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Examining Ontario's universal influenza immunization program with a multi-strain dynamic model

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ABSTRACT

Seasonal influenza imposes a significant worldwide health burden each year. Mathematical models help us to understand how changes in vaccination affect this burden. Here, we develop a new dynamic transmission model which directly tracks the four dominant seasonal influenza strains/lineages, and use it to retrospectively examine the impact of the switch from a targeted to a universal influenza immunization program (UIIP) in the Canadian province of Ontario in 2000. According to our model results, averaged over the first four seasons post-UIIP, the rates of influenza-associated health outcomes in Ontario were reduced to about half of their pre-UIIP values. This is conservative compared to the results of a study estimating the UIIP impact from administrative data, though that study finds age-specific trends similar to those presented here. The strain interaction in our model, together with its flexible parameter calibration scheme, make it readily extensible to studying scenarios beyond the one explored here.
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1. Introduction

Seasonal influenza is responsible for a significant health burden each year, infecting roughly a tenth of the world's population (e.g. [1]). Large-scale changes in a population's vaccination patterns provide a good "natural laboratory" for better understanding the dynamics of an infectious disease such as influenza, and for testing epidemiological models. Just such a scenario took place in the province of Ontario, Canada, which in 2000 initiated the world's first large-scale universal influenza immunization program (UIIP), whereby influenza vaccination was provided for free to all residents. Subsequently, Kwong et al. [2] utilized provincial administrative data to study the impact of the UIIP on influenza-related health outcomes. Here, our objective was to develop a general-purpose seasonal influenza model, use it to simulate Ontario's UIIP adoption, and to test the results against those of [2].

Several key factors determined the design of our model. First and foremost, with a basic reproduction number R_0 estimated to range from 1.6 to 3.9 [3,4], the infectiousness of influenza is sufficiently low that herd immunity is important even at modest levels of vaccine coverage within a population; self-consistently accounting for herd immunity requires a dynamic transmission model. Second, we strove to make the model robust and flexible enough to be applied to a wide range of scenarios beyond the one explored here. Public health systems worldwide have a wide array of existing (e.g. inactivated, live-attenuated, adjuvanted, unadjuvanted) and new (e.g. quadrivalent, cell-cultured) seasonal vaccines to choose from, and with numerous additional influenza vaccines on the horizon [5], the selection is likely to become wider still. Mathematical models can serve as powerful tools to assist policymakers in the optimal adoption of these technologies.

We wanted to implement a transmission model sophisticated enough to reproduce the key dynamics of seasonal influenza – herd immunity, strain interaction, waning immunity, dependence on population contact patterns – while at the same time simple enough to be straightforwardly calibrated to real-world data. Accordingly, we chose a Susceptible–Infected–Recovered–Vaccinated compartmental model as our basic paradigm. We extended this approach to explicitly model the four dominant strains/lineages of seasonal influenza, with cross-protection where relevant. To our knowledge,

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previous age-structured influenza models have included a maximum of three strains, and no three-strain models have considered cross-protection [6,7]. Furthermore, we equipped the model with an approximate Bayesian computation (ABC) [8] parameter fitting scheme which is robust, flexible, and directly propagates the effect of parameter uncertainty to the model results.

Explicitly modeling both lineages of influenza B introduces an added level of complexity in how vaccination is implemented within the model. The reason is that current seasonal trivalent influenza vaccines (TIVs) include both dominant circulating subtypes of influenza A (H1N1, H3N2), but only one of the two circulating influenza B lineages (Victoria, Yamagata). Hence, there is the possibility of influenza B vaccine lineage mismatches: For example, B/Victoria is chosen for inclusion in a given season's TIV, but B/Yamagata ends being the dominant B lineage circulating that season. Historically, such a mismatch has occurred in roughly half of all seasons. Thus, when modeling the efficacy of TIV against influenza B over multiple seasons, care must be taken that the match/mismatch proportion reflects what happens in real life. This becomes especially important if one wishes to use the model for a comparison of TIV with quadrivalent (QIV) vaccines, which includes both B lineages; having too low or too high a rate of B lineage match for the TIV will under- or over-estimate, respectively, the effectiveness of TIV relative to QIV.

