The potential cost-effectiveness of Next Generation Influenza vaccines in the UK: a modelling analysis

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Study in context:

Evidence before this study

While there have been cost-effectiveness studies on the implementation of seasonal influenza vaccines in many countries, several next generation vaccines are currently in clinical trials. Possible dynamics of these have been studied (Saad-Roy et al., 2019), but their potential impacts and value for money are still uncertain. Their dynamics have been s The only cost-effectiveness study of such next generation vaccines was conducted for Kenya, where influenza circulates all year round. Here it was shown that depending on the willingness-to-pay threshold used, next generation vaccines could be cost-effective in some circumstances, albeit with a relatively low per-dose threshold price.

Added value of this study

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Cost-effectiveness studies on seasonal influenza vaccination in high-income countries with temperate climates have contributed to changes in public policy, such as the extension of influenza vaccination to children in the UK. Next generation influenza vaccinations are being developed, but their potential benefits across populations, and therefore their implementation potential, remain unclear. We therefore evaluate the cost-effectiveness of such next generation vaccines in the UK, in order to inform decision-making bodies such as the Joint Committee on Vaccination and Immunisation about the potential benefits of the vaccines, as well as to inform developers about the potential market for such vaccines. Our cost-effectiveness analysis in the UK shows the high cost-effectiveness of next generation influenza vaccines, even those minimally improved above currently available vaccines.

Implications of all the available evidence

This study, showing the high cost-effectiveness of next generation influenza vaccines bolsters the investment case for such vaccines and suggests that such vaccines may be viable in the UK market. The high threshold price that countries like the UK may be willing to pay is particularly of interest due in the context of the significantly lower threshold prices required in Kenya for such vaccines, raising the potential for differential pricing of the vaccines.

Key words: influenza; vaccination; cost-effectiveness; economic evaluation; universal vaccines; next generation vaccines; mathematical modelling

Summary:

Background

Next generation influenza vaccines are in development and have the potential for widespread health and economic benefits. Determining the potential health and economic

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impact for these vaccines is needed to drive investment in bringing these vaccines to the market, and to inform public health policy.

Methods

We used a mathematical modelling approach to estimate the epidemiological impact and cost-effectiveness of next generation influenza vaccines in England and Wales. We used data from an existing fitted model, and evaluated new vaccines with different characteristics ranging from improved vaccines with increased efficacy duration and breadth of protection, to universal vaccines. We calculated the cost effectiveness of new vaccines in comparison to the current seasonal vaccination programme. We calculated and compared the Incremental Cost-Effectiveness Ratio and Incremental Net Monetary Benefit for each new vaccine type.

Findings

We show that next generation influenza vaccines may result in a 21% to 77% reduction in influenza infections, dependent on vaccine characteristics. Our economic modelling shows that using any of these next generation vaccines at 2019 coverage levels would be highly cost-effective at a willingness to pay threshold of £20,000 for a range of vaccine prices. The vaccine threshold price for the best next generation vaccines in 2019-GBP is £197 (95%CrI £160 - £235) per dose, but even minimally-improved influenza vaccines could be priced at £14 (95%CrI £12 - £17) per dose and still remain cost-effective.

Interpretation

This evaluation demonstrates the promise of next generation influenza vaccines for impact on influenza epidemics, and likely cost-effectiveness profiles. We have provided evidence towards a full value of vaccines assessment which bolsters the investment case for development and roll-out of next-generation influenza vaccines.

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Introduction

Seasonal influenza has a substantial health burden in the United Kingdom (UK), resulting in 28,000 hospitalisations and 7,000 deaths in the UK per year (1,2), along with widespread economic losses. This is despite vaccination availability in the UK, which has been expanded to include children and adults over 50, as well as at-risk groups and healthcare workers and is annually reaching higher coverage levels.

Current influenza vaccines must be reformulated annually to match circulating strains (3). Despite this the vaccine does not match circulating strains in many years, which results in very low efficacy (4), especially in older age groups (5). However, next generation vaccines are in development which aim to address these shortcomings, with 28 vaccine candidates currently in clinical trials (6), often utilising newer technologies such as nanoparticles and mRNA (7). These next generation vaccines fall into multiple categories, as defined by the World Health Organization's Preferred Product Characteristics (PPCs) for improved influenza vaccines (8): "Improved" vaccines, which have an increase in efficacy or breadth of protection, resulting in immunity that lasts at least 1 year or season; and "Universal" vaccines, which have an increased efficacy and strain breadth, with immunity lasting up to 5 years.

The Joint Committee on Vaccination and Immunisation (JCVI) makes recommendations about new vaccine introduction in the UK, and has a statutory duty to consider cost-effectiveness when making such recommendations. Hence it is important to understand whether only universal vaccines - which represent a step-change in efficacy over current seasonal influenza vaccines - are cost-effective, or whether improved vaccines are also likely to be cost effective, and under what circumstances.

