Vaccine 41 (2023) 6017–6024

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The potential cost-effectiveness of next generation influenza vaccines in England and Wales: A modelling analysis

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ARTICLE INFO

Keywords:
Influenza
Vaccination
Cost-effectiveness
Economic evaluation
Universal vaccines
Next generation vaccines
Mathematical modelling

ABSTRACT

Next generation influenza vaccines are in development and have the potential for widespread health and economic benefits. Determining the potential health and economic impact for these vaccines is needed to drive investment in bringing these vaccines to the market, and to inform which groups public health policies on influenza vaccination should target.

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, defined in line with the World Health Organisation (WHO) Preferred Product Characteristics (PPC). 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. All analysis was conducted in R.

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 is £230 (95% CrI £192 - £269) per dose, but even minimally-improved influenza vaccines could be priced at £18 (95%CrI £16 - £21) per dose and still remain cost-effective.

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.

1. Introduction

Seasonal influenza has a substantial health burden in England and Wales, resulting in 27,237 (95% CI 0–63,027) hospitalisations and 6,561 (95% CI 0–17 342) deaths in the UK per year, along with widespread economic losses [1,2]. This is despite a yearly influenza vaccination programme in England and Wales, which has been expanded from at-risk individuals and those over 65, to include children and adults over 50. The programme reaches moderate coverage levels in children (60%) and higher levels in over 65 s (73%) and some risk groups each year [3,4].

One challenge the programme faces is that current influenza vaccines must be reformulated annually to match circulating strains [5]. Despite reformulation, the subtypes in the vaccine do not match the circulating strains/subtypes in many years due to long time frames needed to produce egg-based vaccines and an accumulation of point mutations as the viruses circulate. This is somewhat alleviated by the development of newer vaccine types such as cell culture vaccines, yet

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https://doi.org/10.1016/j.vaccine.2023.08.031
Received 7 June 2023; Received in revised form 11 August 2023; Accepted 14 August 2023
Available online 24 August 2023

despite this, annual vaccine effectiveness can reach very low levels of around 9% in some years[6], especially in older age groups [7]. However, improved vaccines such as high dose and adjuvanted vaccines can slightly improve their effectiveness, particularly in populations with poorer immune response. Additionally, next generation influenza vaccines are in development which aim to address these shortcomings more dramatically, with 28 vaccine candidates currently in clinical trials [8], often utilising newer technologies such as nanoparticles and mRNA [9], which have yet to be approved. These next generation vaccines fall into multiple categories, as defined by the World Health Organization's Preferred Product Characteristics (PPCs) for improved influenza vaccines [10]: "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. Improved vaccines may become available within the next few years, while universal vaccines are not likely to be developed until much later.

The cost-effectiveness of next generation vaccines has so far only been evaluated and published for Kenya [11]. Influenza in Kenya has particular characteristics that may make such vaccines particularly beneficial in this context, such as relatively high influenza-related mortality especially in children, and year-round circulation of influenza. In this setting, at a willingness-to-pay (WTP) threshold of 45% per capita GDP, *universal* vaccines would be cost-effective up to a price of $5.16 per dose.

In England and Wales, the Joint Committee on Vaccination and Immunisation (JCVI) makes recommendations about new vaccine introduction, and has a statutory duty to consider cost-effectiveness when making such recommendations. Hence it is important to understand the prices and circumstances under which improved and universal vaccines are likely to be cost-effective. In contrast to the evaluation in Kenya, this is a high income setting with low paediatric influenza-associated mortality and relatively consistent annual influenza epidemics. Such information will be useful not only to decision-makers in England and Wales and other high-income countries, but also to manufacturers and funders making investment decisions in these vaccines, for which high-income countries will represent the largest source of revenues.

Here we evaluate the cost-effectiveness of next generation influenza vaccines in England and Wales. We evaluate the replacement of seasonal vaccines with improved and universal next generation vaccines.

