshi Nishiura[1]
[1]Graduate School of Medicine, Hokkaido University

Abstract

Background: Measles is a highly infectious disease caused by measles virus, genus Morbillivirus in the family *Paramyxoviridae*. While immunization has successfully reduced local transmissions, imported cases of measles leading to multiple generations of local transmission have been frequently reported in Japan. The aim of this study is to analyse a measles outbreak that occurred in 2017 that involved 60 people in Yamagata Japan.

Methods: Nineteen cases were those whose infectors were not identified. Of the remaining 41 cases, 25 were in the first generation (infected by the index case), and 15 were in the second generation. From the data, the epicurve, f(t), was expressed by convolution:

$$f(t) = R_0 g(t) + R_0 R_1 \sum_i g(t-i)g(i) + R_0 R_1 R_2 \sum_j \sum_i g(t-i-j)g(i)g(j)$$

where R_0, R_1, and R_2 are the average number of first-, second-, and third-generation cases infected by a single case, respectively. We then estimated the risk of infection at driving school/hotel and "the most probable infectors", by picking the person with the probability of infecting the person is the highest, to reconstruct the infection tree.

Results/Conclusions: The reproduction numbers of each generation (R_0, R_1, and R_2) were estimated at 25.09, 1.30, and 0.04, respectively. The risk of infection is 120 times higher at the driving school or hotel than the community infection. The reconstructed tree was comparable with the actual tree drawn from the later article[1].

References

1. Komabayashi K, et al. The Largest Measles Outbreak, Including 38 Modified Measles and 22 Typical Measles Cases in Its Elimination Era in Yamagata, Japan, 2017. Jpn J Infect Dis. 2018 Nov 22;71(6):413-418.

A comparison between HCV JFH-1 and Jc1 strains by quantitative analysis of infection dynamics.

Shoya Iwanami[1], Kosaku Kitagawa[1], Hirofumi Ohashi[2], Yusuke Asai[3], Koichi Watashi[2], Shingo Iwami[4]

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Abstract

Background: Two strains of hepatitis C virus (HCV), JFH-1 and Jc1, have the same genomic sequence in the non-structural region and different sequences in the structural region. While HCV JFH-1 particles assemble on the lipid droplets, Jc1 assembles around the endoplasmic reticulum. Also it is known that Jc1 particles are abundantly secreted at earlier time points after infection compared with JFH-1. In this study, we quantitatively analyzed and compared the dynamics as well as the entry, replication, and secretion efficiencies by using mathematical analysis and experimental data in a cell culture system.

Materials and methods: We developed a mathematical model including dynamics of intracellular virus RNA. Our model was formulated by partial differential equations (PDEs) which is multi-scale model to simultaneously describe intercellular virus infection and intracellular virus replication [1-3]. We analyzed the experimental data of HCV JFH-1 and Jc1 infection in cell culture using the mathematical model and estimated Malthusian parameter (fitness), virus infection rate, virus production rate, fraction of infectious virus among produced virus and growth rate of intracellular virus RNA.

Results: From the mathematical analysis using quantified experimental data, we found that HCV JFH-1 strain had higher growth rate of intracellular RNA and fitness than Jc1 strain. HCV Jc1 strain had higher infection rate and virus production rate than JFH-1 strain, however, the fitness of Jc1 strain was lower than JFH-1 strain due to the small amount of accumulated intracellular virus RNA.

Conclusions: We calculated distributions of the intracellular virus RNA against times after infection by the PDEs model. We confirmed that the amount of intracellular virus RNA of JFH-1 strain gradually became larger than that of Jc1.

