Final Technical Report of International Research Chairs Initiative (IRCI)

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Keywords: infectious diseases, transmission, epidemiology, mathematical modeling, control, China

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Acronym List

IRCI	International Research Chairs Initiative
HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
STD	Sexually transmitted disease
CDC	Center for disease control and prevention
MSM	Men who have sex with men
ART	Antiretroviral therapy
NCAIDS	National Center for STD and AIDS Control and Prevention
IDU	Injection drug use
TasP	Treatment as prevention
GACP	Guangxi AIDS Conquering Project
NFATP	China's National Free Antiretroviral Treatment Program
VL	Viral load
CI	Confidence interval
TLC	Test, linkage and care

i. Project Information

Project title: International Research Chairs Initiative (IRCI): Modelling and controlling infectious diseases (104519-010)

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Project Abstract:

Infectious disease control is a major challenge in China due to China's fast growing economy, changing social networks and evolving health service infrastructures. The success of disease control in China has a profound impact beyond its borders. In support of better disease control, this five year research program was designed to enhance China's national capacity for analyzing, modeling and predicting transmission dynamics of infectious diseases through joint research, training young scientists, and building collaborative relationships. This successful program was led by the National Center for AIDS/STD Control and Prevention (Chinese Centre for Disease Control and Prevention, China) and the Centre for Disease Modeling (York University, Canada), and involved a number of Canadian and Chinese universities in various areas of infectious disease modelling and control. The bilateral collaboration also trained numerous highly qualified personnel and built a network for sustaining collaboration. This capacity building was facilitated by joint projects and bilateral annual meetings in major cities in China and Canada. The research activities on modeling major public health threats of infectious diseases focused on major diseases in China and/or issues of global public health concern including HIV transmission and prevention among high risk population, HIV treatment and drug resistance, influenza, schistosomiasis, mutation and stemma of SIV and HIV, latent and active tuberculosis infection, HBV control and vaccination. The outputs of the project were reported through peer-reviewed publications and modelling–based and science-informed public policy recommendations.

ii. The Research Problem

Infectious disease control is a major challenge in China due to China's fast growing economy, changing social networks and evolving health service infrastructures. The success of disease control in China has a profound impact beyond its borders. Despite growing strong theoretical studies on modeling and analysis, and rapid development of sophisticated public health

surveillance systems, there is a significant gap linking the surveillance data, public health policy and modeling in China and there is an urgent need for a new generation of scientists leading the interface between qualitative science and public health decision making. The objective of this project was to enhance China's national capacity for analyzing, modeling and predicting transmission dynamics of infectious diseases through efforts in joint research, training junior scientists and students, and building collaborative relationship.

The spread of an infectious disease involves characteristics of the agent, the host and the environment in which transmissions take place. The purpose of disease modeling, in relation to public health, is to evaluate the agent-host-environment interface and efforts to alter the interface through intervention to our advantage, be they preventive or therapeutic in nature. In recent years researchers in this area have developed more complex and biologically relevant models that have become important for influencing the design of control programs. Some of these models have been developed for new diseases and others for new treatments; some involve evolutionary aspects and others consider new patterns of social behavior and travel. Recent development of disease modeling theories has also been driven by outbreaks of emerging/reemerging infectious diseases, and cutting-edge techniques involve interactions of deterministic compartmental models, stochastic sensitivity analysis, network modeling and Markov chain Monte Carlo simulations. These techniques are often complemented with computer simulations, which use demographic and disease incidence data, as well as health economic parameters such as costs.

The HIV epidemic in China is regionally diverse. Rural provinces and regions where widespread poverty exists are responsible for a disproportionately high number of HIV cases. One of our study sites was one of the worst affected areas of Sichuan province where the HIV infection rate was about 10% of the total population. In this region, the spread of HIV was from injection drug users to the general population. In addition to our focus on the HIV epidemic, our project team has also made substantial progress in modeling other major infectious diseases including TB and influenza (H1N1, H7N9), which are of considerable interest to public health in China. Key epidemic features of the H7N9 outbreaks in the spring of 2013 have been identified using a novel mathematical approach in a recent study.

iii. Objectives

1. To develop, validate and utilize mathematical models for analyzing and predicting dynamics of communicable diseases such as HIV, tuberculosis, and hepatitis, using Chinese Center for Disease Control and Prevention (China CDC) surveillance data and prospective cohorts from;
2. To provide support for public health decision makers through improved evidence based decision making in disease control policies by using model assisted analyses and predictions;
3. To train young scientists in applying cutting edge techniques of mathematical modeling and analysis in an interdisciplinary public health setting;
4. To organize workshops and professional exchange events that improve collaboration among trainees, researchers and public health officials in China and Canada as well as with other international collaborators; and
5. To extend training and modeling applications derived from this project into countries where there are needs, professional alliances and strategic opportunities.
6. Collect and further analyze the data from a pilot study initiated in Liangshan in 2013. This pilot study will be used to assess the impact of an integrated approach to control HIV/AIDS in one of China's high epidemic regions through real world data in order to adjust the management and policy strategy for its future scale-up;
7. We will conduct data analysis and modeling of HIV transmission from partner to partner. The significant parameters of relevant data for modeling will be collected through epidemiological and molecular studies currently underway at China CDC. The further modeling analysis will inform the public health decision on drug adherence education and management, resistance surveillance, and harm reduction;
8. The modeling of HIV incidence infections and epidemic trends will be used at the provincial and prefectural level. More detailed and accurate dataset will be used to validate and improve our modelling work. Combined with the mathematic modeling, our new methods of high-accuracy identification of incident HIV-1 infections and accurate determination of the transmission direction of HIV between individual will provide insights and prediction of HIV transmission dynamics and epidemic trend;
9. To continue to engage young scientists, using an interdisciplinary approach involving the China CDC's public surveillance data and prospective cohorts for developing, validating and utilizing mathematical models for analyzing and predicting disease dynamics, in support public health decision making.

iv. Methodology

A key feature of the project in developing methodologies has been interdisciplinary collaboration involving expertise in epidemiology, virology, bioinformatics, biostatistics, dynamic modeling, stochastic simulations and sensitivity analysis. Another important feature is the heavy influence of public health policy on the design, analysis and simulations of mathematical models, as well as the translation of these modeling analysis into policy recommendation that has, in a few cases, direct influence on the decision making and government's investment on disease prevention and control (with focus on marginalized population and ethnic minority). Equally important, this project also led to the development of cutting-edge mathematical modeling frameworks and analytic techniques motivated by real public health issues faced in China. Finally, we have been very careful in balancing the capacity building and project completion by involving a large number of highly qualified individuals and by organizing annual events to bring the team and their Canada-China collaborators together.

Based on a broad spectrum platforms for infectious disease interventions and the excellence in surveillance and diagnostics at the China CDC, this project has drawn on expertise and research capacity at the Chinese CDC and Centre for Disease Modelling in York University to launch a new era of bilateral collaboration. Together, we have developed new methodologies and theoretical models as well as applying mathematical, bioinformatics, statistical, and computational tools capable of impacting the health of the people of China and Canada for guiding public health policy decision making under the aegis of the Ministries of Health in Canada and China. Besides HIV modeling, we have updated data in modeling other major infectious diseases including TB and influenza (H1N1, H7N9) of considerable interest to the public health in China.

