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Method Article

A method for evaluating the cost-benefit of different preparedness planning policies against pandemic influenza

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A B S T R A C T

- Our work presents a unifying method to calculate the net-benefit of different preparedness policies against different pandemic influeunza strains. Unlike previous methods, which have focused on evaluating specific strategies against specific pandemics, our method allows assessment of mass immunisation strategies in presence and absence of antiviral drugs for a large range of pandemic influenza strain characteristics and programme features. Overall, the model described here combines two parts to evaluate different preparedness planning policies against pandemic influenza.
- The first part is adaptation of an existing transmission model for seasonal influenza to include generalisation across large number of pandemic influenza scenarios.
- The second part is development of a tailor-made health economic model devised in collaboration with colleagues at the UK Department of Health and Social Care.

A R T I C L E I N F O
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Specification Table

Subject Area:	• *Mathematics*
More specific subject area:	• *Mathematical modelling and cost-benefit analysis*
Method name:	*Transmission model and cost-benefit analysis for pandemic influenza planning*
Name and reference of original method:	1. Original model for influenza transmission was developed in: M Baguelin, S Flasche, A Camacho, N Demiris, E Miller, WJ Edmunds. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study PLoS Med, 10 (2013), p. e1001527. 2. Modelling tool that incorporates the model and introduces the "fluEvidenceSynthesis" package applicable in R programming language was outlined in: van Leeuwen E, Klepac P, Thorrington D, Pebody R, Baguelin M. fluEvidenceSynthesis: An R package for evidence synthesis based analysis of epidemiological outbreaks. PLoS Comput Biol. 2017 Nov 20;13(11):e1005838. doi:10.1371/journal.pcbi.1005838.
Resource availability:	Repository containing the "fluEvidenceSynthesis" package described in reference 2 can be found at https://github.com/MJomaba/flu-evidence-synthesis

Method details

Impact model for control of pandemic influenza transmission

The modelling framework used is age (i) and risk (j) group stratified deterministic and dynamic transmission model that captures the temporal evolution of different cohorts within the population.

$$\frac{dS_{ij}}{dt} = bN_{ij}(t) - \beta c I_{ij} S_{ij} - \mu S_{ij} \tag{1}$$

$$\frac{dE_{ij}}{dt} = \beta c I_{ij} S_{ij} - \gamma_1 E_{ij} - \mu E_{ij} \tag{2}$$

$$\frac{dI_{ij}}{dt} = \gamma_1 E_{ij} - \gamma_2 I_{ij} - \mu I_{ij} \tag{3}$$

$$\frac{dR_{ij}}{dt} = \gamma_2 I_{ij} - \mu R_{ij} \tag{4}$$

Here *S(t), E(t), I(t)* and *R(t)* represent the cohorts of susceptible, pre-infectious (exposed), infectious and recovered individuals respectively at time t, b is per capita birth rate and μ is per capita mortality rate, *N(t)* is the total population, β is the transmission probability, c is the number of social contacts, γ_1 is the rate at which individuals become infectious, calculated as 1/(exposure period) and γ_2 is the rate at which individuals recover from being infectious, calculated as 1/(infectious period). We note that the SEIR model presented here is a simplification of the SEEIIR model used within Public Health England and presented in the references [1–3]. The model in [1] was initially developed, parametrised and calibrated against historic cases of seasonal H1N1 influenza in England, and had the exposed (E) and infected (I) groups stratified into two separate compartments. Additionally, separate vaccine components were also stratified by age and risk and calculated within the model. A subsequent extension and an R-package that synthesises the model were published in 2017 [2]. The aim of this package is to derive a readily available framework which can be adapted to explore the impact of a range of vaccination options against seasonal influenza in England. The implementation of the model in R programming language has been recently made available in [3].