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Prediction of antagonism/synergistic effect of multidrugs against hepatitis C virus considering drug interactions

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Abstract

The hepatitis C virus (HCV) is a main cause for liver cancers around the world[1]. So far, lots of direct-acting-antivirals(DAAs) directly inhibiting HCV life cycle have been developed. In particular, combination therapy using multiple drugs is more effective than mono therapy. Drug interactions among multiple drugs are well-known to affect drug concentration in patients, which may cause less anti-viral effects. Recently, a novel model describing the drug interactions has been proposed[2]. However, the interaction on DAAs is not investigated yet. Therefore, in this study, we applied the novel model to predict the antagonism/synergistic effect of multidrugs of DAAs. We analyzed the experimental data using HCV replication system and 6 DAAs[3]. We demonstrated that the proposed model is more enough to explain the data, compared to Bliss model which considers independent effect between 2 drugs. Moreover, the Bliss model overestimates drug efficacies of DAAs. This suggests that the antagonism/synergistic effect should be considered to accurately evaluate anti-viral effects. In addition, the drug interaction network of 6 DAAs is estimated. This finding indicates that DAAs inhibiting same process of HCV life cycle can be antagonism whereas the ones inhibiting distinct process may be synergistic.

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Estimation of reporting ratio of sentinel influenza surveillance using seroprevalence data

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Abstract

The cumulative incidence of infectious disease is an essential information to asses the disease burden. However, as for influenza, the cases are tracked only in sentinel medical institutions (SMIs), and we need to somehow estimate the cumulative incidence from such a sample. In this study, we consider employing seroprevalence elevation during one epidemic season for the estimation of incidence rate. Season 2009/10 was induced by pandemic virus 2009pdm and hence vaccination administrated in 2008 is expected to yield very limited gain in seroprevalence. Mizumoto el al. [1] estimated age-specific incidence rates and concluded that the reported proportion is much higher in children while very low in elderly people. Unlike to conventional methods, including the so-called multiplier one [2,3] and utilization of medical linked to influenza-like illness (ILI) [4], which captures clinical incidences, the proposed one captures biological flu cases including asymptomatic ones.

We verify the proposed method by applying the same procedure to both of 2009/10, 10/11 and 15/16 seasons. Though the estimations are limited by large confidence intervals due to the number of serosurveillance participants (n = ~500 per age group), the estimate against 2009/10 coincides with those against the other two within the CI except certain age groups. Age-dependence of the proportion reported is roughly the same as that provided by a single season. The detail will be explained in presentation. The estimate of proportion reported against 2009/10 provides roughly three-times larger incidence than those provided by conventional methods [2,3]. Taking a metanalysis, which stating that the net cases are twice large as symptomatic ones, our estimation may be interpreted to include people who experienced further faint influence from flu than the so-called asymptomatic cases. We also carry out an estimation of the proportion reported referring the data of both the two seasons, employing a simplified SIR-like state transition model accounting vaccination effect. However, its age-dependence is roughly the same as each single-season-based estimation.

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Evolutionary selection of HIV-1 mutant among specific immune-background populations

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Abstract

It is well known that the mutant-type virus (MT-virus) sometimes emerges during the wild-type virus (WT-virus) spread depending on host immune-background. Usually, this evolutionary selection is understood by "invasion problem" of MT-virus into host population. In this study, we investigated how the MT-virus compete and invade into (i) the WT-virus endemic and (ii) the WT-virus spreading host population in the context of HIV-1 pandemic. Interestingly, we found the lower and upper boundary of the probability for the MT-virus major outbreaks among the different immune-background populations.

Simulation-based assessment of model selection criteria during the application of benchmark dose method to quantal response data

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Abstract

Benchmark dose (BMD) method has been increasingly used for risk assessment practice, including the determination of the point of departure for toxicological assessment of chemical substances[1]. Besides, model selection criteria have been highly variable by existing guidelines of different organizations. Here we implemented a simulation-based investigation to identify the optimal model selection criteria as applied to quantal response data.

Using standard distributions that consist of one or two parameters, the BMD method was employed to analyze three different empirical datasets, each for a single chemical substance, and we first identified the best fit model using the Akaike Information Criterion (AIC). We regard the identified best model for each chemical substance as the unbiased true model with a known lower bound of the benchmark response level at 10% (i.e. unbiased BMDL10). Subsequently, we randomly generated 1,000 sets of data from the best model. For each dataset, we optimized all standard distributions again and compared if a proper BMDL10 estimate, which should be (i) lower than unbiased BMD10 and (ii) ideally close to the unbiased BMDL10, would be recovered by a specified model selection criterion, including model averaging method.