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The cost-effectiveness of next generation vaccines has so far only been evaluated for Kenya (9). Kenya has particular characteristics that may make such vaccines particularly beneficial, such as relatively high influenza-related mortality especially in children, and year-round circulation of influenza. In this setting, at a willingness to pay threshold of 45% per capita GDP, *universal* vaccines would be cost-effective up to a price of $5.16 per dose. Here we evaluate the cost-effectiveness of next generation influenza vaccines in the UK, a high income setting with low paediatric influenza-associated mortality and relatively strong and consistent annual seasonality. We evaluate the replacement of seasonal vaccines with improved and universal next generation vaccines.

Methods

We have extended *FluEvidenceSynthesis,* a Bayesian modelling analysis of influenza epidemics and vaccination in England and Wales using epidemiology from 1995-2008 (10) that was previously used to assess the cost effectiveness of extending the influenza vaccine programme to include paediatric populations(11). Our extended model consisted of three elements (Figure 1a): (1) tracking vaccinations given across years, (2) tracking infections, and (3) calculating economic outputs. The second model is an adaptation of *FluEvidenceSynthesis* extended to include next generation influenza vaccines with longer durations of immunity, higher efficacy and/or broader sub-type cross-protection (Figure 1), as in our previous work in Kenya (9) and described below. All code is available at https://github.com/NaomiWaterlow/NextGenFlu_UK.

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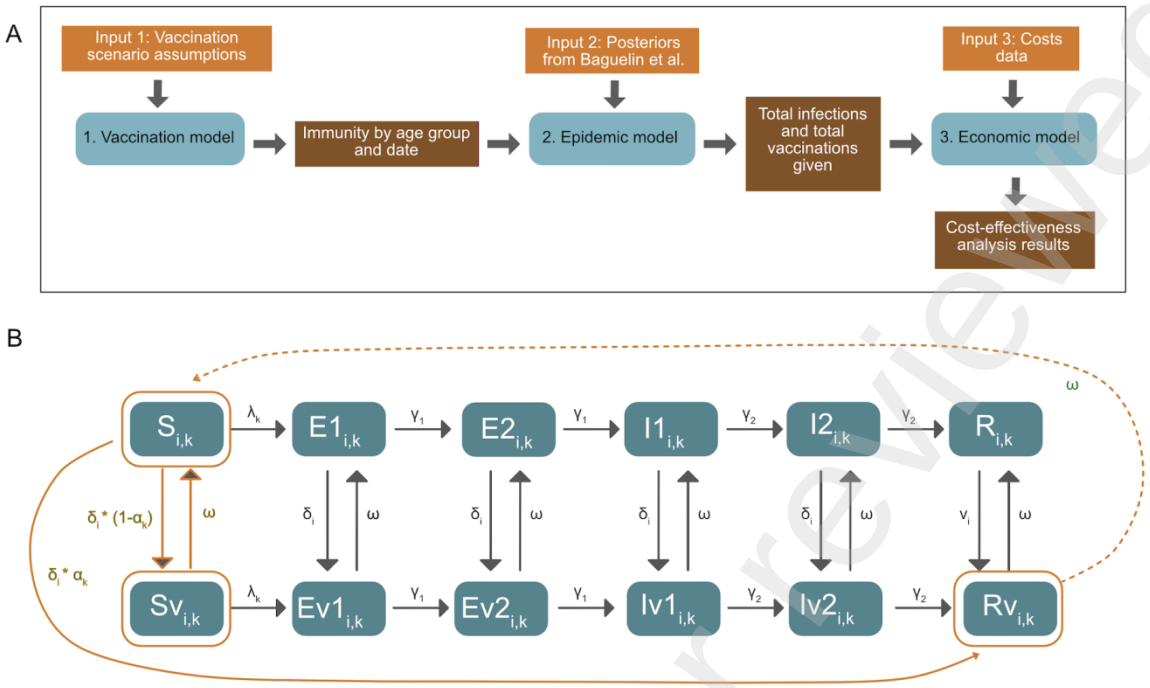

Figure 1: A) Overview of modelling steps. Orange indicates inputs, brown indicates outputs and blue shows the modelling steps. B) Elements in solid orange are included in both the vaccination and the epidemic models. Transitions in grey are included only in the epidemic model, and transitions in orange are included only in the vaccination model. States are: Susceptible (S), Exposed (E1, E2), Infectious (I1, I2) and Recovered (R), and their vaccinated counterparts (Sv, Ev1, Ev2, Iv1, Iv2, Rv). Both the E and I populations consist of two compartments, to achieve a gamma distributed waiting time. Each compartment is also stratified by age (i) and influenza subtype (k). δ is the rate of vaccination in age group i, α is the efficacy by subtype, ω is vaccine-derived immunity waning. Table S3 has further parameter details. The model is run separately for each influenza subtype (A(H1N1), A(H3N2), B). For the epidemic model, in both vaccinated and unvaccinated compartments, susceptibles who are infected with the viral subtype enter the first Exposed (E) compartment. They then progress through the E and I compartments. After ceasing to be infectious they enter the R compartment, whereupon they cannot be re-infected during the same epidemic period. Adapted from Waterlow et al. (2022)(9).