2. Methods

We have extended a Bayesian modelling analysis of influenza epidemics and vaccination in England and Wales [12] that was previously used to assess the cost-effectiveness of paediatric vaccination [13] and which informed the introduction of paediatric vaccination in 2013. This is implemented in an R package called *FluEvidenceSynthesis* [14]. We used the fitted model from previous work by sampling from the joint posterior distribution of the fitted parameter sets, and extended the forward simulation model to include universal vaccines with mechanism of action lasting multiple years/seasons. Our extended simulation model consisted of three elements (Fig. 1a): (1) vaccination strategies with next generation vaccines, (2) tracking infections across years and seasons, and (3) calculating economic costs. This is the same analysis framework used in our previous work evaluating next-generation vaccines in Kenya [11] and described below. The model is an extension of the *FluEvidenceSynthesis* R package, and all analysis code is available at https://github.com/NaomiWaterlow/NextGenFlu_UK.

The modelled population was stratified into six age categories: Infants (age 0), young children (ages 1–4), school children (ages 5–14),

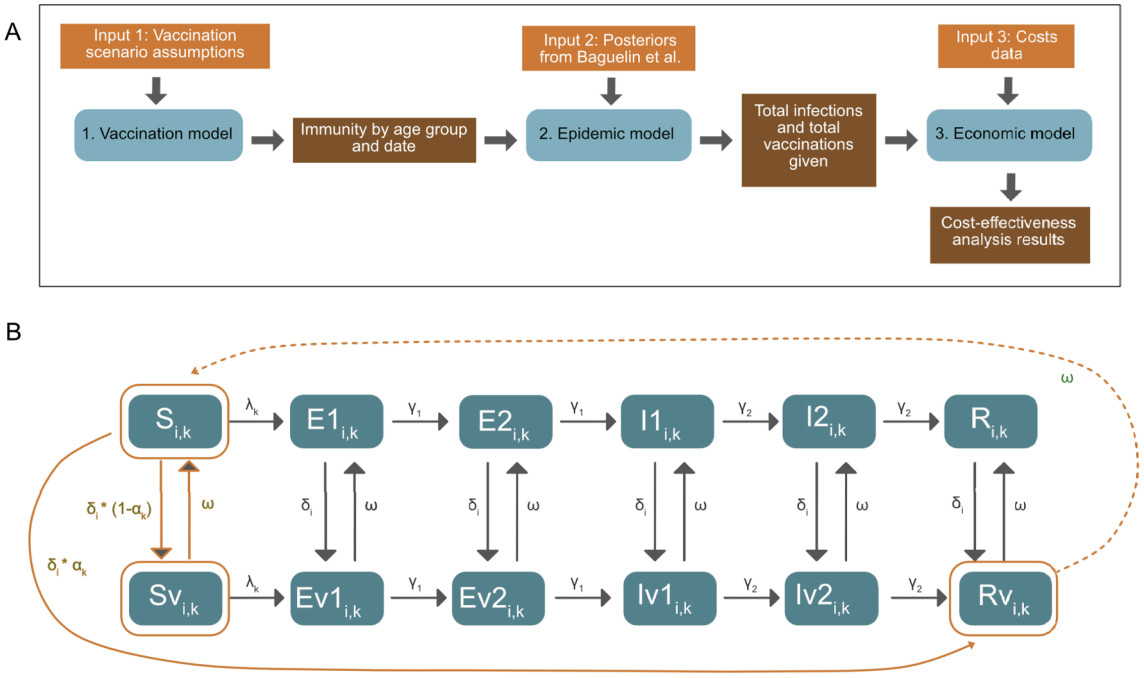

Fig. 1. A) Overview of modelling steps. Orange indicates inputs, brown indicates outputs and blue shows the modelling steps. B) Elements in solid orange are included in both the vaccination and the epidemic models. Transitions in grey are included only in the epidemic model, and transitions in orange 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-risk group *i*, α is the efficacy by subtype, ω is vaccine-derived immunity waning. Table S2 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).

young adults (15–44), adults (45–64) and older adults (65 +). In addition, because presence of pre-existing conditions affects the risk of severe outcomes of influenza, the population was stratified into age-group specific low- and high-risk groups, which receive different vaccination coverage levels (see Table S1). The population was 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 [15]. All individuals were assumed to be born susceptible. Infected individuals can experience symptomatic (mild) infections, symptomatic (fever) infections, hospitalisations and deaths, at proportions by age and high- and low-risk status (supplement Table S3).