Datasets with frequent testing at doses either with high or low response rates alone as well as datasets with doses involving both high and low response rates were examined. For the data with high response rates alone and that with both high and low response rates, model averaging of three best-fit models yielded the most appropriate estimate of BMDL10. The use of AIC was slightly superior to the model averaging method for the data with low response rates alone. The use of the lowest BMDL10 was not optimal even after removal of bad fit models by goodness-of-fit test (p-value) or using the rejection rules of thumb as BMD10/BMDL10>10.

Among the examined datasets, the use of model averaging and AIC were theoretically supported. The use of the lowest BMDL10 was too conservative, especially for the datasets with only small sample size. Except for “near linear” dose-response curves, the model averaging method may act as an essential technique to implement toxicological risk assessment using the BMD method.

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Estimation of the basic reproduction number using viral sequence data and the number of reported cases per sentinel

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Abstract

Background: The basic reproduction number R0 is the average number of secondary cases generated by a single infected individual. R0 is used to predict the final size of an outbreak or to set a goal of vaccination coverage and it is considered as one of the most important indexes in developing health policies and countermeasures. However, estimation of R0 is a very difficult task since necessary data is based on the report of symptomatic cases and such data is usually biased and often missing especially in the beginning of outbreaks or small outbreaks. In this talk, we use both viral sequence data and the reported number of cases and develop more robust method to estimate R0.

Material and method: Viruses often mutate when new infections occur. This means the diversity of viral sequences reflects the variety of infected population, i.e. the number of the infected humans. Asymptomatic patients as well as patients who do not come to hospitals are not reported, hence not counted as cases and this causes serious underestimation of the size of an outbreak. However, this issue can be avoided by tracing the diversity of the viral sequences. The influenza A(H1N1) genome data was collected from Genbank and it was divided into clusters based on coalescent tree. The growths of infected population on the tree as well as the number of reported cases were described in the form of likelihood function.

Results: The constructed likelihood functions were applied to the detected influenza A(H1N1) 2009 viral sequences in Japan and the number of reported cases per sentinel in each prefecture. The intrinsic growth rate and reporting rate were estimated and the basic reproduction number R0 was computed using the obtained parameters.

Conclusions: Through this study, we confirmed that our method successfully estimated R0 by viral sequence data and the reported number of cases. In real time analysis, we often encounter situations in which available data is quite limited and the transmission pattern is not clear. We believe that our approach plays an important role in R0 estimation.

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Estimating the force of infection with *Helicobacter pylori* in Japan

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Abstract

Background: Whereas the seroprevalence against *Helicobacter pylori* (*H. pylori*) in Japan has declined over the birth year[1], Japanese people have yet exhibited a relatively high risk of gastric cancer[2]. The present study employed mathematical models to estimate the time- and age-dependent force of infection with *H. pylori* in Japan, predicting the future seroprevalence by time and age.

Methods: We investigated the published seroprevalence data against *H. pylori* in Japan from 1980-2018. Solving the McKendrick partial differential equation model, the seroprevalence was modeled as a function of survey year and age. Maximum likelihood estimation was conducted to estimate parameters governing the time- and age- dependent force of infection.

Results: Among all fitted models, the time-dependent and age-independent model with an exponentially decaying force of infection over years was most favored. Fitted models indicated that the force of infection started to decrease during and/or shortly after the World War II. Using the parameterized model, the predicted fraction seropositive at the age of 40 years in 2018 was 0.22, but it is expected to decrease to 0.13 in 2030 and 0.05 in 2050, respectively.

Conclusion: The time-dependence was consistent with the decline in the force of infection as a function of birth year. The force of infection has continuously and greatly declined over time, implying the diminished transmission of *H. pylori* through the time course and small chance of persistence. These findings are critical to anticipate the future decline in gastric cancer incidence.

