Applying mathematics to evaluate vaccine effectiveness

The development of a successful vaccine and immunisation programme depends on the collaboration of different partners from industry and academia. Dr Jianhong Wu and his colleagues from York University, Canada, and the researchers at Sanofi Pasteur, *Canada's largest vaccine provider, have been developing a comprehensive and integrative mathematical modelling framework that analyses randomised-controlled trial (RCT) data, to evaluate the effectiveness of vaccination programmes in overcoming the public health and economic burden associated with the outcomes of influenza and pertussis infection.*

Seasonal influenza and its resulting complications pose significant public health and economic burdens across many countries. It is difficult to estimate the true impact of influenza, due to its seasonal variability, its wide range of presentation and the diverse range of complications it can cause, from pneumonia to adverse cardiovascular events. It is important to devise methods that can capture the true annual burden of influenza, so that adequate prevention and control policies, including vaccinations, can be put in place worldwide.

While the toll of influenza on health and livelihood is mainly felt among the elderly, a highly contagious pathogen, *Bordetella pertussis*, is at the root of more severe complications among young children. It is estimated to cause 16 million cases of pertussis, resulting in 195,000 paediatric deaths around the world every year. Vaccination is the most effective measure to reduce the burden of pertussis. However, recent high rates of the disease worldwide have elicited concerns from public health experts on the effectiveness of current pertussis control programmes.

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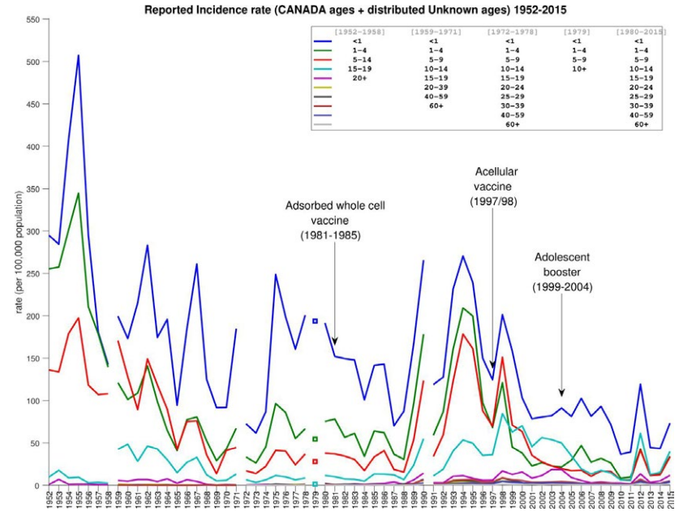
AN ACADEMIC–INDUSTRY COLLABORATION EMERGES

Dr Jianhong Wu and his team from York University, Canada, have partnered with *Sanofi Pasteur*, the largest Canadian vaccine provider, to establish the Industrial Research Chair in Vaccine Mathematics, Modelling and Manufacturing (IRC), which has been developing cutting-edge mathematical technologies and training the next generation of mathematical modelling experts to meet the significant challenges faced by Canadian vaccine manufacturers.

The IRC aims to develop a comprehensive model that analyses randomised-controlled trial (RCT) data, to quantify the public health and economic burden associated with the onset of complications from influenza and childhood diseases including pertussis infections among the most vulnerable populations. In collaboration with *Sanofi*, Dr Wu and his team have developed a dedicated resource that is capable of providing strategic inputs, data and advice, and enhanced research capacity in mathematical modelling for targets relevant to the Canadian vaccine industry's product pipeline. The partnership supports data analytics for impact and safety assessment, rapid production response, and retroactive evaluation of vaccine programmes. The mathematical models and datasets collected by Dr Wu's team can be an invaluable asset for the evaluation of transmission dynamics and risk projections of disease spread through population mobility, demographic shift and contact mixing.



Canadian yearly adjusted age-stratified pertussis incidence rates for combined age-supplied reported cases and proportionally-distributed unknown group, calculated via the bootstrapping method.

QUANTIFYING THE UNDERESTIMATION OF INFLUENZA TRANSMISSION

An understanding of the true annual burden of influenza is important to support prevention and control policy development, and to evaluate the impact of preventative measures such as vaccination. Dr Wu and his collaborators published a study in 2020 showing that monitoring representative groups within a population may aid the effective modelling of the transmission of infectious diseases such as influenza.

The authors propose that models should be optimised to take into consideration different factors that can significantly affect transmission, such as belonging to a certain age group or being part of specific settings like multi-dwelling households, crowded workplaces or schools. In this respect, using carefully designed RCTs in models may enhance the accuracy of estimates of key epidemiological parameters.

