Research Assessment Exercise 2020
Impact Case Study

University: The Hong Kong Polytechnic University (PolyU)
Unit of Assessment (UoA): 11 Mathematics and Statistics

Title of case study:
Chickenpox Vaccination and Other Disease Prevention Strategies Improved by Infectious Disease Modelling

(1) Summary of the impact

PolyU's mathematical modelling of disease outbreaks has changed Chickenpox vaccination strategy in the Chinese city of Shenzhen (pop. 20 million). This model has informed the adoption of new policies developed by Shenzhen Centre for Disease Control and Prevention (a governmental technical organization specialising in disease control and prevention as well as public health) to prevent around 8000 chickenpox cases annually. PolyU modelling also provided evidence to support guidance on reducing Zika virus transmission including European Commission advice and provided evidence to support public health risk-mitigation and planning for Yellow Fever outbreaks in Angola and Nigeria.

(2) Underpinning research

Vaccine-preventable infectious diseases account for more than 3 million deaths worldwide annually. Understanding transmission patterns is a powerful weapon in developing effective policies to limit mortality and prevent diseases spreading. Research by the Department of Applied Mathematics at The Hong Kong Polytechnic University (PolyU), led by Dr He Daihai (2012-present), has focused on the mathematical modelling of Chickenpox, the Zika virus and Yellow Fever transmission.

We have developed new mathematical models and fitted these models to reported epidemiological data via a likelihood-based inference framework through iterated filtering to build a tool that captures the observed epidemic and simulates the outcomes of different control measures thereby identifying the best control method.

Chickenpox (also known as 'varicella'): Dr He's group developed agent-based simulation models capturing the two annual chickenpox epidemic waves from 2013 to 2015 in Shenzhen, China [1]. The results suggested that a school-based vaccination strategy could effectively prevent large-scale varicella outbreaks. Large school-level outbreaks could be effectively controlled with a 97% probability if vaccination starts when 5 cases are reported. This probability dropped to 75%, if a threshold of 10 cases was set. We also provided research results and modelling on the effect of a two-dose rather than one dose policy in the city, for non-school based vaccinations.

Working with the Shenzhen Centre for Disease Control and Prevention (CDC), we accessed data on chickenpox reported cases, Shenzhen's population size, the age groupings of children aged 15 or under, and school and class distribution. We developed an Agent-Based Susceptible-Exposed-Infectious-Recovered (ABM-SEIR) Model that considered within-class, class-to-class and out-of-school transmission modes. A 'no intervention' scenario is the current case in Shenzhen. Our intervention scenario was that a school-wide vaccination intervention would occur when an outbreak threshold was reached within a school. We varied this threshold level from 5 to 10 cases. We compared disease outbreak reduction sizes and estimated the key epidemiological parameters under the intervention strategy. Our ABM-SEIR model provided a good fit to the two annual chickenpox epidemic waves from 2013 to 2015 and our modelling structure was more biologically reasonable than previous studies.

Yellow Fever: Dr He's work on Angola's 2015-16 Yellow Fever (YF) outbreak showed that the timely vaccination campaign there likely saved about 3200 lives [2]. This paper won the *Outstanding Research Articles in Biosurveillance Award (second place*) from the *International Society of Disease Surveillance* [H]. This is the first time that a Hong Kong team has won this award. We developed a new compartmental model (since such a YF model was rarely studied), incorporating both human and mosquito populations. The human population was divided into susceptible, exposed, severe/hospitalized cases, asymptomatic case and deaths. We estimated key parameter values (such as virus transmission rate) by fitting the model to observed case data with a powerful plug-and-play likelihood-based inference framework developed by Dr He and collaborators.

Zika virus: In 2011, the possibility that the Zika virus could also be transmitted through sexual contact was raised. However, it was not known how important this transmission mode was compared to transmission via mosquitos. During the severe South American outbreak starting in Brazil in April 2015, PolyU research proposed a first-of-its-kind mathematical (compartmental, differential equations) model for the Zika virus diseases for both transmission routes: mosquito borne and sexual contact [3].