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Model of lung cancer considering smoking status and prediction of future trend of lung cancer

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Abstract

Background: Smoking is one of important risk factors of lung cancer[1]. In Japan, smoking prevalence is decreasing. In particular, smoking prevalence in male was 82.3% in 1965 and 29.7% in 2016[2]. On the other hand, aging of Japan's society is proceeding. In these circumstances, the incidence of lung cancer goes on increasing because elderly population tend to be affected by lung cancer. The aim of this study is developing a simple mathematical model to describe the population dynamics concerning smoking status and carcinogenesis of lung cancer and predicting future trend of lung cancer for male and female population.

Materials and methods: We consider a compartmental model dealing with smoking status and lung cancer, which is based on McKendrick partial differential equation. There are four compartments: never-smoker, smoker, ex-smoker, and population of lung cancer. The model is transformed to the ordinary differential equation for each one-year age class by using method of characteristics. Unknown parameters are estimated by maximum likelihood estimation from the following data: number of population, number of deaths, number of lung cancer incidences, number of deaths due to lung cancer, and smoking prevalence.

Results: We obtain estimates of parameters and future trends of lung cancer incidence and deaths. Lung cancer incidence of total male and female population is going to continue to increase by the mid-2020s and the mid-2030s, respectively. As for male lung cancer, the incidence reaches 77,723 at 2024 and the number of deaths reaches 64,510 at 2026. As for female lung cancer, the incidence reaches 42,945 at 2035 and the number of deaths reaches 32,845 at 2036.

Conclusions: Transforming the compartmental model based on McKendrick equation to the ordinary differential equation of one-year age class, we can fit the model to the data. This model takes account of demography and is useful to predict lung cancer incidences and lung cancer deaths in a rapidly aging society.

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Modeling of cell to cell infection in a growing plaque

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Abstract
In this talk, we present a mathematical model for plaque growth when we see the amplification of the virus during plaque growth as a reaction. Assumption of modelling is introduced to account for the infected cells are injected with cells fixed in the plate. We consider the changes of infectious cell, target cell, eclipse phase cell, infectious cell and dead cell during cell to cell infection. Considering the arrangement of cells in the plate based on cell size, we present process of mathematical modeling and numerical results according to time and space. This model provides a means of exploring how changes in the host interactions of the virus will appear in growing growth.

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Population attributable fraction of Helicobacter pylori for gastric cancer in Japan

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) is known as the most important cause of gastric cancer. The population attributable fraction (PAF) for noncardia gastric adenocarcinoma was estimated at 89% in a published study. However, the seroprevalence of *H. pylori* in young generations is decreasing rapidly in Japan, and it is anticipated that the PAF estimate will also vary with time, potentially confusing people in interpreting the results. The present study aimed to identify the impact of decreasing incidence of infection on the resulting PAF estimate of cancer.

Materials and methods: We investigate PAF of *H. pylori* that is considered as responsible for gastric cancer in the world and in Japan from 1997 to 2017. We described the relationship between the change in prevalence of *H. pylori* and of PAF of gastric cancer in Japan is compared.

Results: The incidence of *H.pylori* infection appeared to have been decreasing in Japan. The PAF in Japan is decreasing as the prevalence is decreasing.

Conclusions: Biologically important fraction should not be estimated by ordinary calculation of PAF. The estimation of PAF requires careful attentions for the population with time-dependent prevalence change.

Infectious Disease Modeling with Infectious-Age Dependency for Parameter Estimation of the Dynamics of Human Papillomavirus and Cervical Cancer

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Abstract

Background: Cervical cancer is one of the most serious diseases threatening lives of women. Nearly all cervical cancer are known to be caused by infection of Human papillomavirus (HPV). Because HPV is a common viral infection by sexual intercourse with which most sexually active women and men are infected at least once in their lives, it is the important task to administer vaccine into adolescents before they become sexually active. It is an interesting subject to predict the number of future patients of cervical cancer corresponding to each vaccination strategy by composing mathematical model which describes the process toward cervical cancer via HPV. Mathematical model is useful to investigate the relation between vaccination and canceration. Force of infection of HPV depends strongly on age, and transition to cancer is so slow that demographic state changes meantime. Therefore age dependency is essential.