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Modelling Vaccine immunity

The vaccination model element tracked the percentage of the population vaccinated over time and consisted of three compartments: Susceptible (S), Susceptible-vaccinated (Sv) and Recovered-vaccinated (Rv). We ran the model independently for influenza A subtypes A(H1N1) and A(H3N2), and for the two B lineages combined, as in Baguelin *et al.* 2013 (10). We assumed no interaction between the subtypes.

Vaccine doses were assumed to be distributed independent of prior vaccine or infection status (see discussion), and a proportion of those vaccinated was assumed to become immune to infection, entering the Rv compartment, with the proportion defined by vaccine efficacy. The inverse of this proportion entered the Sv compartment, Vaccine-induced immunity was therefore assumed to be all-or-nothing. Vaccine immunity waned exponentially at a different rate for each vaccine type (Table 1), and individuals with waned immunity returned to the S compartment. Vaccines could be matched or mismatched to circulating strains, with an efficacy of 70% in those <65 and 46% in those 65 and older in years where the vaccine strains match, and for mismatched years 42% and 28% respectively, per Baguelin *et al.* (2013).

The model was stratified into six age categories: Infants (age 0), young children (ages 1-4), school children (ages 5-14), young adults (15-44), adults (45-64) and older adults (65+). In addition the population was stratified into low- and high-risk groups, which receive different vaccination coverage levels.The population aged annually on 1 March (by moving a proportion out of each age group - e.g. ¼ of the age group containing ages 1-4 will move into the next age group each year), at which point the population size is also updated to reflect the current year's size (12). All individuals were assumed to be born susceptible.

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We generated 6 scenarios regarding characteristics of next-generation vaccines and vaccination target groups (Table 1). We generated two scenarios were counterfactuals representing use of current seasonal influenza vaccines. *Current seasonal (2013 coverage)* used actual coverage in the time period simulated (1995-2008), as in the base scenario from Baguelin *et al.* 2013 (10). In *Current seasonal (2019 coverage)* the coverage and target ages were expanded to match 2019 levels, including those 50 or older at the coverage levels observed in 2020 (13–15), and reduced the efficacy of A(H3N2) vaccination to 14% in line with observed trends (5). From 2013 to 2019, vaccination was expanded to school age children from 2013/14 onwards. Further scenarios simulated next generation vaccines as described in the WHO PPC (8), with three *Improved* vaccines (*minimal, broader strain breadth, higher efficacy)* and one *universal* vaccine. Coverage matched uptake levels by month in England (see supplement section 1).

In the first year of simulation (1995), we vaccinated to reach the target coverage in all age groups. If vaccine-induced immunity duration lasts a year or less, the same target coverage is reached every year. However, if the immunity duration is longer than a year, we reduce the coverage in line with the duration of vaccine immunity, as people will not need to get revaccinated every year, i.e.. if vaccine immunity lasts for 2 years, in all years after the first year, coverage is divided by 2.

Table 1: Vaccine scenarios

Scenario name	**Mis-matched seasons?**	**Efficacy (Matched <65 / >65 Mis-matched <65 / >65)**	**Immunity Duration (exponential)**	**Coverage**	**Note**
Current seasonal vaccines	Yes	70% / 46% 42% / 28%	6 months	As in Baguelin 2013.	Used only for validation

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(2013 coverage)					
Current Seasonal Vaccines (2019 coverage)	Yes	70% / 46% 42% / 28% Except subtype A/H3 which is 43% all ages match 14% all ages mismatch	6 months	2019 UK coverage applied annually (including coverage of school age children, and enhanced coverage in older adults, see Supplement, Table S1)	Base case scenario to compare NextGen vaccines too
Improved vaccines (Minimal)	Yes	70% / 46% 42% / 28% Except subtype A/H3 which is 43% all ages match 14% all ages mismatch	1 year	2019 UK coverage applied annually (Supplement, Table S1)	Base case scenario in sensitivity analysis (Supplement Section 9)
Improved Vaccines (Efficacy)	Yes	90% / 70% 70% / 40%	2 years	2019 UK coverage (Supplement, Table S1 in 1st year, then Table 2 *½ in subsequent years)	
Improved Vaccines (Breadth)	No	70% / 46%	3 years	2019 UK coverage (Supplement, Table S1 in 1st year, then Table 2 * ⅓ in subsequent years)	
Universal Vaccines	No	90% / 70%	5 years	2019 UK coverage (Supplement, Table	

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				S1 in 1st year, then Table 2 *⅕ in subsequent years)	

Tracking Infections

We simulated annual epidemics of each influenza virus type/subtype (A/H1N1, A/H3N2 and B) from 1995 to 2008, starting on the 1 October each year, with each simulation running for 364 days. We sampled 1000 values for each of the parameters (for each season: transmission rate, proportion susceptible, number of infections at the start) from the joint posteriors of the individual season fits in Baguelin *et al.* 2013 (10) (Table 2). At the start of each season, the proportion immune by vaccination was extracted from the vaccination model and used as an input to the epidemic model, as the percentage of the population that are in the S, Sv and Rv compartments (Supplement Section 2).