2.1. 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 [13]. 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 effectiveness. The complement of this proportion entered the Sv compartment: vaccine-induced immunity was therefore assumed to be all-or-nothing. Vaccine-induced immunity waned exponentially at a different rate for each vaccine type (Table 1), and individuals returned to the S compartment.

When the strains that have been included in current seasonal vaccines are a good match for circulating strains vaccine effectiveness is higher than if there is a "mismatch". Further, there is evidence that seasonal vaccines are more effective in younger individuals. Therefore, we assume that vaccine effectiveness is 70% in those <65 and 46% in those 65 and older in years where the vaccine strains matched, and 42% and 28% respectively in mismatched years. These are the same assumptions in Baguelin *et al.* (2013) and subsequent papers and are drawn from the literature [11,16]. Since 2013, new evidence estimates the effectiveness of seasonal vaccines against the A/H3 subtype at 43% so we use this value in simulations.

We generated 6 scenarios regarding characteristics of next-generation vaccines and vaccination target groups (Table 1), with two scenarios representing use of current seasonal influenza vaccines. The scenario *Current seasonal (2013 coverage)* used actual coverage in the time period simulated (1995–2008), as in the base scenario from Baguelin *et al.* 2013 [12]. In *Current seasonal (2019 coverage)* the coverage and target ages were expanded to match those observed in 2019, and also includes vaccination of those 50 or older, which is an extension to the programme introduced in the England and Wales during the Covid-19 pandemic. For coverage of 50–65 year olds we used coverage observed in 2020 [3,4,17],and reduced the effectiveness of A (H3N2) vaccination to 14% in line with observed trends [7]. From 2013 to 2019, vaccination was expanded to school age children from 2013/14 onwards, so we include it in all years our *Current seasonal (2019 coverage)*. The *Current seasonal (2019 coverage)* scenario therefore represents the modelled output for 1995–2008 if the current England and Wales vaccination policy (and coverage) was in place during that time.

Further scenarios simulated next generation vaccines as described in the WHO PPC [10] (Table 1). In the three *Improved* vaccine scenarios, *minimal* improved vaccines last longer but have the same effectiveness, *efficacy* vaccines have higher effectiveness and last longer, *breadth* vaccines have the same effectiveness in all ages and last longer. In addition, there is one *universal* vaccine scenario which has higher effectiveness and duration. In all cases, coverage matched uptake levels by month in England (see supplement section 1).

In the first year (1995) we assumed that the vaccination programme would reach the target coverage in all age groups. For scenarios where vaccine-induced immunity lasts a year or less, vaccination at the same coverage occurs every year. However, if the immunity duration is longer than a year we reduced the number vaccinated in line with the duration of vaccine immunity, e.g. if vaccine immunity lasts for 2 years, in all years after the first year, coverage is assumed to be half the coverage reached in the first year.

Table 1
Vaccine scenarios.

Scenario name	Mis-matched seasons?	Effectiveness (Matched <65/>65 Mis-matched <65/>65)	Mean immunity Duration (exponential waning)	Coverage	Note
Current seasonal vaccines (2013 coverage)	Yes	70%/46%42%/28%	6 months	As in Baguelin 2013.	Used only for validation
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 England and Wales 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 to
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 England and Wales 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 England and Wales coverage (Supplement, Table S1 in 1st year, then Table 2 *½ in subsequent years)	
Improved Vaccines (Breadth)	No	70%/46%	3 years	2019 England and Wales coverage (Supplement, Table S1 in 1st year, then Table S1 * $^1/_3$ in subsequent years)	
Universal Vaccines	No	90%/70%	5 years	2019 England and Wales coverage (Supplement, Table S1 in 1st year, then Table 2 S1 *1/5 in subsequent years)	

2.2. 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 [12] (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 probability of infection following an infectious contact. 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 population-level immunity levels the following year (Supplement Section 3). However, we included two sensitivity analyses with different assumptions on changes to susceptibility (supplement section 7).