The five-year collaboration project has enabled China CDC to build a national interdisciplinary network for mathematical modeling and analysis with participating scientists and research nodes distributed through some of the best Chinese universities. Additional funding over two years expanded the network to include a new participating team from Shaanxi Normal University. In addition to Chinese national surveillance public data, the two-year project extension generated several prospective cohort studies led by Dr. Shao. Key partners of local CDCs (Beijing, Liangshan in Sichuan, Guangxi) supported these cohort studies among several high risk populations and HIV patients. These cohort studies provided high quality data to parameterize, validate and utilize the mathematical models developed and to be developed. Model based analysis helped the evaluation of various control and intervention programs implemented in the relevant cohort studies, and help the development of suggested improvement.

We describe the methodologies and techniques below for sub-projects.

Theme 1: HIV/AIDS Surveillance, Treatment and Prevention

Sub-theme: Treatment-as-prevention in serodiscordant couples in China
Project 1.1: Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003-11): a national observational cohort study

Method: In this retrospective observational cohort study, we included treated and treatment-naive HIV-positive individuals with HIV-negative partners of the opposite sex who had been added to the national HIV epidemiology and treatment databases between Jan 1, 2003 and Dec 31, 2011. We analysed the annual rate of HIV infection in HIV negative partners during follow-up, stratifi ed by treatment status of the index partner. Cox proportional hazards analyses were done to examine factors related to HIV transmission.

Main finding: We calculated a 26% relative reduction in HIV transmission (adjusted hazard ratio 0·74, 95% CI 0·65–0·84) in the treated cohort. The reduction in transmission was seen across almost all demographic subgroups and was significant in the first year (0·64, 0·54–0·76), and among couples in which the HIV-positive partner had been infected by blood or plasma transfusion (0·76, 0·59–0·99) or heterosexual intercourse (0·69, 0·56–0·84), but not among couples in which the HIV-positive partner was infected by injecting drugs (0·98, 0·71–1·36). which suggests that the treatment-as-prevention approach is a feasible public health prevention strategy on a national scale in a developing country context. The durability and generalisability of such protection, however, needs to be further studied.

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Sub-theme: A mathematical modeling study for innovation prevention of the HIV transmission in the Liangshan Prefecture of the Sichuan Province of China
Project 1.2: A mathematical modeling study of the HIV epidemics in the Liangshan Prefecture of the Sichuan Province of China

Methods: A mathematical model was set up to describe the population dynamics of HIV transmission in study area. The model was calibrated by fitting it to the HIV testing and treatment data from 2005 to 2008. Validation of the model was done by comparing its predicted value of HIV prevalence in 2010 to the prevalence data obtained in the 2010 population wide HIV testing. The validated model was used to produce estimation of HIV incidence, prevalence and death.

Main finding: Our model estimations show that population-based HIV interventions have significantly slowed down the rise of the HIV epidemic in the two townships. Over the five-year period from 2005 to 2010, the year-over-year rate of increase in HIV incidence, prevalence, and death has declined by 91.5%, 28.7%, and 52.3%, respectively. Mathematical models, when integrated with epidemiological and surveillance data, can be an effective tool for predicting the temporal dynamics of HIV and assessing the impacts of HIV interventions.

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Project 1.3: A mathematical modeling study of the effectiveness of the Green Home intervention for controlling HIV transmission among IDUs in the Liangshan Prefecture of the Sichuan Province of China
Methods: Injection drug use (IDU) is the main pattern of HIV transmission in the Liangshan Prefecture of the Sichuan Province of China. Such rural areas where widespread poverty exists are responsible for a disproportionately high number of HIV cases. Green Home is an innovation intervention strategy that provided HIV care, ART treatment, methadone maintenance therapy, occupation education and employment. A mathematical model was set up to investigate the effectiveness of the intervention of Green Home in controlling the HIV transmission via taking drugs. The model without Green Home was calibrated by fitting it to the data of newly diagnosed HIV-positive cases infected via taking drugs during 2010-2016. Then, based on the parameter estimation, the model with Green Home was used to produce the estimation of HIV incidence and prevalence.
Main finding: Our model estimations show that the basic reproduction number among drug users in Liangshan is still higher than 1 for the recent years. Currently, voluntary detoxification center could not significant reduce the HIV new infection or basic reproduction number. With the Green Home, the reproduction number (control reproduction number) quickly decreases below 1. Our numerical simulations show that the Green Home intervention significantly slowed down the transmission of HIV in terms of newly diagnosed HIV-positive cases and new HIV-infections (including the undiagnosed HIV-infections) when at least 30-60% of injection drug users participate in Green Home.

Sub-theme: HIV transmission and incidence studies
Project 1.4.: Modeling for HIV transmission among men who have sex with men in China
Method: Men who have sex with men (MSM) are much more likely to be infected with HIV than the general population. China has a sizable population of MSM, including gay, bisexual men, male prostitutes and some rural workers. So reducing HIV infection in this population is an important component of the national HIV/AIDS prevention and control program. We develop a mathematical model using a sex-role-preference framework to predict HIV infection in the MSM population and to evaluate different intervention strategies.
Main finding: HIV will spread very fast in the MSM population unless intervention measures are implemented urgently. Antiretroviral therapy can have substantial impact on the reduction of HIV among the MSM population, even if disinhibition is considered. The effect of protected sexual behavior on controlling the epidemic in the MSM population largely depends on the sex-ratio preference of different sub-populations.
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Project 1.5: Modelling the effects of adherence to the HIV
Methods: Recently, the first drug in a new class of antiretroviral HIV drugs was approved, the fusion inhibitor enfuvirtide. We develop a mathematical model that describes the binding of the virus to T cells. We model the effect of enfuvirtide upon this process using impulsive differential equations.
Main finding: We compared the equilibrium value between no therapy and with therapy with perfect adherence. We determined analytical thresholds for the dosage and dosing intervals to ensure the disease-free equilibrium remains stable. We also explore the effects of partial adherence. Our theoretical results suggest that partial adherence may, at times, be worse than no therapy at all, but at other times may in fact as good as perfect adherence. It follows that patients should be counselled on the importance of adherence to this new antiretroviral drug.
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Project 1.6: Develop a genetic method recognizing the HIV transmission direction between linked pair.