We collaborated with the authors to transfer this model for seasonal influenza to a model for pandemic influenza. To do this we, firstly, simplified the original model by removing the stratification of the population by age and risk group. Furthermore, in our adaptation, we only used one exposed (E) and one infected (I) compartment and grouped all the vaccinated compartments into one group and not stratified by age or risk groups. Then we removed the seasonality of the model and we recalculated the mixing matrix by assuming an average number of contacts using the POLYMOD

dataset [4] rather than stratified by age and risk groups. We also adjusted the periods of exposure (latency period) and infection (infectious period) to be those reported for the UK: we assumed a latency period of 2 days [5] and an infectious period of 4 days [6]. The parameters describing the size of the UK population and the number of infected individuals at the time point considered to be the "start of the pandemic" within the model were fixed.

Although previous work has used dynamic modelling to evaluate different immunisation strategies, in the past they have been restricted to specific scenarios. Our method described here, instead, gives a unifying approach that is translatable to different settings, cohorts and applicable to any pandemic scenarios defined by their transmissibility (via R_0 changes) and or fatality (via CFR changes).

To answer specific questions in our analysis, we adapted the model from [1], to compute additional cases brought by a possible second pandemic once the initial pandemic has petered out. To do so we constructed a "dummy" pandemic with a moderately low level of initial susceptible cohort (50%), a moderately high basic reproduction number (R0) (2.2), a medium case fatality ratio (CFR) (0.2%). For this "dummy" pandemic, we used the SEIR model to estimate the reduction in number of infections, hospitalisations and deaths obtained from an "instant" (i.e. within one day) immunisation. We then used the obtained numbers as additional cases associated with this second pandemic weighted by the probability of second pandemic that we treated as a dimension of our parameter space.

We also extended the model to incorporate use of antiviral countermeasures in parallel to immunisation. We modelled antivirals as a binary option: "with" and "without" antivirals. In the "with" antivirals scenario we assumed that infectious period is reduced by 1 day, transmissibility is reduced by 14% and deaths are reduced by 50%. These are based on personal communication with the Health Protection Analytical Team within the UK Department of Health and based on work within [7].

We note that within the model there is a balance equation between duration of infectious period (γ_2), transmission probability (β) and R_0 such that for a fixed R_0, if we decrease γ_2, β needs to increase hence increasing the number of infections. To overcome this balancing issue, we imposed a decrease in both γ_2 and β so that in presence of antivirals we end up with lower effective R_0.

The model outputted the estimated number of susceptible, exposed, infected and recovered individuals each day for a year following the start of a pandemic. From these the daily number of influenza-like illnesses (ILIs) were calculated and then the number of clinical cases, the number of hospitalisations and the number of deaths associated with ILIs were calculated. We note that the multipliers for transferring ILIs to clinical cases and hospitalisations were derived from existing literature, whereas the multiplier transferring ILIs to deaths was the CFR which was treated as a dimension in our parameter space.

When we considered different preparedness policies we projected the following quantities from the transmission model:

A_{cases} = avoided clinical cases from a given intervention (compared to "no intervention")
A_{hosp} = avoided hospitalisations from a given intervention (compared to "no intervention")
A_{deaths} = avoided deaths from a given intervention (compared to "no intervention")

Economic model for mass immunisation against pandemic influenza

We compared different policies P in different scenarios based on associated economic net benefit as well as utility (QALY) gain/loss. To compute these measures we developed two economic models in collaboration with colleagues at the UK Department of Health.

- **A "pre-purchase vaccine" economic model.** This model assumes that vaccines are pre-purchased and stockpiled in advance of a possible pandemic. Stocks are replenished based on vaccine shelf-life. We considered three possible values of vaccine shelf-life {1, 2, 5} years.
- **A "responsive purchase" economic model**. We assessed the possibility of buying the needed vaccines after the start of a pandemic under the assumption that technological improvements allow a strain-specific vaccine to be manufactured in due time after a pandemic onset.

Benefit components

For calculations of benefit components we need to first define Quality Adjusted Life Years (QALY). A QALY is a measure of state of health of a person and corresponds to 1 year of life in perfect health [10]. In our economic model, we valued one QALY to have monetised value of £60,000 in agreement with recent impact assessment documents by the UK Government (e.g. [11])".