Natural immunity was assumed to be leaky, reducing the chance of infection as opposed to inhibiting infection completely. We assumed that infection-derived immunity at the start of each season is not influenced by vaccination, as we found little correlation between the number of infections one year and immunity levels the following year (supplement section 3). However we include two sensitivity analyses with different assumptions on changes to susceptibility (supplement section 7).

Table 2: Model parameters

Parameter	**Symbol**	**Model assumption**	**Value (if fixed)**
Age-specific vaccination rate	δ_i	Vaccine assumption based on weekly coverage achieved.	see table 1

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Parameter	Symbol	Model assumption	Value (if fixed)
Vaccine efficacy	α	Vaccine assumption	see table 1
Contact rates between age groups i and j	c_{ij}	Fixed based on UK POLYMOD (16)	Age specific, see (16)
Latency period	$2 * 1/\gamma_1$	Fixed *fluEvidenceSynthesis* package	0.8 days
Infectious Period	$2 * 1/\gamma_2$	Fixed *fluEvidenceSynthesis* package	1.8 days
Vaccine immunity duration	ω	Vaccine assumption	see table 1
Age specific proportion in vaccinated compartments at start of epidemic	ηv_i	Vaccine assumption / Model	-
Age specific proportion in Rv vs Sv compartments at start of epidemic	ηRv_i	Vaccine assumption / Model	-
Age specific force of infection	λ_i	Posterior estimated in Baguelin 2013	-
Transmission rate	β	Posterior estimated in Baguelin 2013	-
Age-specific susceptibility	ζ_i	Posterior estimated in Baguelin 2013	-

Economic modelling

To estimate the cost-effectiveness of each vaccination scenario compared to the *current seasonal (2019 coverage)* scenario, we calculated the incremental quality adjusted life years (QALYs) gained and costs for each scenario (supplement section 4). Total QALYs lost were calculated from symptomatic (mild) infections, symptomatic (fever) infections,

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hospitalisations and deaths (supplement Table S3). QALYs lost as a result of death were calculated using remaining life expectancy from UN Population Division life tables (17) discounted to the year in which the death occurred, and taking into account the population size and risk of death at each age.

Costs consisted of vaccine delivery costs, costs of GP visits and costs of hospitalisation (supplement Table S3), as we took a payer rather than a societal perspective, as recommended in the UK (18). Costs were inflated to 2019-£ using the Hospital and Community health services index(19). The cost-effectiveness analysis was conducted according to the guidelines set by the Joint Committee on Vaccination and Immunisation (JCVI) (20) and the reference case used by the National Institute for Health and Care Excellence (NICE) (21). In particular, we discounted outcomes to the year 1995, our reference year for costs as we're using 1995-2008 epidemiology, using a rate of 3.5% for costs and 1.5% for QALYs. This was then inflated to reporting values of £-2019

We calculated Incremental Cost-Effectiveness Ratios (ICERs) and Incremental Net Monetary Benefits (INMBs) for each scenario, by monetising QALYs at a WTP threshold value of £20,000, with a sensitivity analysis of 90% at £30,000 (see supplement). We also calculated vaccine threshold prices based on this WTP threshold.

We conducted a probabilistic sensitivity analysis by drawing 1000 random samples for each parameter from its corresponding probability distributions. We used beta distributions fitted to the proportion symptomatic and proportion with fever from Carrat *et al*. 2008 (22) to estimate the number of infections that result in symptoms and fever respectively. We used age- and risk-specific samples taken from Baguelin *et al.* 2015 (11) for the proportion of infections that result in a visit to a General Practitioner (GP), hospitalisation and death. Costs were sampled from log-normal distributions parameterised based on Baguelin *et al.* 2015 (11).

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Sensitivity Analyses

We ran a range of sensitivity analyses to evaluate the impact of our assumptions.

- We increased the susceptibility to influenza infection from the same subtype in years following vaccination by 10% or 20%, to simulate a loss in infection-derived immunity as a result of vaccination.
- We assumed a different vaccine price, based on the range of vaccine prices presented in Baguelin *et al*. (2015)(11). The low price was £12 and the high price was £20.
- There are indications from the literature that current vaccine-derived immunity may last longer than one season(23). Therefore we ran the economic modelling taking the *Improved (minimal)* scenario as the base scenario, where the duration of immunity lasts for 1 year (exponentially distributed). The improved vaccine scenarios are then the *Improved (efficacy)*, *Improved (breadth)* and *Universal*.
- We set the vaccine threshold price to £30,000.