2. Materials and methods

2.1. Age structure and demographics

Our model was age-stratified [6,9], enabling us to include age-dependent contact patterns in calculating the force of infection. Births, deaths and aging were implemented; age-specific birth and death rates can be specified for the population, and these can be made to vary on a year-by-year basis. More detail on age structure and demographics in the model is given in A.1.

2.2. Epidemiology

The model explicitly tracks the two dominant A strains (H1N1, H3N2), and the two B lineages (Victoria, Yamagata) comprising seasonal influenza. We assumed that A and B cross-protection, both natural and vaccine-conferred, is negligible, and only allowed for the possibility of pairwise cross-protection between the two A strains, and between the two B lineages, respectively. We modeled seasonality in transmission as a sinusoidal variation in the force of infection, with a period of one year.

Immunity to influenza strains conferred by infection is only temporary, due to a combination of declining antibody levels and the continual antigenic drift of the influenza virus; see e.g. [10]. We assumed that individuals lose their immunity to a given strain k at a constant rate θ_k [6,11,12]. The inverse, $1/\theta_k$, is then the mean duration of natural immunity. Details of the transmission model are given in Appendix A.2.

2.3. Vaccination

Vaccination occurs over a finite time window, the yearly start time and length of which are input parameters. The vaccine is characterized by its efficacies against each of the circulating strains/lineages of influenza. TIV contains two A strains and only one B lineage, thus each season one of the B lineages is matched by the vaccine, while the other is mismatched. Hence, for B, the model requires both a matched and a mismatched efficacy as input. How well a given season's vaccine protects against influenza B is determined by the proportion of matched and mismatched B lineages that are in circulation that season; in a dynamic model, as in real life, this proportion is not known *a priori*. In light of this we made the accuracy of the choice a fitted parameter which can vary anywhere from a random choice to a "best guess". Details are given in Appendix A.3.

Vaccine-conferred immunity also wanes due to declining antibody levels and antigenic drift, and this process was implemented in the model analogously to the waning of natural, infection-conferred immunity, i.e. via a constant rate of immunity loss Θ_k for strain k. Since vaccine-conferred immunity is generally thought to be less robust than natural immunity, it was considered important that the model allow the two to wane at different rates. Details are given in Appendix A.3.

3. Model calibration

Since our understanding of the natural history of influenza is still far from complete, choosing realistic values for some of the parameters in the model poses a significant challenge. We adopted an approximate Bayesian computation (ABC) scheme [8] analogous to one used previously for fitting human papillomavirus models [13,14]:

(1) Each model input parameter to be fitted is given a uniform prior distribution between some minimum and maximum;
(2) Model outputs (model summary statistics) to be fitted are chosen. For each, a minimum and maximum value are chosen, thus defining an allowable target interval.
(3) Sets of parameters are drawn from the prior distributions. Latin hypercube sampling [15] is used in order to obtain a more even coverage of the parameter space with fewer samples than simple random sampling would yield.
(4) Each set of parameters drawn is used in one model run. The posterior parameter distribution consists of all sets of parameters which result in a model run in which all outputs simultaneously satisfy their respective allowable target ranges.

In this way, even though we may know little or nothing about the true value of an *individual* parameter (e.g. natural cross-protection; see Table 1), the posterior parameter distribution will consist only of *combinations of parameters that yield reasonable model outputs*. We restricted our fitting to natural history parameters, that is, parameters intrinsic to influenza itself, rather than parameters describing the population (e.g. birth rate, vaccine uptake, contact patterns), since natural history parameters are in general much more uncertain. Also, natural history parameters can be considered largely independent of the population, thus a posterior distribution obtained for one setting can be applied to another, as long as both populations possess a broadly similar lifestyle and average health status (e.g. if both are developed countries). This allowed us to exploit the availability of more suitable calibration target data for the US rather than for Canada; we conducted our natural history calibration in the former setting and applied the results to the latter. A total of 5000 fitting simulations were run, yielding 181 posterior (i.e. accepted) parameter sets. Details are given in Appendix B.

4. Modeling Ontario's transition to universal influenza immunization

Using the posterior parameter sets yielded by our model calibration above, we performed simulations of Ontario's adoption of a universal influenza immunization program (UIIP). For each simulation, one of the 181 posterior parameter sets was drawn at random, together with a new random seed (thus preventing two draws of the same parameter set from producing identical simulation results). Sets of 100, 500 and 1000 such

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