(3) References to the research

PolyU authors in bold

[1] Tang X, **Zhao S**, **Chiu A**, Ma H, Xie X, Mei S, Kong D, Qin Y, Chen Z, Wang X, **He D** (**2017**) Modelling the transmission and control strategies of varicella among school children in Shenzhen, China. PLOS One. e0177514

[2] **Zhao S**, Stone L, Gao D, **He D** (**2018**) Modelling the large-scale yellow fever outbreak in Luanda, Angola, and the impact of vaccination. PLOS Neglected Tropical Diseases. doi: 10.1371/journal.pntd.0006158.

[3] Gao D, **Lou Y**, **He D**, Porco T, Kuang, Y, Chowell G & Ruan S (2016) Prevention and Control of Zika as a Mosquito-Borne and Sexually Transmitted Disease: A Mathematical Modeling Analysis. Nature Scientific Reports 6, http://www.nature.com/articles/srep28070

(4) Details of the impact (indicative maximum 750 words)

Dr He has worked closely with policy makers to ensure that his research is impactful. Major policy impacts have arisen from his on-going collaboration with the Shenzhen Centre for Disease Control. The team has proactively reached out to health professionals in other countries to share relevant findings that can inform disease control policy. Three examples are given below:

1. Changing Shenzhen's Chickenpox Vaccination Policy

Shenzhen province has a population of 20 million and there are about 10,000 reported cases of chickenpox among children age 0-15 per year. Chickenpox is a major public health concern as the disease can cause serious complications including pneumonia, inflammation of the brain (encephalitis) and bloodstream infections (sepsis), sometimes leading to death. Deaths can occur even in healthy, unvaccinated children and adults [A]. An effective vaccination programme is vital to reducing and eliminating these risks both through individual and herd protection.

Reported chickenpox cases increased considerably from 2013 to 2015 in Shenzhen. The city's chickenpox vaccination program did not include a school-based policy, and followed the National Immunization Program's one-dose policy, with parents charged around $140 for the dose. That policy has a low uptake rate. Public health officers at the Shenzhen Centre for Disease Control and Prevention (CDC) sought to review the local vaccination strategy's effectiveness and asked PolyU in early 2017 to undertake research specifically modelled on the Shenzhen population. The Shenzhen CDC is a government branch that provides evidence-based policy advice to regional government departments and is the first line responder to public health outbreaks. Working with the CDC, we provided evidence about the efficacy of a two-dose policy, and our model simulation showed that a

school-oriented vaccination strategy can effectively prevent chickenpox outbreaks but that its effectiveness depends on recognising the optimum threshold (i.e. number of cases) to trigger a vaccination campaign.

Our research findings helped convince Shenzhen CDC to recommend vaccination policy changes in Shenzhen to their regional public health authorities. Following our research, between 2017 and 2019 the CDC have proposed improved strategies to local government and have seen three changes to local vaccination policy adopted: firstly, a two-dose vaccination has been made available at local clinics since October 2017; secondly these vaccinations were made free-of-charge in September 2018; and thirdly in March 2019 it was announced that emergency vaccination will be initiated if two cases of chickenpox are recorded in a school or other collective unit [B].

With Shenzhen's population of 20 million our work has extensive impact. We estimate that the policy changes informed by our research will prevent outbreaks and reduce chickenpox cases by around 8000 annually. As well as health benefits, this brings economic benefits as studies have estimated that for every dollar invested in vaccination, $2.79 to $3.42 (USD) are saved in societal costs (e.g. work loss) due to chickenpox, and that the net economic benefit of each case prevented is around US$95.96 (in Taiwan) [C]. Using that estimate, 8000 cases averted will bring Shenzhen a net benefit of US$0.77 M on average every year.

Before the policy change, families had to voluntarily go to clinics in the city and pay for a single - dose vaccination. Now clinics provide two doses for free. Each dose costs around HK$ 140, so these free vaccinations have saved families money (with an average of 1.6 children per family, this is an average saving of around HK$224 per family in an area where average annual wages are just HK$100 K).

2. Supporting public health policy to combat Zika virus transmission

Zika virus infection during pregnancy can cause premature birth and miscarriage, as well as microcephaly and other congenital malformations in infants. Adults and children also risk neurologic complications. With no vaccines or specific treatments available, prevention is of the utmost importance. Brazil's 2015-2016 outbreak was designated a *Public Health Emergency of International Concern* by the *World Health Organisation* (WHO). 2791 cases of microcephaly were identified [D]. As Zika is primarily a mosquito-borne disease, sexual transmission was only first considered a possibility in 2011. Whilst policy guidelines in early 2016 promoted safe sexual practices, whether cases of human-to-human sexual transmission were rarities or not remained unclear.