Dr Wu and his collaborators highlight the importance of quantifying the annual incidence of influenza by using mathematical models incorporating transmission settings of high disease burdens that estimate the true levels of transmission. Insufficient consideration of these transmission settings can result in a large underestimation factor, which can be attributed to a failure to predict, among other factors, the number of asymptomatic cases. The mathematical models developed by Dr Wu's team accurately quantify the underestimation factor associated with seasonal influenza, so that prevention measures can be planned accordingly, to best reduce the annual incidence of seasonal influenza as well as associated hospitalisations and deaths.

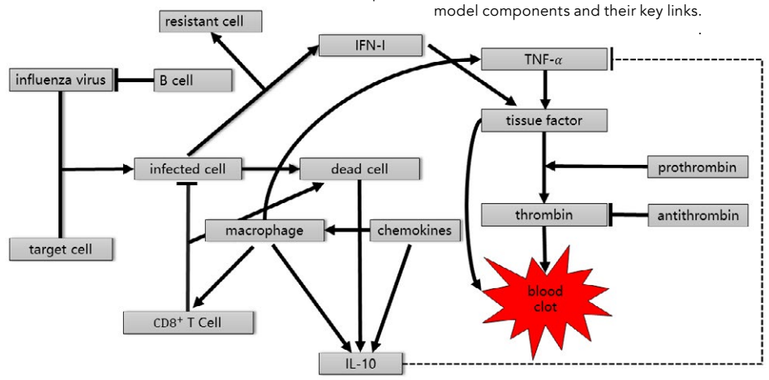
These mathematical models and the datasets will be an invaluable asset for evaluation of disease transmission and immunisation programmes.

PREDICTING THE RISK OF CARDIOVASCULAR COMPLICATIONS FROM INFLUENZA

Influenza infection is often associated with severe cardiovascular events, including thrombosis, myocardial infarction and stroke. These adverse effects have been linked to multiple biological pathways in humans. Dr Wu and his team have developed a model that incorporates some key elements of the host immune response, inflammation cascade, and blood coagulation pathways. The team integrated these elements into a modelling framework to show how the extent of blood clotting and its severity may be connected to influenza virus infection.

A key result of the study, which was published in 2020, is the quantification of the levels of the inflammatory cytokine TNFα that are linked to the development of thrombotic events. The model predicts that TNFα levels that go beyond a certain threshold initiate tissue factor induction and the subsequent blood clotting cascade. The study implies that TNFα levels may be used as a biomarker for cardiovascular risk. The team also expects the magnitude of TNFα levels to vary based on the health status and the age of individuals. The threshold will be higher for young

Depiction of the established model in terms of the model components and their key links.



individuals compared to older individuals or those with underlying health conditions, who may be more susceptible to blood clotting. Future work will be needed to quantify the exact threshold levels and identify specific at-risk groups.

PERTUSSIS IMMUNISATION PROGRAMME EVALUATION

Vaccination is the most effective measure to reduce the burden of pertussis. In the US, vaccine programmes introduced in the 1940s have led to a drop in the rate of disease from 150 cases per 100,000 inhabitants to 1 case per 100,000 by the 1970s.

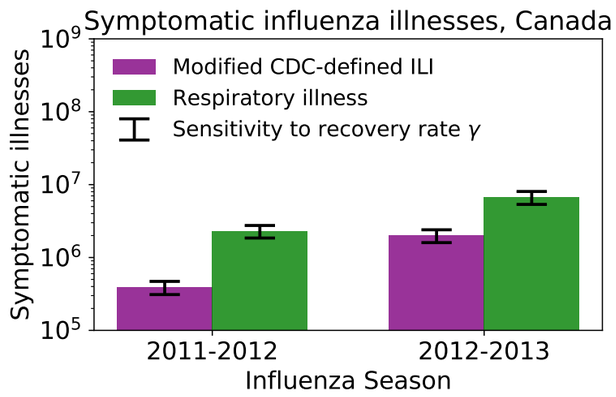
Protection acquired against infection and disease, however, is not life-long and wanes over time. Groups of individuals susceptible to infection can build up over time, creating the conditions for community outbreaks to occur. The rate of reported pertussis has reached national levels of 15 cases per 100,000 inhabitants in recent years, eliciting concerns from public health experts that waning protection, particularly after the adolescent booster, is a major contributor to the increasing US pertussis incidence.