Let us define the following quantities:

q_{mon} = monetised value of a QALY
ql_{cases} = number of QALY loss associated with a clinical case
ql_{hosp} = number of QALY loss associated with a hospitalisation
ql_{deaths} = number of QALY loss associated with a death
c_{cases} = NHS monetary cost associated with a clinical case
c_{hosp} = NHS monetary cost associated with a hospitalisation
b_{abs} = economic cost for absenteeism due to a clinical case

We can then compute the benefit components associated with policy P by combining transmission model outputs' A_{cases}, A_{hosp} and A_{deaths} with these quantities:

Benefit component (£)	Formula
QALY gain from avoided clinical cases	$Q_{cases} = ql_{cases} \cdot \cdot q_{mon} \cdot A_{cases}$
QALY gain from avoided hospitalisations	$Q_{hosp} = ql_{hosp} \cdot q_{mon} \cdot A_{hosp}$
QALY gain from avoided deaths	$Q_{deaths} = ql_{deaths} \cdot q_{mon} \cdot A_{deaths}$
Benefit from avoided absenteeism	$B_{abs} = b_{abs} \cdot A_{cases}$
NHS savings from clinical cases	$S_{cases} = c_{cases} \cdot A_{cases}$
NHS savings from hospitalisations	$S_{hosp} = c_{hosp} \cdot A_{hosp}$

All of these benefit components are assumed to occur only in pandemic years, and their definition is valid for both the pre-purchase and the responsive-purchase model versions.

Cost components

Let us define the following quantities:

c_{vacc} = cost of buying a dose of vaccine
c_{admin} = cost of administering a dose of vaccine
c_{stor} = cost of storing a dose of vaccine
c_{distr} = cost of distributing a dose of vaccine
c_{disp} = cost of disposing of a dose of vaccine
d = doses of vaccines required per vaccinated person (2)
w = cover for wastage (10% of bought doses)
sl = vaccine shelf-life (in years)

Pre-purchase of a pandemic vaccine

The following cost components are associated with policy P in case of pre-purchase strategy.

Cost component (£), pre-purchase model	Formula
Vaccine purchase costs (every sl years)	$C_{vacc} = c_{vacc} \cdot d \cdot (1+w) \cdot N$
Cost of administering vaccine (only in pandemic years)	$C_{admin} = c_{admin} \cdot d \cdot N$
Cost of storing the vaccine (every year)	$C_{stor} = c_{stor} \cdot d \cdot (1+w) \cdot N$
Cost of distributing the vaccine (only in pandemic years)	$C_{distr} = c_{distr} \cdot d \cdot (1+w) \cdot N$
Cost of disposing of the vaccine (every sl years, only in case there is no pandemic)	$C_{disp} = c_{disp} \cdot d \cdot (1+w) \cdot N$

Responsive purchase of a pandemic vaccine

The following cost components are associated with policy P in case of responsive purchase strategy.

Cost component (£), responsive purchase model	Formula
Vaccine purchase costs (only in pandemic years)	$C_{vacc} = c_{vacc} \cdot d \cdot (1+w) \cdot N$
Option cost (every year)	$C_{option} = F$
Cost of administering vaccine (only in pandemic years)	$C_{admin} = c_{admin} \cdot d \cdot N$
Cost of distributing the vaccine (only in pandemic years)	$C_{distr} = c_{distr} \cdot d \cdot (1+w) \cdot N$

where F = option cost incurred to "reserve vaccine order"

Please note that cost of storage and disposal are absent in the responsive purchase model as vaccines are assumed to be bought as needed. However, an option cost is incurred every year to reserve the vaccine order.

Computing present values of economic net benefit and of QALY gain

In agreement with Health Protection Analytical Team's analysis at the UK Department of Health and Social Care, we used discount rates of 3.5% for monetary costs (including NHS cost savings) and 1.5% for health benefits (i.e. QALY gain) to determine present values, with a time horizon of 10 years.