Materials and Methods: We constructed an age-dependent Kelmack-McKendrick type partial differential equation (model A). Moreover, we composed the model related to three independent variables: time, age, and infectious-age (model B). We performed the maximum likelihood estimation. The likelihood function was calculated from data: population, death, cervical cancer incidence, deaths of cervical cancer, and prevalence of HPV. The data were collected from National Cancer Center and Health, Labour and Welfare Statistics Association and earlier studies.

Results: The model A was able to capture carcinogenesis from the cohort which has large infected population. However, it could not represent recent trend of cancer incidence. In recent years, the incidence of cervical cancer in relatively young people is rapidly increasing, and as a result incidence of cervical cancer tends to have a bimodal age distribution. But the model shows a unimodal one. On the other hand, in the model B this trend was observed clearly. Mortality of cervical cancer were well represented, and the infection rate was estimated to be considerably less than it actually was.

Conclusions: HPV is an example showing the effectiveness of considering a mathematical model depending on time, age and infected age in data analysis of infectious diseases by mathematical model. Meanwhile, we need data not only on population and cancer but also

on HPV prevalence in order to accurately estimate the balance between force of infection and hazard that controls the mechanism leading to cancer via infection.

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Quantifying the intracellular dynamics of hepatitis B virus using Primary Human Hepatocyte system

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Abstract

Hepatitis B Virus (HBV) is widespread infectious disease and more than 240 million people are chronic infected until today[1]. The reason why patients have chronic infection is the existence of reservoir of hepatitis B virus, which is known as covalently closed circular DNA (cccDNA)[2]. Although it is well understood that cccDNA remains in infected so long time, quantitative understanding such as how and how long does this cccDNA remain in infected cells is poorly understood. In this study we tried to investigate the mechanism of cccDNA persistence combining mathematical model and Primary Human Hepatocyte (PHH) experimental system. Interestingly, our analysis indicated that the mechanism of cccDNA persistence is the long half-life of cccDNA and small amount of recycling of cccDNA.

Acknowledgement

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Age-structured SIS epidemic model in a periodic environment

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Abstract

In this talk, we discuss existence and stability of periodic solutions for the age-structured SIS epidemic model in a time-periodic environment. For the autonomous case, the age-structured SIS model has been studied by several authors ([1]-[3]), while the time-periodic case, Kuniya and Inaba [4] proved the existence of a periodic solution by traditional integral equation method. Here we consider the periodic case again based on the idea of the basic reproduction number for time-heterogeneous environment.

For simplicity, we assume that the host population already attained a time periodic solution $P^*(t,a)$ with period $\theta > 0$, which is the age-density function of host population at time t (a denotes age variable). Then the age-density function $I(t,a)$ of the infected population satisfies a single equation:

$$\frac{\partial I(t,a)}{\partial t} + \frac{\partial I(t,a)}{\partial a} = \lambda(t,a)(P^*(t,a) - I(t,a)) - (\mu(t,a) + \gamma(t,a))I(t,a), \quad (1)$$

where $\lambda(t,a) = \frac{1}{N^*(t)} \int_0^{a_\dagger} \beta(t,a,\sigma) I(t,\sigma) d\sigma$ $N^*(t) := \int_0^{a_\dagger} P^*(t,a) da$, λ denotes the force of infection, β is the transmission coefficient, μ the death rate and γ the recovery rate, all parameters have time-period θ. Since we neglect the vertical transmission, we assume that $I(t,0) = 0$.

First based on the evolution semigroup approach, we calculate the basic reproduction number R_0 and show that the zero solution (corresponding to totally susceptible periodic host population) is globally asymptotically stable. Next existence and uniqueness problem of periodic solution is formulated as a fixed point problem of the corresponding evolution semigroup. Finally we discuss that the periodic endemic solution is globally stable.

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