Results

To ensure our extended modelling framework was accurately reproducing results in previous publications (10), we determined that our *current seasonal (2013 coverage)* scenario showed results in line with previous work by Baguelin *et al.* with the epidemic incidence peak for each age group falling within the confidence interval of previous results, and peaking within a week of the peak (see supplement section 5).

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The *current seasonal (2019 coverage)* scenario was then used to compare currently available vaccines to our range of next generation vaccines. The *improved (minimal)* scenario resulted in a reduction of 21% (95%CrI 19%-24%) of infections, followed by the *improved (breadth)* scenario with 60% (56%-65%) and the *Improved (efficacy)* with 62% (58%-69%) reduced. *Universal* vaccines resulted in the biggest reduction in infections of 77% (73%-81%), while also using the fewest vaccines (Figure 2). In the *Universal* vaccine scenario, circulation of H1N1 and B were virtually eliminated after the first season (see supplement section 6). Compared to the *current seasonal (2019 coverage)* vaccines, improved (minimal) resulted in an extra 0.16 - 0.24 infections averted per vaccine dose. This increased for *improved (efficacy)* vaccines to 0.94 - 1.23, for *improved (breadth)* vaccines to 1.30 - 1.67 and 2.45 - 3.12 extra infections averted per vaccine dose for *universal* vaccines.

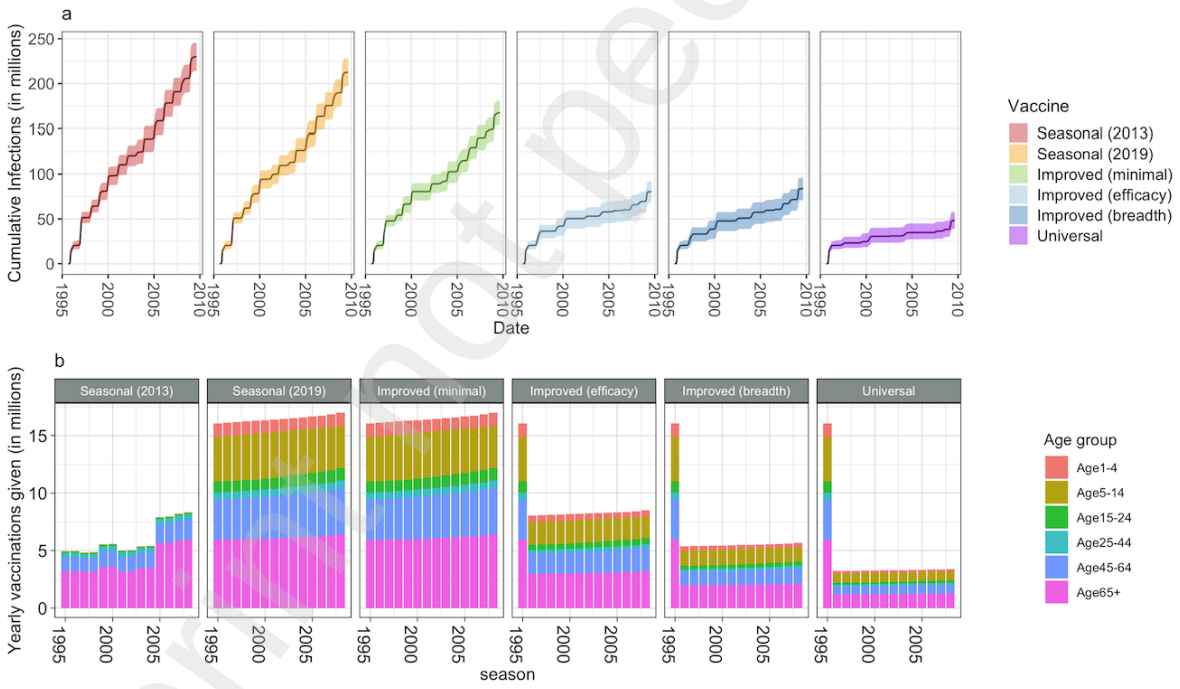

Figure 2: A) Cumulative incidence of infections over time, for each vaccine scenario. The black line displays the median value, and the coloured interval the 95% Credible Interval (95% CrI). B) Cumulative vaccinations given over time, for each vaccine scenario by age group.

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The scenarios resulted in a wide range of hospitalisations, with the *current seasonal (2019 coverage)* resulting in a median annual 14,285 (range 988 - 40556) hospitalizations across years. This compares to the *improved (minimal)* scenario with an median annual 11,196 (range 0 - 37,302) hospitalisations across years, the *improved (efficacy)* scenario with 2,943 (range 0 - 30,834) hospitalisations across years, the *improved (breadth)* scenario with 3,652 (range 0 - 30,895) hospitalisations across years and the universal scenario with 159 (range 0 - 30513) hospitalisations across years.