Method: Derived a set of common patterns from the HIV-1 viral sequences which differ in their coreceptor usage.
Main finding: The number of unique common patterns in viral sequences decreased with transmission but remained almost constant with the progress of disease in an individual. This number was then used as an estimator to determine transmission direction.
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Sub-theme: Prediction of B-cell epitopes
Project 1.7: B-cell epitopes and HIV sequence
Methods: We developed a novel computational method BEST (B-cell Epitope prediction using Support vector machine Tool) and an ensemble method to predict b-cell epitopes using antigen sequence information. The models can predict both linear and conformational b-cell epitopes.
Main finding: Our method, BEST and an ensemble method can predict both linear and conformational b-cell epitopes using antigen sequence with higher accuracy.
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Sub-them: HIV transmission and prevention modeling
Project 1.8: Dynamical model of HIV epidemic and prevention intervention
Methods : Based on available data on cases of HIV infection and AIDS in mainland China from current surveillance system, we analyzed the characteristics of the HIV/AIDS epidemics and used model simulations to estimate the reproduction number, predict potential infection of the HIV/AIDS in China.
Main finding: (1) We estimated a mean reproduction number and other HIV epidemiological parameters. Our results based on a spatially stratified population dynamical model show that that we need to not only pay attention to the epidemic in severely affected provinces but also focus on the provinces with the epidemic quickly spreading and/or mobility sensitive ones. (2) The HIV/AIDS models with HAART demonstrate that the impact of HAART on the new infection depends on the HAART coverage and the infectivity reduction of the HAART patients. We obtained a threshold value of the infectivity reduction rate. The higher HAART coverage may lead to more infection if the infectivity reduction rate is not good enough.
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Project 1.9: Early HAART Initiation May Not Reduce Actual Reproduction Number and Prevalence of MSM Infection: Perspectives from Coupled within- and between-Host Modelling Studies of Chinese MSM Populations
Method: We proposed an individual based model by coupling within-host dynamics and between-host dynamics and conduct stochastic simulation in the group of men who have sex with men (MSM).
Main finding: The mean actual reproduction number is estimated to be 3.6320 (95% confidence interval: [3.46, 3.80]) for MSM group without treatment. Stochastic simulations show that given relatively high (low) level of drug efficacy after emergence of drug resistant variants, early initiation of treatment leads to a less (greater) actual reproduction number, lower (higher) prevalence and less (more) incidences, compared to late initiation of treatment. This implies early initiation of HAART may not always lower the actual reproduction number and prevalence of infection, depending on the level of treatment efficacy after emergence of drug resistant virus variants, frequency of high-risk behaviors and etc. This finding strongly suggests early initiation of HAART should be implemented with great care especially in the settings where the effective drugs are limited. Coupling within-host dynamics with between-host dynamics can provide critical information about impact of HAART on disease transmission and thus help to assist treatment strategy design and HIV/AIDS prevention and control.
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Sub-them: HIV modeling for HIV treatment and prevention in Guangxi
Project 1.10: The First Decline in HIV Case Report and Incidence in China Occurred in Guangxi Zhuang Autonomous Region in the Context of Combined National and Unprecedented Local HIV Control Initiative
Methods: In response to a severe HIV epidemic in the Guangxi Zhuang Autonomous Region,

the Guangxi People's Congress passed an AIDS Control Act and the Guangxi government launched the 5-year (2010-2014) Guangxi AIDS Conquering Project (GACP). During GACP implementation, HIV control efforts in Guangxi were greatly enhanced to enlarge HIV testing and antiretroviral treatment (ART) and other intervention measures. We hypothesized that the GACP would reduce reported HIV/AIDS and sexually transmitted disease (STD) cases as well the HIV incidence in the scale up control measures. We design a study to systematically evaluate the impacts of GACP on HIV epidemic in Guangxi. Epidemiological methods and a SIDT compartmental mathematical model were used to estimate trends in HIV epidemic and incidence. HIV surveillance, testing and counselling, and ART data were used as time dependent parameters to fit the model. The model was also used to describe the reproduction number of R_c in HIV infection in Guangxi.

Main finding: With strong political, legal and financial supports, HIV testing and ART coverage increased 2.6 and 4 fold during GACP, which was far above the national average. Guangxi's HIV and STD case reports peaked in 2011 and then declined steadily from 2012-2014 under GACP; in contrast, HIV and STD reports continued to rise nationally. Our model found a 3.34% reduction in the R_c of HIV infection per year during the GACP. Guangxi is China's first province to demonstrate a decline in HIV and AIDS case reports and HIV incidence. The HIV epidemic turning-point is attributed to the strong local GACP initiatives combined with the National AIDS Control Policy.

Project 1.11: Effects of CD4 and viral load testing on mortality among HIV patients receiving antiretroviral treatment: an observational cohort study in rural southwest China
Methods: Recent studies have suggested that CD4 cell count monitoring has little added value in patients who are virologically suppressed and immunologically stable if viral load (VL) testing is routinely available. These conclusions have not been directly assessed by mortality as a study endpoint in a real-world setting. This HIV treatment cohort study from 2008 to 2014 was conducted in Guangxi, China. We used a Cox regression model to analyze associations between CD4 and VL testing frequency and death.
Main finding: Compared to testing CD4 counts at least three times within the first year of ART initiation, as currently suggested by The Chinese National Free Antiretroviral Treatment Program (NFATP), testing CD4 counts less than twice per year within the first year of ART initiation was significantly associated with death; however, testing CD4 counts twice in the first year of ART initiation did not significantly increase mortality. Compared to testing VL at least once within the first year of ART initiation, as currently suggested by NFATP, no VL tests in the first year of ART initiation was significantly associated with higher mortality. Routine CD4 cell count monitoring did not have an impact on death among HIV patients with VL <1000 copies/mL or CD4 ≥ 350 cells per microliter after 12-months post-ART initiation. Our study suggests that CD4 testing can be reduced to two times within the first year of ART initiation, and be reduced or stopped for patients who have achieved virological suppression or immunologically stability after 12-months of treatment.
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Theme 2. Other emerging infectious disease challenges in China

Sub-theme: Brucellosis control studies
Project 2.1: Modelling for studying Brucellosis
Methods: Brucellosis, a bacterial disease caused by members of the genus Brucella, is a serious zoonosis and a significant cause of reproductive losses in animals. We investigated the transmission dynamics of Brucellosis in Jilin province and Hinggan League of Inner Mongolia, China and presented some control strategies.
Main finding: If culling, sterilizing and decreasing the number of outer importing are used together, dairy cattle brucellosis will be well controlled in Jilin province. Moreover, combination of prohibiting mixed feeding between basic ewes and other sheep, vaccination, detection and elimination are useful strategies in controlling human brucellosis in Hinggan League.
References:
Ref. 2.1. Ming-Tao Li, Gui-Quan Sun, Juan Zhang and Zhen Jin, Global dynamic behavior of a multigroup cholera model with indirect transmission, Discrete Dynamics in Nature and Society 2013, (2013) 703826.
Ref. 2.2. Ming-Tao Li, Gui-Quan Sun, Yan-Fang Wu, Juan Zhang, Zhen Jin, Transmission dynamics of a multi-group brucellosis model with mixed cross infection in public farm, Applied Mathematics and Computation 2014, (237) 582-594.
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Sub-theme: The effectiveness of H1N1/H7N9 control measures
Project 2.2: Prevention study for H1N1/H7N9
Methods: During the influenza A/H1N1 pandemic, very stringent interventions were implemented for the control. We examined the effectiveness of those measures using dynamical modeling along with sensitivity analysis. The model was parametrized using data of initial laboratory-confirmed cases in the province of Shaanxi, and the Markov-chain Monte-Carlo (MCMC) simulations were used to estimate the reproduction number.
Main finding: Our results supported that strengthening local control strategies (quarantine and hygiene precaution) was most effective in mitigating outbreaks and inhibiting the successive waves.
References:
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Ref. 2.6. Zhang Jin, Xiao Yanni, Modeling Strategies for controlling H1N1 outbreaks in China. Int. J. Biomath., 5(2012), 1250017, DOI: 10.1142/S1793524511001593.
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Sub-theme: Hospital infection evaluation
Project 2.3: Modelling for hospital infection control
Methods : We formulated and analyzed deterministic and stochastic mathematical models to examine the roles of environmental contamination and the presence of volunteers played in the nonsocomial transmission (hospital infection) dynamics of antimicrobial drug resistance, and we utilized semi-stochastic simulations and available data from a Chinese hospital to estimate key epidemiological parameters, and then used the parametrized model to assist numerical simulation that concludes that environmental contamination is a key threatening factor for hospital infection in some Chinese hospitals.
Main finding: The basic reproduction number was estimated to be 0.9753. Numerical simulations show that environmental contamination is a threat to hospital infection and free-living bacteria in the environment can promote transmission and initiate infection even if an infection has died out among HCWs (health-care workers) and patients. Sensitivity analysis indicates that a contaminated environment and volunteers contribute substantially to MRSA transmission in hospital infections, and hence effective control measures should be targeted. Hand hygiene of volunteers and cleaning are more effective in reducing the mean prevalence of colonized patients than isolation of newly admitted MRSA-positive patients and hand hygiene of HCWs. Isolation of newly admitted MRSA-positive patients could be influential and dominant in reducing the prevalence of infection when the environment within a ward is sufficiently clean.
References:
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Ref. 2.9. Wang Xia, Xiao Yanni, Wang Junrui, Lu Xinxin, Stochastic disease dynamics of a hospital Infection model, Math. Biosci. 2013, 241: 115–124.