Net benefit

Let us assume that:

- p is the annual chance of a pandemic actually happening. We think of this as the probability of a pandemic happening per year, based on the occurrence of past ones. The value used was agreed with our colleagues at DH & SC.
- m is a multiplier for NHS costs to account for foregone opportunity costs. In agreement with our colleagues at DH, it was assumed that every £1 spent on NHS resources generates a benefit of £m. Therefore, to divert NHS resources away from their current use onto a PPV programme, we considered the opportunity costs foregone, which translates into multiplying any costs or costs savings falling on the NHS by m".
- In order to compute present values of the components listed in the previous sections:
- all cost components as well as S_{cases} and S_{hosp} are multiplied by m;
- all components only incurred in pandemic years are multiplied by p and assumed to be incurred every year;
- all components only incurred in non-pandemic years are multiplied by $(1-p)$ and assumed to be incurred every year;
- C_{vacc} and C_{disp} are assumed to be incurred every sl years.

Total costs are subtracted from total benefit (and discounted) to determine the net benefit associated with either a pre-purchase or responsive purchase vaccine strategy. Let us denote the discounted components with "prime" symbol (e.g. C'_{vacc}, Q'_{cases}, etc.). Then:

Net benefit for pre-purchase model	$NB_{pre} = [Q'_{cases} + Q'_{hosp} + Q'_{deaths} + B'_{abs} + S'_{cases} + S'_{hosp}] - [C'_{vacc} + C'_{admin} + C'_{stor} + C'_{distr} + C'_{disp}]$
Net benefit for responsive purchase model	$NB_{resp} = [Q'_{cases} + Q'_{hosp} + Q'_{deaths} + B'_{abs} + S'_{cases} + S'_{hosp}] - [C'_{vacc} + C'_{option} + C'_{admin} + C'_{distr}]$

QALY gain. The total QALY gain associated with a given policy is then calculated by simply extracting $Q'_{cases} + Q'_{hosp} + Q'_{deaths}$

From NB_{pre} and NB_{resp}

Affordability of policy

Here we define our approach to establish whether a given policy is affordable. We assumed that the affordability of a policy is determined by assessing the upfront costs to buy and maintain a vaccine stockpile against a given threshold th_{AFF}.

Pre-purchase of pandemic strategy. For a pre-purchase vaccine strategy, we considered the following (non-discounted) upfront cost components to assess the affordability of a policy:

- In case of a pandemic year: $G_{pand} = C_{vacc} + C_{admin} + C_{stor} + C_{distr}$
- In case of a non-pandemic year: $G_{non-pand} = C_{vacc} + C_{stor} + C_{disp}$

Responsive-purchase strategy. For a responsive-purchase strategy, we considered the following (non-discounted) upfront cost components to assess the affordability of a policy:

- In case of a pandemic year: $G_{non-pand} = C_{option}$
- In case of a non-pandemic year: $G_{non-pand} = C_{option}$

Note: for the responsive-purchase strategy, upfront costs are the same in pandemic and non-pandemic years. In both cases, a given policy is considered to be affordable if the following condition is satisfied:

$$\max\left\{G_{pand}, G_{non-pand}\right\} \leq th_{AFF}$$

i.e. for every year in the time horizon, the costs associated with the policy do not exceed the given threshold.

Overall projections

For different preparedness policies, we calculated the net-benefits for the pre-purchase model and the responsive purchase model (respectively NB_{pre} and NB_{resp}). We then checked if the policy was affordable. Our method can be used to simulate different preparedness policies and project the net benefit. Examples of the applicability of the methodology described can be found in work by our group published elsewhere [8] and [9].

Supplementary material *and/or* additional information

This work showcases a method to calculate the net-benefit of different preparedness planning policies for pandemic influenza. Unlike previous methods which have focused on evaluating specific strategies against specific pandemics, our method gives a unifying approach that allows assessment of a large portfolio of scenarios and pandemic influenza strains. Overall, we have adapted an existing transmission model for seasonal influenza and combined it with a corresponding economic model, which we devised in collaboration with colleagues at the UK Department of Health and Social Care. Combining these, we can generate a large number of combinations of influenza and policy scenarios.

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Declaration of Competing Interest

The authors confirm that there are no conflicts of interest.

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