As all the vaccine scenarios used the same or fewer vaccine doses than the baseline scenario (assumed to have the same cost per dose) and resulted in increased health benefits, the scenarios were all cost-saving. Consequently, all scenarios had a positive INMB, ranging from a median of £1.98 billion for *incremental (minimal)* vaccines to a median of £11.16 billion for *universal* vaccines (Figure 3), assuming a WTP threshold of £20,000. We calculated threshold prices (i.e. the median price at which INMB = 0, compared to the *current seasonal (2019 coverage)* scenario), resulting in a threshold price of up to £230 (95%CrI £192 - £269) for *universal* vaccines (Table 3). However, even for *Improved (minimal)* vaccines the purchase price could reach over three times that of currently available vaccines, with these vaccines being cost-effective at a price of £18 (95%CrI £16 - £21).

In sensitivity analyses, assuming current vaccines already performed as well as *Improved (minimal)* vaccines, resulted in slightly reduced threshold prices, although still reaching £185 (95%CrI £158 - £217) for *universal* vaccines (supplement section 9).

Across our sensitivity analyses on vaccine prices the threshold price for the vaccines stayed high, with medians ranging from £212 to £249 for *universal* vaccines across different assumptions. We found that the results were sensitive to the assumptions behind infection-derived immunity (supplement section 7). As a sensitivity, inline with JCVI recommendations,

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we also calculated prices where 90% of simulations reach a threshold of £30,000, which resulted in higher threshold costs of £275) for *universal* vaccines. (supplement section 8).

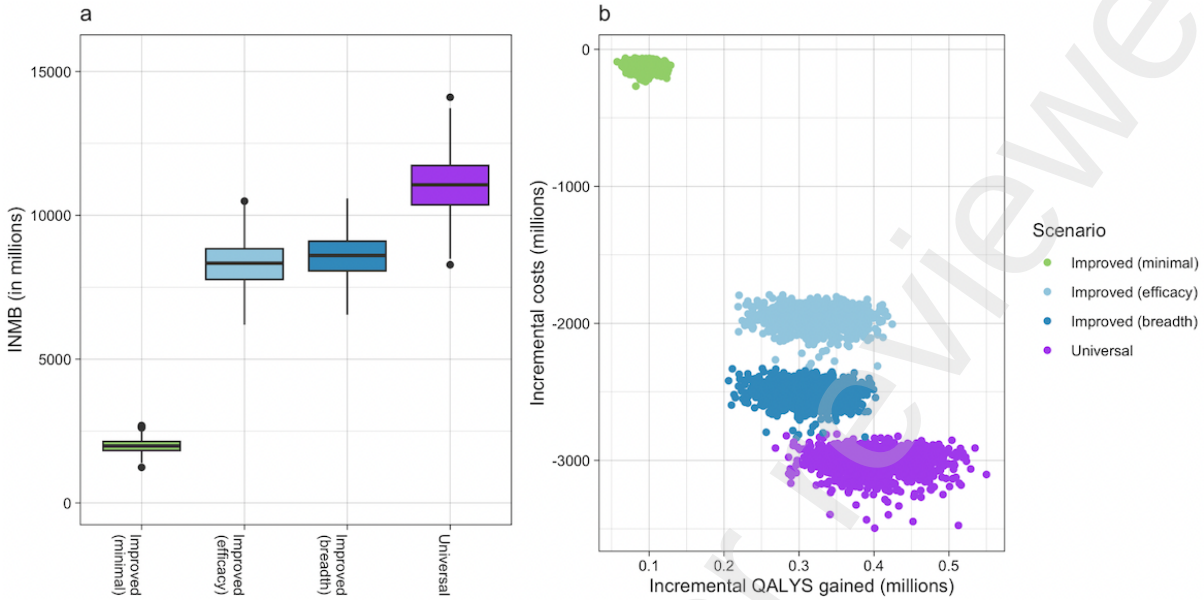

Figure 3: a) Incremental Net Monetary Benefits (in millions) for each vaccine type, compared to the current seasonal (2019 coverage) scenario. b) Cost-effectiveness plane showing Incremental costs against Incremental QALYs gained.

Table 3: Vaccine threshold prices for each vaccine, displayed in 2019-£s.

Scenario	Lower	Median	Upper
Improved (minimal)	16.0	18.3	21.0
Improved (efficacy)	76.2	90.7	105.7
Improved (breadth)	107.4	126.7	147.5
Universal	192.4	229.9	268.6

Discussion

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Our study indicates that next generation influenza vaccines could have substantial health and economic benefits in the UK. While a universal vaccine had the greatest benefits, a substantial improvement in health and reduction in healthcare costs was seen even with minimally improved vaccines. Implementing next generation vaccines could have resulted in a 21% to 77% reduction in influenza infections in epidemics from 1995-2008 compared to the current vaccine (at 2019 coverage), depending on vaccine characteristics. Implementing next generation vaccines may be cost-effective for vaccine prices up to £230 (95%CrI £192 - £269) for universal vaccines, with increases in the threshold price of the vaccine as the vaccine improves from baseline.