SUB-Theme: Tuberculosis infection projection
Project 2.4: Modelling for TB infection
Methods : We developed several tuberculosis (TB) transmission models, incorporating important public health policy issues in China such as case detection, distinct treatment stages, seasonal variation of incidence rate and floating (mobile) population. These models were used to describe TB transmission patterns in China, and model parameter values were estimated according to demographical and epidemiological data in China. The simulation results were used to describe TB transmission features and to forecast its epidemic trends.
Main finding: (1) The numbers of the whole population, the latent individuals, the infectious individuals, and the new cases from 2005 to 2015 in China will keep increasing slowly. The PPD positive rate will decrease a little, the prevalence rate will increase a little, and the incidence rate will not change much. (2) For children in China, the progression rate from latent TB infection to active disease in children is the highest during the first year after infection, 5.58%. From the second year, the risk declines rapidly, 2.31%. In the third and fourth years, the risk continues to decline, 1.43% and 1.2%, respectively.
References:
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Ref. 2.11. Hui Cao, Yicang Zhou. The discrete age-structured SEIT model with application to

tuberculosis transmission in China. Mathematical and Computer Modelling 55, 2012, 385–395.

SUB-Theme: Modeling HBV/HCV transmission in China
Project 2.5: HBV/HCV modelling
Methods : We developed mathematical models for the HBV/HCV infection dynamics in China. Different vaccination strategies with special consideration of immunity waning were evaluated and simulated.
Main finding: The model simulation shows that the antibody responses induced by recombinant vaccine is early than the blood borne vaccine. The antibody peak of the recombinant vaccine is higher than that of the blood-borne vaccine. The life span of the memory B cells and the long-lived plasma cells has a large influence on the antibody.
References
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Sub-theme: Infection dynamics of generic disease transmission
Project 2.6: Infection dynamics of generic disease transmission
Methods : We studied the dynamics (long-term dynamic behaviors) of some mathematical models of infectious diseases, linking mathematical analysis to real issues of disease prevention and control in China.
Main finding: We developed novel and refined existing mathematical technologies to accommodate the dynamics analysis, such as defining and estimating critical thresholds (basic reproduction numbers), global dynamical behaviors of asymptotical autonomous system and the limit system, the Poincare-Bendixson property, the theory of the compound matrices, Lyapunov function and graph theoretical approach.
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Ref. 2.22. Na Chen, Yicang Zhou, Dynamics of a TB Model with vaccination, Advances in Applied Mathematics, 2012, 1, 1-11.
Ref. 2.23. Zhenguo Bai, Yicang Zhou. Existence of multiple periodic solutions for an SIR model with seasonality，Nonlinear analysis-theory, method & applications, 74(11) 3548-3555, 2011.
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Ref. 2.26. Yang Youping, Xiao Yanni, The effects of population dispersal and pulse vaccination on disease control. Math. Computer Modelling 2010, 52: 1591-.1604.

Sub-theme: Other emerging diseases: West Nile virus, Ebola, Dengue, Zika
Project 2.7: Modelling and dynamics of other infectious diseases including West Nile virus, Ebola, Dengue, Zika and etc and suggests some important control strategies.
Method: Multiple mathematical models, including ODE, the impulsive differential equations, non-smooth models and infection-age structured models, have been formulated to describe transmission dynamics of a certain disease. We theoretically analyze the dynamics of the proposed models, define the threshold value which governs whether or not the disease goes to the extinction. On the basis of the surveillance data we parameterize the formulated model, estimate the unknown parameter, give the value of the basic reproduction number. Further, we carried out the sensitive analysis and obtain the most sensitive parameters. We have also studied the dynamics of epidemic models.
Main finding: For HFMD, our findings suggest that enhancing vaccinations strategy and the frequent cleaning of the environment and enhancing individual sanitation (e.g. regular hand-washing) are effective measures in controlling HFMD infections. For Ebola, we find that shortening the duration between death and burial and improving the effectiveness of isolation are two effective interventions for controlling the outbreak of Ebola virus infection. For Dengue, our findings indicate that quick and persistent impulsive implementation of vector control result in an effective reduction in the control reproduction number and hence lead to significant decline of new infections. We have defined the basic reproductive numbers of epidemic models and got the extinction threshold of the epidemic models.
References:
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Sub-theme: Bioinformatics methods and techniques
Project 2.8: Analysis and prediction of antigen-antibody complex, DNA-binding proteins, and ion-channels using bioinformatics methods.
Methods: A new bioinformatics tool was proposed to identify ion channels and four major subtypes of voltage-gated channels, potassium, sodium, calcium and anion ion channel; A mathematical model was set up to describe the antigen-antibody complex using the convex hull. We build analysis the different depth function for B-cell epitopes and non-epitopes. Ion channels are a class of membrane protein, which is potential drug target; DNA-binding proteins play a pivotal role in gene regulation. We proposed *newDNA-Prot*, a DNA-binding protein predictor that employs support vector machine classifier. We also construct mini metabolic network of beta amyloid and acetylcholine, which stimulate the Alzheimer's disease. A reweighted sparse subspace clustering was proposed (RSSC). The algorithm would be widely used in computer

vision such as motion segmentation and human face clustering.

Main finding: We proposed a method to identify ion channels and four subtypes of voltage gated channels. The predictor achieves accuracy 85.4% and 68.3% for prediction of ion channels and their types; We show the usefulness of mathematical tool using the k-th surface convex hull and depth function; The proposed new method *newDNA-Prot* outperforms the iDNA-Prot, DNAbinder and DNA-Prot methods; We show that possible causes of Tacrine, donepezil, galantamine and huperzine A cannot improve the level of Ach which is against to their original design purpose but they still prevent Alzheimer disease to be worse as beta amyloid deposition appeared; The proposed RSSC performance better than the state-of-the-art algorithms.