2.3. Economic modelling

To estimate the cost-effectiveness of each vaccination scenario we used the *current seasonal (2019 coverage)* scenario as the comparator, and calculated the incremental quality-adjusted life years (QALYs) gained and costs for each scenario (supplement section 4) over the 1995–2008 time period. We used this extended time period because vaccination impacts lasted longer than a year.

QALY changes were calculated for symptomatic (mild) infections, symptomatic (fever) infections, hospitalisations and deaths (supplement Table S3). QALYs lost due to death were calculated for each age group using remaining life expectancy from UN Population Division life tables [19] discounted to the year in which the death occurred, and including the population size and risk of death at each age.

The cost-effectiveness analysis was conducted according to the guidelines set by JCVI [20] and the reference case used by the National Institute for Health and Care Excellence (NICE) [21]. In particular, as per the guidelines, we discounted outcomes to their value in 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 2019 British pounds (£2019). This year was chosen to avoid transient changes in healthcare costs that occurred during the COVID-19 pandemic. Calculated costs included vaccine delivery costs, costs of GP visits and costs of hospitalisation (supplement Table S3), as we took a healthcare payer (i.e. National Health Service) rather than a societal perspective, as recommended in NICE guidelines [22]. Costs were inflated using the Hospital and Community health services index [21].

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. We calculated an additional scenario at which at least 90% of probabilistic samples had an ICER below £30,000 as recommended in JCVI guidelines (see supplement section 10). We also calculated vaccine threshold prices needed to meet both these thresholds.

In the economic model, 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 [23] 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 [13] 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 [13].

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
Vaccine efficacy	α	Vaccine assumption	see Table 1
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	$\eta R v_i$	Vaccine assumption/Model	–
Contact rates between age groups i and j	c_{ij}	Fixed based on UK POLYMOD [18]	Age specific, see [18]
Latency period	$2*1/\gamma_1$	Fixed *fluEvidenceSynthesis* package	0.8 days
Infectious Period	$2*1/\gamma_2$	Fixed *fluEvidenceSynthesis* package	1.8 days
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	–
Proportion of population infected at the start of an epidemic	ι	Posterior estimated in Baguelin 2013	–

2.4. Sensitivity analyses

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

In the transmission model, 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 increased vaccination.

Some evidence in the literature suggests that vaccine-derived immunity from current vaccines may last longer than one season [24]. Therefore, we ran the economic model 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*.

Additionally, we assumed a different vaccine unit price, based on the range of vaccine prices presented in Baguelin *et al.* (2015)[13]. The low price was £12 and the high price was £20.

3. Results

To evaluate whether our extended model accurately reproduced results in previous publications [12], we determined that our *current seasonal (2013 coverage)* scenario showed results in line with previous work by Baguelin *et al.* The epidemic incidence peak for each age group fell within the confidence interval of previous results, and peaked within a week of the peak of previous work (see supplement section 5).