In a review published in 2018, Dr Wu and his collaborators propose that most statistical studies that evaluate the efficacy of the pertussis adolescent booster focus on relative vaccine efficacy – calculated against a population that had been given prior doses of pertussis vaccine – rather than on absolute efficacy, which is calculated against a pertussis-vaccine-naïve, or unvaccinated, population. Dr Wu's team conducted a meta-analysis of the publications reporting pertussis vaccine effectiveness, transforming the relative estimates of vaccine effectiveness to absolute estimates. The authors concluded that when the data were analysed in absolute terms, the effectiveness observed after the adolescence booster was in fact higher than generally appreciated in recent studies conducted in the US. Nevertheless, the authors point out that the findings of their study should not take away from the broader concerns regarding the recent increases in cases of pertussis.

CHILDHOOD DISEASE EPIDEMIOLOGY

Vaccination programmes have lowered the level of reported disease in Canada, and the nature of pertussis disease surveillance in Canada has also evolved over time. Dr Wu and his team have embarked on an ambitious programme using an extrapolation method that enables them to attribute all of those cases collected without age information to a particular age group.

This work has revealed that the adjusted age-specific incidence of pertussis occurring between 1969 and 1988 in those below the age of 20 years is substantially higher than existing estimates. The new extrapolated data suggest that the surge in the average yearly incidence of pertussis that began in 1988 was weaker than previously inferred. In addition, contrary to past findings, in those below age five the average yearly incidence of pertussis from 1999 to 2015, when the incidence dropped again, has been lower than it was from 1969 to 1988. Despite these findings, Dr Wu points out that there is still no consensus in the interpretation of the temporal trends of pertussis epidemiology in Canada. A first step towards such a consensus would be to have accurate age-specific information for these temporal trends. This would help identify the key drivers for the variation of incidence data between disease outbreaks.



Quantifying the underestimation factor of influenza cases is important for planning effective prevention measures.

INFLUENCING POLICY

Disease transmission and its burden on the most vulnerable sectors of society, which includes seniors and children, depends on the patterns of contact mixing within the general population. Transmission can be altered by both pharmaceutical interventions, such as immunisation, and other, non-pharmaceutical measures, including government policies and legislation. The Sanofi-York Industrial Research Chair project team has been developing a general framework, with particular attention to the Canadian population. This IRC capacity has been activated and used intensively during the Covid-19 pandemic by the team, which has responded to the societal call for rapid evaluation, through mathematical modelling, of the effectiveness of the different intervention programmes. Dr Wu and his collaborators published a study in 2020 that quantified the shift in social contact patterns during a period when social distancing measures were in place. The team hopes to lay down a technical foundation for policymakers when identifying priority groups for targeted, cost-effective pharmaceutical interventions.

Transmission can be altered by immunisation and other measures, including government policies and legislation.

Behind the Research

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Research Objectives

Vaccine mathematics, modelling and manufacturing.

Detail

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Jianhong Wu is a University Distinguished Research Professor and the founding Director of the Laboratory for Industrial and Applied Mathematics at York University. He has been a senior Canada Research Chair in Industrial and Applied Mathematics and is currently the NSERC/Sanofi Industrial Research Chair in Vaccine Mathematics, Modelling and Manufacturing.

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Collaborators
A team of faculty members and trainees at York University and research scientists from *Sanofi Pasteur* Canada, and its global network. Contributors also include participants of various workshops and study groups, organised by the *Sanofi*-York Vaccine Mathematics team at the Fields Institute.

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Personal Response

Many have speculated that immunity to influenza might have waned during the COVID-19 pandemic, as cases of fallen due to mask wearing and other restrictions. Has the IRC partnership evaluated the risk posed by the COVID-19 pandemic in conjunction with influenza and other respiratory viruses for the winters to follow?

" In 2020, the IRC partnership conducted a study on the benefits of a mass influenza vaccination campaign in the time of COVID-19. The study was based on a model focusing on the management of people with non-specific symptoms and complaining of influenza-like illness, potentially at risk of developing COVID-19 or other emerging respiratory infections during their investigation and work-up in the health-care setting. Our simulations showed that by increasing the influenza vaccination coverage rate, the need for stringent public health interventions to counteract the COVID-19 outbreak can be significantly reduced. This early study remains valid now with COVID-19 vaccination rollout and variants of concern emergence. Increasing influenza and COVID-19 vaccination rate is key to economic recovery, by protecting public health and reducing workplace absenteeism. "

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