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v. Project Activities

1. The IRCI research program built an interdisciplinary research and training network that analyzed, modelled and predicted transmission dynamics of infectious diseases that, in collaboration and coordination with other international research centers, enhanced Chinese national capacity to support data analysis, program evaluation, and inform decision making related to communicable disease control. The IRCI support provided the basis to sustain the research and knowledge translation activities of a research team with important insights into "real-word" considerations related to public health capacity and control strategies. This also provided the much needed experience in transparent, collaborative university-public partnerships. Good public health policies rely on analysis and prediction of disease transmission dynamics, which requires high quality data and a comprehensive system for data analysis. The development of mathematical models takes on added importance both as a possible tool for the comparison of strategies to plan for an epidemic or pandemic, and to deal with a disease outbreak in real time. This program is taking advantage of the expertise of the Canadian team in conducting large-scale interdisciplinary research and in training the next generation, in order to build a critical capacity at the China CDC in this important area, which in turn will contribute to future collaboration between Canada and China.
2. Postdoctoral fellows and graduate students, have been recruited to the program and jointly conducted some carefully selected, policy-driven statistical/mathematical model-based research projects. These students were selected from a variety of backgrounds, and have been interacting and meeting on a regular basis to report their progress. The two group meetings introduced the students to the frontiers of research and to international leaders.
3. This program was designed and implemented successfully to train Chinese leaders in the highly interdisciplinary interface between mathematical modeling/analysis and public health decision making and program evaluation. The program was expected to involve and has indeed engaged relevant industries (e.g., the vaccine and biological sectors) using the China CDC's linkage to provide trainees with important insights into "real-word" considerations related to public health capacities and control strategies, and to help provide leadership in transparent, collaborative university-public- partnerships. IDRC funded projects provide a unique opportunity for Chinese disease modeling personnel to collaborate with researchers affiliated with the China CDC, and thus to their fundamental research on practical issues and major public health policy.
4. Special issue and a new journal: We have started to edit a special issue "Mathematical modelling of Infectious Diseases for Public Health" in the new journal Infectious Disease Modelling. We have selected the contributors. A significant portion of the manuscripts will focus on HIV-AIDS epidemics, where model frameworks are formulated to target at the epidemics feature and intervention practice in China, and the other portion will cover a range of methodologies and infectious diseases based on published work that the China-China team produced in the last seven years. Discussions to have them published in both Chinese and English simultaneously promoted us to contact a number of publishers and ultimately led to the current development of a new journal "Infectious Diseases Modelling" with Keli: http://www.keaipublishing.com/en/journals/infectious-disease-modelling/, a joint adventure between ELSEVIER and Science Press, China's largest STM publisher.
5. In relation to disseminating our results and facilitating knowledge translation, Yiming Shao was a co-chair of the Gates Foundation Annual meeting of Grand Challenges at Oct. 18-21,

2015, in Beijing and Jianhong Wu an invited speaker to this major international event to share our Canada-China experience on using public health data and modeling to inform decision.

6. On June 2-5, 2017, the International Conference of China - Canada International Conference on Disease (CCICDM), sponsored by The IDRC-CRC International Research Chair in Infection Disease Modeling and Management, and the Department of Mathematics of Shanghai University, was successfully held. The conference was jointly funded by the project of "mathematics discipline" and key projects of the National Natural Science Foundation. More than 120 experts, scholars and students from scientific research colleges and universities attended the meeting. The opening ceremony of the China-Canada Joint Center for Infectious Disease (China-Canada Joint research Center for the modeling of Infectious diseases) was also held. Professor Jianhong Wu (Canada Research Chair) and Dr. Yiming Shao (The Chief Expert of National Center for AIDS/STD Control and Prevention (NCAIDS), China CDC) together addressed the opening ceremony.

Additional Funding Related to the IRCI research program

This IRCI program has played an important role in catalyzing (Chinese) national, Canada-China bilateral, and international collaborations with additional funding support from many other agencies. Additional supports and collaboration, in turn, have furthered the IRCI program objectives to build a Chinese focused group for interdisciplinary research and training in analyzing, modeling and predicting transmission dynamics and spread patterns of infectious diseases that, in collaboration and coordination with the Canadian team and other international research centers, and provide the much needed Chinese national capacity to support data analysis, program evaluation, and optimal decision making related to communicable disease control. The involvement and leadership of the China CDC in the development and implementation of public health policy in China has been critical to secure these additional supports due to China CDC's role in facilitating the transfer of modeling data-based scientific discoveries of disease transmission dynamics to optimize the design of intervention strategies. The involvement of York University's CDM has further facilitated this transfer and help to sustain the development of problem-driven and solution-oriented mathematics for public health in China. The IRCI support and the additional support from other sources have been promoting each other in many useful ways as outlined below. In particular, the huge success of the Chinese team in securing the funding support from the Chinese National Science Foundation is a direct consequence of the quality of this bilateral collaboration which identified public health questions and identified theoretical modeling research gaps.

Project title	Funding Agency	Your role in the project	Start date (year) / end date (year)	Value (indicate currency)
Multi-component HIV Intervention Packages for Chinese MSM	NIH/NIAID, USA	PI, Yiming Shao	2011-2015	658,878 US$
"Analysis and application of	FDUROP in Fudan University	Instructor, Wei Yao	2012-2013	2,000 RMB

network model simulation"				
"Application of network model-simulation of infectious disease propagation in campus"	FDUROP in Fudan University	Instructor, Wei Yao	2013-2014	2,000 RMB
The study of the discrete TB models with various immunization strategies and effect	National Natural Science Foundation of China，Grant# 11301314	PI, Hui Cao	2014-2016	RMB230,000
Evolutionary Dynamics of Biodiversity Formation and Loss	National Natural Science Foundation of China, Grant# 11201368	PI, Jian Zu	2013-2015	RMB220,000,
The new theory of singular perturbation with applications to ecological and epidemiological models	National Natural Science Foundation of China，Grant# 11171267	PI, Zhien Ma	2012-2015	RMB480,000
Study of effect of virus dynamics based on individual level on macroscopical epidemic of infectious disease	National Natural Science Foundation of China， Grant#11171268	PI, Yanni Xiao	2012-2015	RMB 460,000
Modeling HIV transmission among floating population with space heterogeneity	National Natural Science Foundation of China，Grant# 11001215	PI, Tailei Zhang	2011-2013	RMB 180,000
Study of modeling HIV progression and treatment after infection	National Natural Science Foundation of China，Grant# 11971063	PI, Yicang Zhou	2010-2012	RMB 260,000
Modeling HIV/ADIS epidemic (individual/population level) in China	National Mega-project of Science , 2008ZX10001-003,	PI, Yanni Xiao	2008-2010	RMB 955,000
Modeling effects of HAART on HIV transmission	National Mega-project of Science, 2012ZX10001-001	PI, Yanni Xiao	2012-2015	RMB 943,000