The threshold vaccine prices represent the maximum that could be paid per dose of vaccine for it to be cost-effective, and are high compared to market prices of other vaccines. This suggests that next generation vaccines are likely to be priced at levels that make them cost-effective in the UK. As a comparison to other threshold prices, HPV vaccination in girls has a threshold dose price of £56-108 in the UK (24). The evidence presented in this study, combined with that from other studies on the cost-effectiveness of next generation influenza vaccines in other countries may help guide pharmaceutical companies on development and investment decisions as well as vaccine introduction decisions by countries such as the UK. We used a healthcare payer perspective for costs, as is recommended in the UK (18). Including societal costs in the cost-effectiveness analysis would likely result in even greater cost-effectiveness, since it would incorporate a reduction in lost working hours.

We made the assumption that vaccination occurs regardless of previous vaccination status, and vaccines may therefore be delivered to individuals who are already protected through recent vaccination. In reality, repeat vaccination during the period of vaccine immunity may be less ikely if guidelines are given to wait a certain time before getting revaccinated, and next generation vaccination may therefore be more cost-effective than calculated in this paper. However this effect may not be large, as due to variations in waning of vaccine

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immunity, individuals may still get re-vaccinated. There will likely still be a significant group of individuals that will not get vaccinated, due to personal healthcare decisionmaking or vaccine hesitancy (25). Our assumption lies between these two alternative scenarios of behaviour.

Our model tracks immunity from vaccination over multiple years, which allowed us to track the longer-lasting immunity that may occur as a result of next generation vaccines. Using such a transmission model also allowed us to capture the indirect effects of vaccination, which have previously shown to be very important for the epidemiology of influenza (26,27). We modelled each of the influenza types/subtypes independently (A/H1N1, A/H3N2, B), as in the Baguelin paper that our study is based on. This does not allow any interaction between the viral subtypes. Whilst previous evidence suggests interaction may play a role (28–32) by providing some cross-immunity between subtypes, we based our study on fitted epidemics, so any interaction may already have been captured in the fitted transmission rates. We assumed that a lack of infection-derived immunity as a result of vaccination did not impact the susceptibility of the population the following year. There is some evidence from other studies that vaccine derived immunity may propagate less well than infection-derived immunity (32). However, we explored the correlation between epidemic size and susceptibility in the following year and found little effect. This suggests that immunity to influenza is more complex than a simple function of immunity from the previous epidemic immunity (33). However, despite resulting in unrealistic outbreaks, our sensitivity analysis showed this assumption had a large impact, so should be further studied. The change in infection-derived immunity may have further implications on influenza pandemics.

Overall, our study provides a strong case for investing in next generation vaccines, indicating that they are likely to be cost effective in the UK, and other similar countries, if available at reasonable price points. Even minimally improved vaccines may have a large health impact and be cost-effective.

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References

1. Burden of disease [Internet]. [cited 2022 Nov 9]. Available from: https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/burden-of-disease
2. Matias G, Taylor RJ, Haguinet F, Schuck-Paim C, Lustig RL, Fleming DM. Modelling estimates of age-specific influenza-related hospitalisation and mortality in the United Kingdom. BMC Public Health. 2016 Dec;16(1):481–481.
3. Vaccines [Internet]. [cited 2022 Nov 9]. Available from: https://www.who.int/teams/global-influenza-programme/vaccines
4. CDC Seasonal Flu Vaccine Effectiveness Studies | CDC [Internet]. 2022 [cited 2022 Nov 9]. Available from: https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm
5. Belongia EA, McLean HQ. Influenza Vaccine Effectiveness: Defining the H3N2 Problem. Clin Infect Dis. 2019 Oct 30;69(10):1817–23.
6. Universal Influenza Vaccine Technology Landscape | CIDRAP [Internet]. [cited 2022 Apr 5]. Available from: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape
7. Moore KA, Ostrowsky JT, Kraigsley AM, Mehr AJ, Bresee JS, Friede MH, et al. A Research and Development (R&D) roadmap for influenza vaccines: Looking toward the future. Vaccine. 2021 Oct 29;39(45):6573–84.
8. WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines [Internet]. [cited 2022 Jan 6]. Available from: https://www.who.int/publications-detail-redirect/9789241512466
9. Waterlow NR, Radhakrishnan S, Dawa J, Leeuwen EV, Lambach P, Bresee J, et al. Potential health and economic impact of paediatric vaccination using next generation influenza vaccines in Kenya: a modelling study [Internet]. medRxiv; 2022 [cited 2022 Aug 28]. p. 2022.08.26.22279262. Available from:

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4343747

https://www.medrxiv.org/content/10.1101/2022.08.26.22279262v1

10. Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds WJ. Assessing Optimal Target Populations for Influenza Vaccination Programmes: An Evidence Synthesis and Modelling Study. PLoS Med [Internet]. 2013;10(10). Available from: http://researchonline.lshtm.ac.uk/1273063/
11. Baguelin M, Camacho A, Flasche S, Edmunds WJ. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: a cost-effectiveness study. BMC Med. 2015 Oct 13;13(1):236.
12. Population estimates - Office for National Statistics [Internet]. [cited 2022 Nov 9]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates
13. Seasonal influenza vaccine uptake in children of primary school age. :24.
14. Seasonal influenza vaccine uptake in GP patients: winter season 2020 to 2021. Final data for 1 September 2020 to 28 February 2021. 2020;53.
15. Seasonal flu vaccine uptake in GP patients: winter 2019 to 2020 [Internet]. GOV.UK. [cited 2022 Nov 14]. Available from: https://www.gov.uk/government/statistics/seasonal-flu-vaccine-uptake-in-gp-patients-winter-2019-to-2020
16. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. Riley S, editor. PLoS Med. 2008 Mar;5(3):0381–91.
17. World Population Prospects - Population Division - United Nations [Internet]. [cited 2022 Nov 9]. Available from: https://population.un.org/wpp/Download/Standard/CSV/
18. Economic evaluation: health economic studies [Internet]. GOV.UK. [cited 2022 Nov 9]. Available from: https://www.gov.uk/guidance/economic-evaluation-health-economic-studies
19. Unit Costs of Health and Social Care 2021 | PSSRU [Internet]. [cited 2022 Nov 9]. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4343747

and-social-care-2021/

20. Immunisation and High Consequence Infectious Diseases Team, Global and Public Health Group. Cost-effectiveness methodology for vaccination programmes - Consultation on the Cost-EffectivenessMethodology for Vaccination Programmes andProcurement (CEMIPP) Report. Department of Health and Social Care; 2018.
21. NICE health technology evaluations: the manual. :195.
22. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol. 2008 Apr 1;167(7):775–85.
23. Young B, Sadarangani S, Jiang L, Wilder-Smith A, Chen MIC. Duration of Influenza Vaccine Effectiveness: A Systematic Review, Meta-analysis, and Meta-regression of Test-Negative Design Case-Control Studies. J Infect Dis. 2018 Feb 14;217(5):731–41.
24. Datta S, Pink J, Medley GF, Petrou S, Staniszewska S, Underwood M, et al. Assessing the cost-effectiveness of HPV vaccination strategies for adolescent girls and boys in the UK. BMC Infect Dis. 2019 Jun 24;19(1):552.
25. Influenza vaccine hesitancy amongst healthcare workers. 2022 Nov 22 [cited 2022 Nov 22]; Available from: https://www.bmj.com/content/360/bmj.k1141/rr
26. Eichner M, Schwehm M, Eichner L, Gerlier L. Direct and indirect effects of influenza vaccination. BMC Infect Dis. 2017 Apr 26;17(1):308.
27. Friedman L, Renaud A, Hines D, Winter A, Bolotin S, Johnstone J, et al. Exploring indirect protection associated with influenza immunization – A systematic review of the literature. Vaccine. 2019 Nov 20;37(49):7213–32.
28. Andreasen V, Lin J, Levin SA. The dynamics of cocirculating influenza strains conferring partial cross-immunity. J Math Biol. 1997 Aug;35(7):825–42.
29. Sonoguchi T, Naito H, Hara M, Takeuchi Y, Fukumi H. Cross-Subtype Protection in Humans During Sequential, Overlapping, and/or Concurrent Epidemics Caused by H3N2 and H1N1 Influenza Viruses. J Infect Dis. 1985 Jan;151(1):81–8.
30. Koutsakos M, Illing PT, Nguyen THO, Mifsud NA, Crawford JC, Rizzetto S, et al. Human

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=4343747

CD8+ T cell cross-reactivity across influenza A, B and C viruses. Nat Immunol. 2019 May;20(5):613–25.

31. Yang W, Lau EHY, Cowling BJ. Dynamic interactions of influenza viruses in Hong Kong during 1998-2018. Viboud C, editor. PLOS Comput Biol. 2020 Jun;16(6):e1007989–e1007989.

32. Hill EM, Petrou S, Lusignan S de, Yonova I, Keeling MJ. Seasonal influenza: Modelling approaches to capture immunity propagation. PLOS Comput Biol. 2019 Oct 28;15(10):e1007096.

33. Knight M, Changrob S, Li L, Wilson PC. Imprinting, immunodominance, and other impediments to generating broad influenza immunity. Immunol Rev. 2020 Jul;296(1):191–204.

Declarations of Interest

No conflicts of interest.

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