We then used the *current seasonal (2019 coverage)* 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 (Fig. 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

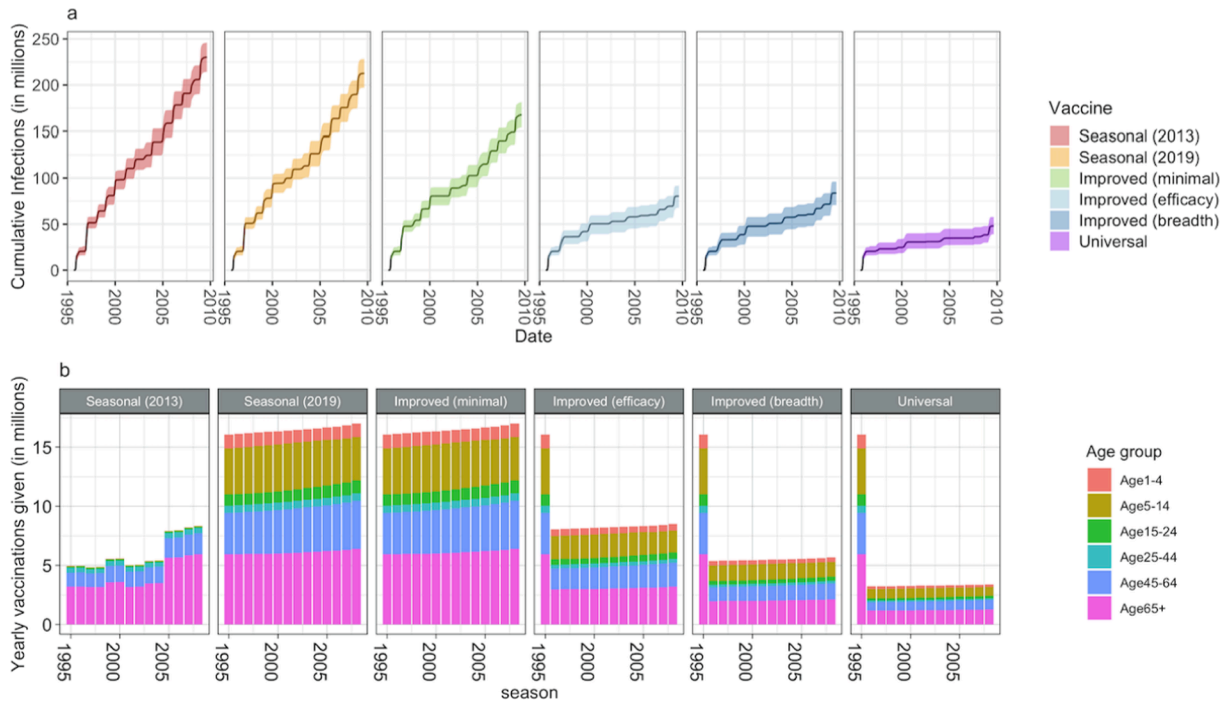

Fig. 2. A) Cumulative incidence of infections over time, for each vaccine scenario. The black line displays the median value, and the coloured interval the 95% Credible Interval (95% CrI). B) Cumulative vaccinations given over time, for each vaccine scenario by age group.

(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.

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 a 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*