dynamics in China				
The HIV-1 and HCV transmission bottleneck in Chinese injection drug users	National Natural Science Foundation of China，Grant#81361120407	PI, Yiming Shao	2014-2016	1,800,000 RMB
Study on Filippov system and its application to dynamic control of the infectious diseases	National Natural Science Foundation of China，Grant# 11571273	PI, Yanni Xiao	2016-2019	500,000 RMB
Dynamics and data ananlyses of multi-scale biological systems based on typical diseases	National Natural Science Foundation of China，Grant# 11631012	PI, Yanni Xiao	2017-2021	2,450,000 RMB
The molecular evolution trend of HBV and its influence on the infection dynamics	National Natural Science Foundation of China，Grant# 11571272	PI, Jian Zu	2016-2019	550,000 RMB
Mathematical models and prevention and control strategies of HIV drug resistance for men who have sex with men in China	National Natural Science Foundation of China，Grant# 11471336	PI, Litao Han	2015-2018	700,000 RMB
The graduate summer school on biomathematics	National Natural Science Foundation of China,	PI, Xianming Pan	2015-2018	600,000 RMB
Investigating HIV diversity among Beijing MSM using deep sequencing analysis	National Natural Science Foundation of China, Grant# 81471962	PI, Hui Xing	2015-2018	750,000 RMB

vi. Project Outputs

The IRCI program supported numerous trainees and research outputs. Table 2 identifies all the undergraduate, graduate, PhD and Post-doctoral students involved in the program

Table 2: List of Trainees

	Trainees supervised by Yiming Shao	Trainees supervised by the Iianhong Wu	Trainees co-supervised by Shao and Wu	Trainees supervised by other collaborators
Undergraduate	Ronghua Li; Jinxin Wu; Tao Li; Ningyuan Hu; Haoyu Wang;			
Masters	Jing Wang; Jinjuan Hao; Yang Han; Weixia Lu; Na Wang; Xuefeng Li; Song Fan; Senlin Yang; Zeqin Ma; Xiaoyi Yang; Xuebing Leng; Zheng Li;	Lorianne Donato;		Lingchen Bu; Liumei Wu; Web Du; Hongmei Zhang; Li Xie; Yi Ding; Yabei Li; Lu Chen; Sha Xu; Lisha Chao; Zhaoqun Yang; Yingfen Huang; Youping Yang; Jin Zhang; Xia Wang; Weiwei Shi; Xiaodan Sun; Lili Luo; Na Chen; Yuying Liu; Wenjuan Ji; Xia Ma; Qingbo Bao; Ganggang Wang; Zhixin Lu; RunQing Wang; Yonglin Zhuo; Liang Yu; Lei Liang; Qing Zhang; Sijia Ye; Qian Wang; Jun Xu; Shuli Chen; Wei Zheng; Xingye Qiu; Chen Zhang; Di Ren;

				Mengbai Liu;
Doctoral	Zhenpeng Li; Nidan Wang; Chuanyi Ning; Ping Li; Hai Zhao; Huamian Wei; Heng Zhang;	Yong Yang; Nemanja Kosovalic; Xiaotian Wu; Biao Tang		Jing Yang; Xia-Yu Xia; Wei Yang; Luju Liu; Yali Yang; Xinli Hu; Yan Wang; Zhengguo Bai; Hui Cao; Shifei Wang; Suxia Zhang; Youping Yang; Tingting Zhao; Wei Cui; Yajun Sheng; Yanping Zhang; Xiaotian Wu; Shujuan Cao; Yao Lian;
Post-doctoral		Shu Zhang; Hossein Zivaripiran; Yijun Lou; Venkata Rama Duvvuri; Yao Guo; Xi Huo		Tailei Zhang; Xia-Yu Xia;
Other				

The involvement and supervision provided by Prof. Yiming Shao and Prof. Jianhong Wu, included the following:

- The China CDC organized and built team members from epidemiology, biostatistics, public health decision, mathematics, virology and immunology. This program was also facilitated by various CDC laboratories and taskforces to follow-up and continue cohort studies (IDUs cohort, MSM cohort, disease natural progress cohort, for example) and national surveys (such as, HIV drug resistance, molecule-epidemiology). Meanwhile, several universities were key partners in various summer schools and workshops, by providing and facilitating funding support and expertise of mathematical modeling.
- York University the Center for Disease Modeling (CDM) administrated and coordinated the Canada-China joint programs, and both York University and MITACS have committed funding and administrative support to this project. MITACS has been the major funding organization of various summer schools developed by CDM and these summer schools reserved slots for Chinese students involved in this. York University has provided office spaces for visiting Chinese students and scientists involved in this program, and facilitated their studies during their visits.

- Dr. Shao and Dr. Wu coordinated the overall development including the interaction between the modellers and public health policy decision makers; the outreach to the general mathematical community and biostatistical community; the design and coordination of the special course series and various workshops.
- Overall, we feel the IRCI program significantly enhanced the training environment we could have provided to our students.
- This IRCI program was the first of the kind, in China, to have used public health surveillance data and field cohort data available at the China CDC to train the students and young researchers in an international and interdisciplinary environment. This has been contributing to setting the direction for the training of a generation of Chinese scientific leaders for a highly interdisciplinary interface between real world public health problems and mathematical modeling and analysis. The publications of the Chinese team (most co-authored by the trainees) in high profile public health and medical journals, rather than theoretical biology journals, provide a clear evidence of this training practice and success. Numerous students have secured full time permanent positions in universities and government agencies, such as, Zhenpeng Li at China CDC and Xia-Yu Xia at Peking Union University.
- The financial support by IDRC has made it much easier to put together network activities involving scientists in both countries, a special example is the large presence of the Chinese students in the 2012 Summer School on Mathematics for Public Health the Canadian group organized in Edmonton in May of 2012.

Select Research Outcomes:

1. Using a mathematical model to fit HIV prevalence estimates among MSM from 2000–2010, we projected trends in HIV prevalence and incidence during 2011–2020 under five scenarios: (S1) current intervention levels by averaging 2000–2010 coverage; (S2) increased antiretroviral therapy (ART) coverage with current testing and linkage to care (TLC); (S3) increased TLC/ART coverage; (S4) increased condom use; and (S5) increased TLC/ART plus increased condom use. Our transmission model suggests that Beijing MSM will have a rapidly rising HIV epidemic. Even enhanced levels of TLC/ART will not interrupt epidemic expansion, despite optimistic assumptions for coverage. Promoting condom use is a crucial component of combination interventions.

2. We initially defined a new pair-wise distance to measure the genetic diversity for HIV recent infection estimation. We then modified the method and defined a new homologous clustering based diversity (SCBD) to recognize recent HIV infections. We derived a set of common patterns from the HIV-1 viral sequences which differ in their coreceptor usage. The number of unique common patterns in viral sequences decreased with transmission but remained almost constant with the progress of disease in an individual. This number was then used as an estimator to determine transmission direction.

3. We studied the dynamics (long-term dynamic behaviors) of some relevant mathematical models of infectious diseases, linking mathematical analysis to real issues of disease prevention and control in China. We developed novel and refined existing mathematical technologies to accommodate the dynamics analysis, such as defining and estimating critical thresholds (basic reproduction numbers), global dynamical behaviors of asymptotical autonomous system and the limit system, the Poincare -Bendixson property, the theory of the compound matrices, Lyapunov function and graph theoretical approach.