Our research, published in June 2016, showed that sexual transmission was a small but significant factor in the current Zika epidemic. Our research therefore provided evidence to support existing safe sexual practice policies [E]. The research showed that while sexual transmission alone would not sustain an outbreak, contributing just 3% of total cases, it both increases an outbreak's size and prolongs it. Our study on Zika virus diseases, mathematically proving the impact of sexual transmission for the first time, received wide international media attention in 2016, with the lead researcher interviewed on Canadian national news (CTV) and U.S. National Public Radio [F, G]. This helped improve public understanding of Zika transmission. The lead researcher was also invited to attend a WHO *Research and Development Blueprint Diseases Prioritization Methodological Review* Meeting in Switzerland in November 2016 to present our results. This attention also boosted the profile of safe sex campaigns to contain the spread of the on-going outbreak. Our research was cited in the EU's *European Centre for Disease Prevention and Control Rapid Risk Assessment* for the *Zika Virus Disease Epidemic* (seventh update) on 8 July 2016 [E]. *Rapid Risk Assessments* support countries and the European Commission to prepare and respond to public health threats, and are read by policy and healthcare professionals. The report stated that this research "*supports recommending*

both mosquito-control and personal biting protection as well as safe sexual practices to reduce Zika virus incidence during outbreaks" [E].

3. Encouraging Yellow Fever Vaccination in Africa

In 2015-2016, the largest yellow fever outbreak for 30 years occurred. Centred in Angola, the outbreak claimed 635 deaths among 8296 confirmed and suspected cases there and in neighbouring countries. The WHO's limited vaccine stock generated concerns that their emergency vaccination campaign across the country and neighbouring countries would fail due to lack of supplies. This yellow fever vaccination campaign's effectiveness was not well understood, and there was no evidence supporting whether such a vaccination programme should be repeated at the next outbreak. Our work quantified the effect that a similar large-scale vaccination campaign (4 million doses) would have on the population of a single province of 7 million, finding that it would save around 370 lives, a 5.1-fold reduction in mortality. During the 2016 outbreak we estimated 3200 lives were saved by the vaccination policy in Angola and DR Congo. Our model strongly supports the need for countries to stock the yellow fever vaccine at sufficient levels, informing their risk mitigation strategies and policies. Winning the award from the *International Society of Disease Surveillance* (ISDS) [H] highlighted our findings and their policy relevance to a wide audience. The award was presented at the ISDS annual conference in January 2019 involving 375 professional participants from 28 countries.

We also proactively shared our findings with WHO officers in Angola and Nigeria (another yellow fever affected country), to support their evidence-based policy-making and boost their capacity to employ data-based strategies to combat infectious diseases. Dr Lawan Adamu (*Cohort 9 Resident, Nigerian Field Epidemiology and Laboratory Training Program*) states: "*We have used the research papers and codes you sent us as teaching material to train about 30 of our research trainees. We have a much-improved understanding of the epidemiology of yellow fever and the effectiveness of a timely vaccination campaign. We plan to incorporate the simulation programs you provided in our planning to mitigate epidemics and I am sure it will be very useful… The simulations based on the refined model and program will be used as basis for health policies."* [I].

(5) Sources to corroborate the impact

[A] US Centre for Disease Control online factsheet (archived July 2019)

[B] Letter from Shenzhen Center for Disease Control and Prevention, May 2019

[C] Literature review on the burden of varicella in the Asia-Pacific region: https://doi.org/10.1080/14760584.2019.1594781

[D] Article on the association between Zika virus infection and microcephaly in Brazil 2015–2017, March 2019: https://doi.org/10.1371/journal.pmed.1002755

[E] EU's Rapid Risk Assessment, July 2016

[F] Video clip from Canadian national news – CTV, July 2016: http://www.math.miami.edu/~ruan/07-RAW-ZIKA_MATH.mp4

[G] Radio article from WGCU National Public Radio, July 2016 https://news.wgcu.org/post/zika-virus-research-and-public-education

[H] Award certificate of the Outstanding Research Articles in Biosurveillance by the International Society of Disease Surveillance, 2019

[I] Letter from Dr Lawan Adamu, Nigeria public health officer, August 2019