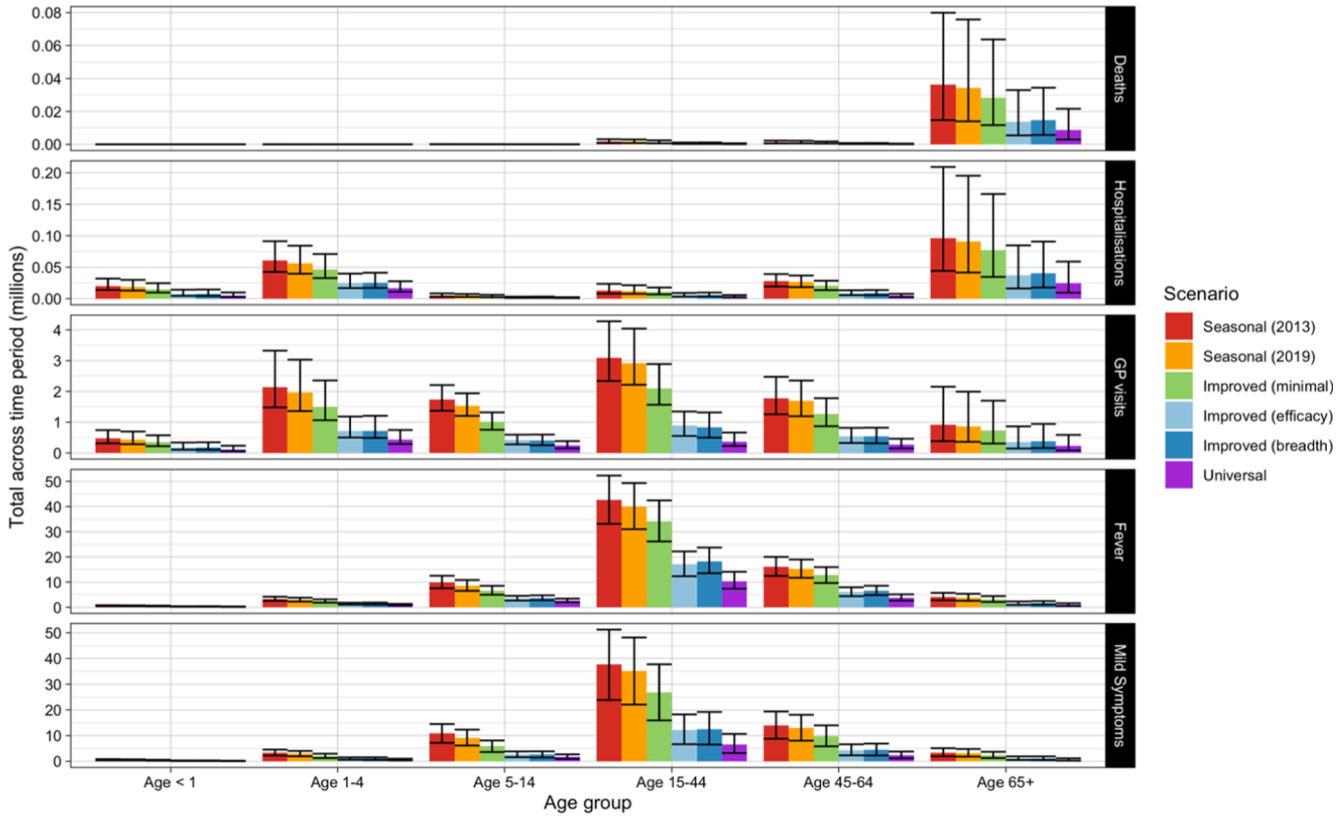

Fig. 3. Health outcomes by scenario and age. Error bars indicate the 95% credible interval.

(breadth) scenario with 3,652 (range 0–30,895) hospitalisations across years and the universal scenario with 159 (range 0–30513) hospitalisations across years (Fig. 3, Supplement section 6).

All the vaccine scenarios used the same or fewer vaccine doses than the baseline scenario (*current seasonal (2019 coverage)),* and were assumed to have the same cost per dose. Therefore, all improved vaccines resulted in increased health benefits, and were cost-saving (Fig. 4b). Consequently, all scenarios had a positive INMB, assuming a WTP threshold of £20,000 (Fig. 3). 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 we set *improved (minimal)* as the baseline, which resulted in slightly reduced threshold prices, although still reaching £185 (95%CrI £158 - £217) for *universal* vaccines (supplement section 9).

We conducted sensitivity analyses on vaccine prices, and in all cases the threshold price for improved vaccines remained high (supplementary section 7). For the *universal* vaccines the median threshold prices ranged from £212 to £249 across different assumptions. We found that the results were sensitive to the assumptions behind infection-derived immunity (supplement section 7). In line with JCVI recommendations - we also calculated prices where 90% of simulations reach a threshold of £30,000. This threshold value was higher than the standard 50% centile for all vaccine types, indicating that the 50% is enough for decision-making. To illustrate, the 90% centile price was £275 for *universal* vaccines. (supplement section 8).