4. We developed several tuberculosis (TB) transmission models, incorporating important public health policy issues in China such as case detection, distinct treatment stages, seasonal variation of incidence rate and floating (mobile) population. These models were used to describe TB transmission patterns in China, and model parameter values were estimated according to demographical and epidemiological data in China. The simulation results were used to describe TB transmission features and to forecast its epidemic trends.

5. During the influenza A/H1N1 pandemic, very stringent interventions were implemented for the control. We examined the effectiveness of those measures using dynamical modeling along with sensitivity analysis. The model was parametrized using data of initial laboratory-confirmed cases in the province of Shaanxi, and the Markov-chain Monte-Carlo (MCMC) simulations were used to estimate the reproduction number. Our results supported that strengthening local control strategies (quarantine and hygiene precaution) was most effective in mitigating outbreaks and inhibiting the successive waves.

6. We formulated and analyzed deterministic and stochastic mathematical models to examine the roles of environmental contamination and the presence of volunteers played in the nonsocomial transmission (hospital infection) dynamics of antimicrobial drug resistance, and we utilized semi-stochastic simulations and available data from a Chinese hospital to estimate key epidemiological parameters, and then used the parametrized model to assist numerical simulation that concludes that environmental contamination is a key threatening factor for hospital infection in some Chinese hospitals..

7. Mathematical models, when integrated with epidemiological and surveillance data, can be an effective tool for predicting the temporal dynamics of HIV and assessing the impacts of HIV

interventions. The centralized management based of farm labour was widely supported by HIV-infected persons and drug users in Liangshan prefecture.

8. TasP may be feasible on a national or regional scale. In addition to other proven preventive strategies such as the use of condoms, ART adherence to maintain viral suppression would then be the key challenge for successful TasP implementation. Guangxi is China's first province to demonstrate a decline in HIV and AIDS case reports and HIV incidence. The HIV epidemic turning-point is attributed to the strong local GACP initiatives combined with the National AIDS Control Policy, such as education, HIV testing and ART. Our study suggests that CD4 testing can be reduced to two times within the first year of ART initiation, and be reduced or stopped for patients who have achieved virological suppression or immunologically stability after 12-months of treatment.

9. We proposed an individual based model by coupling within-host dynamics and between-host dynamics and conduct stochastic simulation in the group of men who have sex with men (MSM). This implies early initiation of HAART may not always lower the actual reproduction number and prevalence of infection, depending on the level of treatment efficacy after emergence of drug resistant virus variants, frequency of high-risk behaviors and etc. This finding strongly suggests early initiation of HAART should be implemented with great care especially in the settings where the effective drugs are limited.

10. We formulate a mathematical model to describe the transmission dynamics of co-infection of dengue and Zika with particular focus on the effects of Zika outbreak by vaccination against dengue among human hosts. Our analysis determines specific conditions under which vaccination against dengue can significantly increase the Zika outbreak peak, and speed up the Zika outbreak peak timing. Our results call for further study about the co-infection to direct an integrated control to balance the benefits for dengue control and the damages of Zika outbreak.

11. We proposed a method PSIONplus to identity the ion channels and their types. The software can be found at https://sourceforge.net/projects/psion/ ; An new algorithm RSSC was proposed to identify segmentation of non-rigid motions. A software package was provide to analyze antigen-antibody complex are available at www.sourceforge.net/projects/chops ; A new method to identify the DNA-binding proteins are available at http://sourceforge.net/projects/newdnaprot/ ;.

12. Drs. Yiming Shao and Jianhong Wu in collaboration with Publisher Elsevier and Science Publisher House, successful launched "Infectious Disease Modeling" (ISSN: 2468-0427) in 2016. The quarterly journal is the world's first specialized journal for infectious modeling with Drs. Yiming Shao and Jianhong Wu, as the Chief editors supported by well-known scientists of the fields from the world's five continents.

Cumulative list of your research outputs by type

Type	Total number of Research Outputs
Journal Articles (published / accepted)	76
Journal articles (still in submission process)	
Conference Papers	7
Presentations (non-academic)	
Books	
Book Chapters	2

Newspapers / other media	
Theses	
- MA / MSc	53
- PhD	30

vii. Project Outcomes

This section highlights some of the main results of the program.

The project led to 74 publications in such high impact scientific journals such as Lancet, Clinical Infectious Diseases, Plos one, and Theoretical Biology.

The work, published in Lancet, has an important impact on treatment as prevention of HIV in China and other developing countries. Treatment as prevention strategies have been implemented on a national or regional scale in China since 2013. Our study also supports for ART adherence, education and risk behavior reduction while implementing this program.

Our study, published in Clinical Infectious Diseases, suggests that CD4 cell counts can be reduced twofold during the first year of ART and be reduced or stopped for patients who have achieved virologic suppression or immunologic stability after 12 months of treatment. This study was significant to revising CD4 cell count and viral load testing frequency in '*National Manual Book for Free Antiretroviral Treatment of HIV/AIDS*' (fourth ed.) This public health policy can reduce testing costs by 100 million RMB Yuan every year in China.

Another project result, based on model-informed control strategies for HIV/AIDS in China's high epidemic regions, has been communicated to leaders of the Ministry of Health, the Liangshan government as well as to the top Chinese central government. A pilot trial based on our Liangshan model show that the basic reproduction number in Liangshan of Sichuan Province of China is still higher than 1 under the current control strategies. Our numerical simulations show that the intervention of Green Home can significantly slow down the transmission of HIV in terms of newly diagnosed HIV-positive cases and newly HIV-infections (including the undiagnosed HIV-infections) among drug injection users. This study strongly supports center and local governments to construct Green Home to reduce HIV infection in Liangshan.

Our approach for high-accuracy identification of incident HIV-1 infections and determination of HIV-1 incidence are being validated and used for evaluation of HIV prevention and control in China. Our approach developed for accurate determination of the transmission direction of HIV between individuals should provide stronger evidence in criminal cases and lead to a clearer picture of the transmission network in a given geographic region.

The IDRC funded projects provided a unique opportunity for Chinese disease modeling community to collaborate with researchers affiliated with the China CDC, and thus greatly enhance the linkage between fundamental research in disease modelling with practical issues and major public health policy. In particular, this continually enhanced linkage has been playing a significant role to facilitate the translation of theoretical study to practical issues by using real data to parametrize abstract models, to seriously address issues identified by China CDC as being of current and significant interest to public health policy development and implementation. This has also been contributing to setting the direction for the training of a generation of Chinese scientific leaders for a highly interdisciplinary interface between real world public health problems and mathematical modeling and analysis.

Finally, an important contribution of this project is the gradually adoption by government

organizations of the mathematical-modeling informed national epidemic data evaluation and scaling up of some pilot studies to a large and national scale. This impact represents a paradigm shift and will have a long lasting impact on policy and decision making.

Using the published datasets generated by national HIV/AIDS surveillance programs, a mathematical modeling study led by Michael Li at University of Alberta as a participating Canadian scientist was carried out to estimate and project the HIV epidemic in China. The study results found there may be an underestimation of both the new HIV infections and HIV/AIDS deaths by the Chinese national estimate dataset. This prompted the Chinese government to reconsider its approach to reporting HIV prevalence.

Another important contribution was to the Guangxi AIDS Conquering Project (GACP). With strong political, legal and financial supports, HIV testing and ART coverage increased 2.6 and 4 fold during the 5-year (2010-2014), which was far above the national average.Guangxi's HIV and STD case reports peaked in 2011 and then declined steadily from 2012-2014 under GACP; in contrast, HIV and STD reports continued to rise nationally. Our model found a 3.34% reduction in the R_c of HIV infection per year during the GACP. Guangxi is China's first province to demonstrate a decline in HIV and AIDS case reports and HIV incidence. The modeling study supported the National AIDS control Policy as it clearly shows that HIV epidemic turning-point is attributed to the strong local GACP initiatives combined with this policy.

In the proposed approach, marginalized community members at high risk for spreading HIV are offered subsidized employment in Rural Economical Enterprises (REE) that provide agricultural and manufacturing jobs while at the same time offering access to healthcare, anti-retroviral therapy (ART), harm reduction measures, education, and skills training. A quantitative analysis of how this policy intervention will impact the Liangshan HIV epidemic was carried out using a mathematical model based on demographic and social data. Thanks to a strong financial investment and support from the local and central governments, pilot trials of the REE model in Liangshan began in 2012. This has provided a new AIDS control measure for fighting the epidemic both at its biomedical front and by addressing social factors contributing to the spread of disease in underdeveloped communities.

viii. Conclusion

The financial support by IDRC has made it much easier to put together network activities involving scientists in both countries, a special example is the large presence of the Chinese students in the 2012 Summer School on Mathematics for Public Health the Canadian group organized in Edmonton in May of 2012.

The IDRC project has raised the profile of the Center for Disease Modelling (York) in the international community. A Brazil-Canada workshop on Health Informatics and Infection Dynamics was held in University of Sao Paulo, February of 2013. This workshop led to the MoU agreement between CDM and BIOMAT, a consortium with memberships from all southern American countries. This also led to the BIOMAT2013 annual meeting to be held in Toronto in November of 2013.

The connections through IDRC and this IDRC project have been highly regarded internationally, as illustrated by the successful proposal of a symposium "Comprehensive Approaches for HIV/AIDS Prevention and Control" to the premier AAAS Annual Meeting in Vancouver, 2012. These connections enable the CRC and IDRC RC to develop initiatives in areas of current significance in global health. For example, CDM is now being invited to organize a special school and research workshop in University of South Africa and University of Pretoria, March 2014; and a special course at IIT, India Sept., 2013.

International Conference of China - Canada International Conference on Disease (CCICDM), sponsored by The IDRC-CRC International Research Chair in Infection Disease Modeling and Management, and the department of mathematics of Shanghai University, was successfully held on June 2-5, 2017. The connections through IDRC and this IDRC project have been highly regarded internationally, as illustrate by disseminating our results and facilitating knowledge translation, Yiming Shao is a co-chair of the Gates Foundation Annual meeting of Grand Challenges at Oct. 18-21, 2015, in Beijing and Jianhong Wu an invited speaker to this major international event to share our Canada-China experience on using public health data and modeling to inform decision.

Both CRC and IDRC RC still strongly believe it is the right time to develop a mechanism to expand this IDRC project to a more permanent and bilateral capacity, in the form of Joint Center of Excellence. It has been difficult to find a strong voice in both governments of Canada and China for this initiative, especially when this IDRC funded project crosses the traditional boundary of natural sciences and medical research and public health policy. The CRC had a chance meeting the Chinese Minister of Health who indicated his support for such a joint centre. In order for the project to achieve its full technical potential and fulfill its impact on improving public health policies, additional technical and policy support from IDRC and other programs of both the Canadian and Chinese government is essential.

ix. Bibliography

Research papers are listed in the body of this report. Additional publications and research outputs are listed below.

Conference Paper:
Derived from the research results in Liangshan, the project research team together with IDRC official Dr. David O'Brien organized a Symposium entitled 'Comprehensive Approaches for HIV/AIDS Prevention and Control' in AAAS annual meeting held in February 20-24 in Vancouver Canada (https://aaas.confex.com/aaas/2012/webprogram/Session4595.html). This symposium reviewed the evolution of national and international efforts to prevent and control HIV/AIDS over the last three decades, highlighting research and practical experiences that can inform the development of future research and programs. Presentations showcase successful efforts in Asia and Africa, in particular those interventions that target both the disease and its social causes. For example, China's campaign to eradicate the spread of sexually transmitted diseases half a century ago included social interventions, such as support for families and alternative jobs for prostitutes, along with conventional treatment programs. This comprehensive approach has lessons for contemporary HIV/AIDS prevention and control strategies nationally and globally. The speakers and their talk titles are:

Myron Cohen, *University of North Carolina*
Past HIV/AIDS Control and Prevention Strategies and Future Challenges

Ying-Ru Lo, *World Health Organization; Reuben Granich, World Health Organization;*
The Use of Antiretrovirals (Arvs) For Prevention of HIV and TB: Time for Action

Yiming Shao, *National Center for AIDS/STD Control and Prenvention; **Jianhong Wu**, York University*
Historical Foundations and Future Directions of China's HIV/AIDS Strategy

Punnee Pitisuttithum, *Mahidol University*
HIV/AIDS Situation and Prevention in Thailand

Nelson Sewankambo, *Makerere University*
The Evolution and Results of Uganda's HIV/AIDS Policies

John Lavis, *McMaster University*
Informing Public Health Policies

1. Zhenguo Bai, Yicang Zhou and Yan Zhang, A Periodic Epidemic Model with Delay and Multiple Pathogens, Proceedings of the 5th International Congress on Mathematical Biology (ICMB2011, ISBN 978-1-84626-091-9), 29-35.
2. Yan Wang and Yicang Zhou, An HIV Model with Antiviral Immune Response and Antiretroviral Therapy, Proceedings of the 5th International Congress on Mathematical Biology (ICMB2011, ISBN 978-1-84626-091-9), 234-239.
3. Xiaodan Sun and Yanni Xiao, A Mathematical Model for HIV Epidemic among Men who Have Sex with Men in China, Proceedings of the 5th International Congress on Mathematical Biology (ICMB2011, ISBN 978-1-84626-091-9), 191-197.
4. Weiwei Shi and Yanni, Optimal Control Strategies of a HIV/AIDS Epidemic Model, Proceedings of the 5th International Congress on Mathematical Biology (ICMB2011, ISBN 978-1-84626-091-9), 581-586.

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Books:

1. Yanni Xiao, Yicang Zhou, Sanyi Tabng, Principles of Mathematical Biology, Xi'an, Xi'an Jiaotong University Press,2012.
2. Yicang Zhou, Hui Cao, Yanni Xiao, Difference Equations with Applications, Beijing, China Academic Press, 2014.

Those two books are written for undergraduate students and graduate students to learn the basic theory and methods in epidemiology modeling. A lot of mathematical models in ecology and epidemiology are formulated and analyzed to demonstrate the modeling process.

Theses:

Master:

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