4. Discussion

We found that next generation influenza vaccines could have substantial health and economic benefits in England and Wales. 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. Next generation vaccines could have resulted in a 21% to 77% reduction in influenza infections, a 19% to 95% reduction in hospitalisations and a 12% to 96% reduction in deaths during epidemics from 1995 to 2008 compared to the current vaccine (at 2019 coverage), depending on vaccine characteristics. Minimally improved vaccine implementation may be cost-effective with vaccine prices up to £18 (95% £16 - £21), with increasing prices possible for the better vaccines, up to universal vaccines which may be cost-effective for vaccine prices up to £230 (95%CrI £192 - £269).

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

Scenario	Lower 95% quantile	Median	Upper 95% quantile
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

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 England and Wales. As a comparison to other threshold prices, HPV vaccination in girls has a threshold dose price of £56-108 in the UK [25]. We used a healthcare payer perspective for costs, as is recommended in England and Wales [22]. Including societal costs, such as personal patient costs like transportation, in the cost-effectiveness analysis would likely result in even greater cost-effectiveness, since it would incorporate a reduction in lost working hours.

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 in settings such as England and Wales. Our paper may be particularly interesting when considered in combination with previous work on next generation influenza vaccinations in Kenya [11], an LMIC setting with all year-round influenza activity. Together, these papers provide a broad based for investment decisions. While the greatest burden of influenza is in low- and middle-income countries [26], the majority of revenues for vaccine manufacturers are likely to come from high-income countries. Hence the finding that the threshold price at which such vaccines will be cost-effective in settings such as England and Wales indicates that vaccine developers are likely to obtain a positive return on investing in vaccine development.

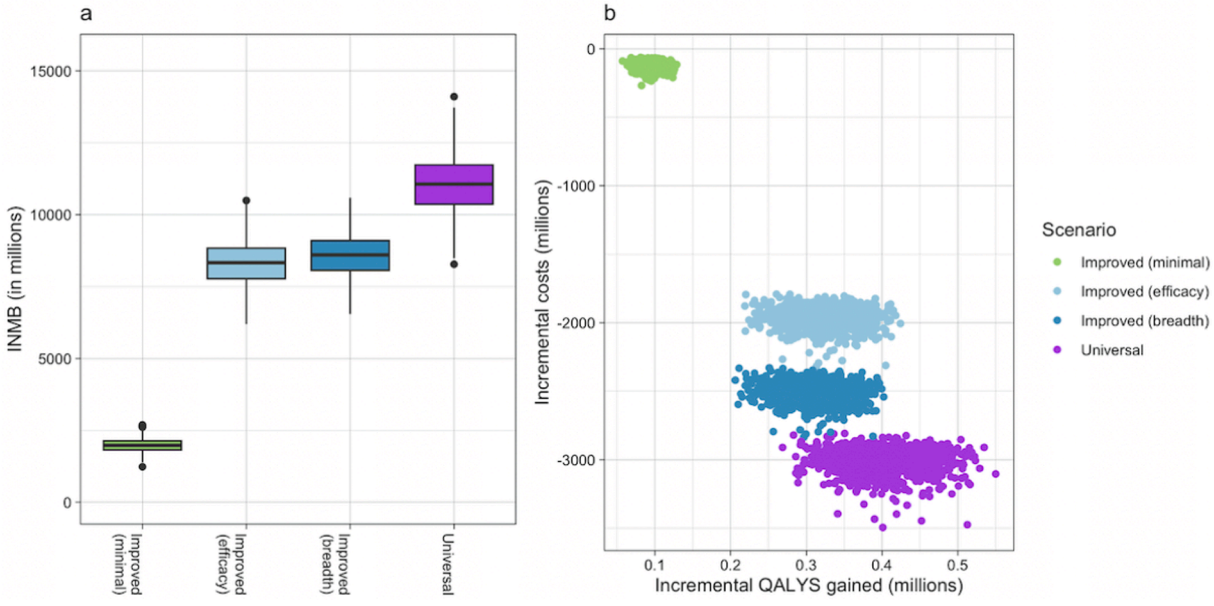

Fig. 4. A) Incremental net monetary benefits (millions) for each vaccine type, compared to the current seasonal (2019 coverage) scenario. b) Cost-effectiveness plane showing incremental costs against incremental QALYs gained.

We assumed that vaccination occurs regardless of previous vaccination status, and vaccines may therefore be delivered to individuals who are already protected through recent vaccination. This is a strong assumption and a limitation of our study, as in reality, repeat vaccination during the period of vaccine immunity may be less likely 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 analysis. However this effect may not be large, as due to variations in waning of vaccine immunity, individuals may still get revaccinated. There will likely still be a significant group of individuals that will not get vaccinated, due to vaccine hesitancy [27]. Our assumption lies between these two alternative scenarios of behaviour.

A further limitation of the study is that there may also be additional benefits of vaccination which we were not able to include in this study. For example, there may be additional benefits for vaccinated individuals who do not become immune, such as a reduction in severe outcomes, which we have not considered. In addition, more downstream effects from a reduction in severe influenza have not been included due to the complexity of doing so. These include potential impacts on a reduction in antibiotic resistance because of fewer antibiotics given for influenza cases, the impact of reduced admissions in hospital on the care of patients with other conditions, and health equity impacts.

Our model tracks immunity from vaccination over multiple years, which allowed us to track the longer-lasting immunity that may occur because of next generation vaccines. Using such a transmission model also allowed us to capture indirect protection from vaccination, which have previously shown to be very important for understanding the full impact of vaccines [28,29]. We modelled each of the influenza types/subtypes independently (A/H1N1, A/H3N2, B), as they were in the original study that we adapted for this analysis. This does not allow any interaction between the viral subtypes, except for within the B subtype, which have neuraminidases in common. Whilst previous evidence suggests interaction may play a role [30–34] by providing some cross-immunity between subtypes, the magnitude of such interactions is unclear. Furthermore, 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 (i.e. if more people get vaccinated, fewer people get infected, but we assume that this does not impact susceptibility the following year). There is some evidence from other studies that vaccine-derived immunity is more short-lived than infection-derived immunity [34]. However, we explored the correlation between epidemic size and susceptibility in the following year and found no association. This suggests that immunity to influenza is more complex than a simple function of immunity from the previous epidemic immunity [35]. However, despite resulting in unrealistic outbreaks where larger epidemics were seen with current vaccines compared to no vaccines, our sensitivity analysis showed this assumption had a large impact, so should be further studied. The change in infection-derived immunity may have stronger implications on influenza pandemics than on seasonal influenza. A further limitation of the study is that we did not take into account the maternal immunization programme in England and Wales, which would provide some protection to young infants through passive immunization. In addition, we have not included the use of antivirals, such as Oseltamivir in this study. These may have an added impact on reducing the symptoms, shedding and thereby transmission of influenza. This is a limitation of this study, as they may have impacts on the wider cost-benefit analysis of influenza interventions.

Overall, our study provides a strong case for investing in next generation vaccines, across the whole spectrum of these vaccines. All of them, but particularly *universal* vaccines, are likely to be cost effective in England and Wales, and other similar settings, if available at reasonable price points. Even minimally improved vaccines may have a large health impact and be cost-effective.

Funding

NRW, SR, SP and RME were funded through the Task Force for Global Health in collaboration with Partnership for Influenza Vaccine Introduction (PIVI), Ready2Respond, Wellcome Trust and Centers for Disease Control and Prevention (CDC). EvL and RME were also supported by the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Modelling and Health Economics, a partnership between UK HSA, Imperial College London, and LSHTM (grant number NIHR200908) and EvL was also supported by the European Union's Horizon 2020 research and innovation programme - project EpiPose (101003688).

The views expressed are those of the authors and not necessarily those of the UK Department of Health and Social Care (DHSC), NIHR, or UKHSA.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All research data and code is available on Github

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.08.031.

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