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Cost-effectiveness of live-attenuated influenza vaccination among school-age children

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ABSTRACT

The current pediatric vaccination program in England and Wales administers Live-Attenuated Influenza Vaccine (LAIV) to children ages 2–16 years old. Annual administration of LAIV to this age group is costly and poses substantial logistical issues. This study aims to evaluate the cost-effectiveness of prioritizing vaccination to age groups within the 2–16 year old age range to mitigate the operational and resource challenges of the current strategy. We performed economic evaluations comparing the influenza vaccination program from 1995–2013 to seven alternative strategies targeted at low risk individuals along the school age divisions Preschool (2–4 years old), Primary school (5–11 years old), and Secondary school (12–16 years old). These extensions are evaluated incrementally on the status quo scenario (vaccinating subgroups at high risk of influenza-related complications and individuals 65+ years old). Impact of vaccination was assessed using a transmission model from a previously published study and updated with new data. At all levels of coverage, all strategies had a 100% probability of being cost-effective at the current National Health Service threshold, £20,000/QALY gained. The incremental analysis demonstrated vaccinating Primary School children was the most cost-efficient strategy compared incrementally against others with an Incremental Cost-Effectiveness Ratio of £639 spent per QALY gained (Net Benefit: 404 M£ [155, 795]). When coverage was varied between 30%, 55%, and 70% strategies which included Primary school children had a higher probability of being cost-effective at lower willingness-to-pay levels. Although children were the vaccine target the majority of QALY gains occurred in the 25–44 years old and 65+ age groups. Influenza strain A/H3N2 incurred the greatest costs and QALYs lost regardless of which strategy was used. Improvement could be made to the current LAIV pediatric vaccination strategy by eliminating vaccination of 2–4 year olds and focusing on school-based delivery to Primary and Secondary school children in tandem.

1. Introduction

In 2013, England and Wales began the phased extension of their seasonal influenza program, which recommended low risk children aged two to 16 be vaccinated with live attenuated influenza vaccine (LAIV Fluenz Tetra®) nasal spray [1,2]. However, by 2025, when the pediatric program reaches full capacity, administering LAIV to all children will pose substantial economic and logistical issues. The 2019/2020 season phased in school year six (11 year olds) to the existing program. To maintain herd immunity at 55% total coverage, the pediatric program will distributed an additional 375,000 LAIV doses to 11 year old children between September and December. The increasing scale of this annual pediatric program, relying on

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trained nurses and a school-based delivery method, is prohibitively demanding of National Health Service (NHS) resources. Prioritizing certain age groups within the 2–16 year old range will mitigate some of the implementation challenges of the strategy.

The basis for the pediatric program is a dynamic model by Baguelin et al. [3] It determined that the LAIV immunization of 2–16 year old children would indirectly decrease the force of infection in the general population; however, the previous analysis did not directly address school age subdivisions. That study included two pediatric interventions among other adult interventions and identified 5–16 year old children as the 'key drivers' of seasonal influenza epidemics [3,4]. At the time, there was also insufficient data to examine seasons 2010–2014 and to integrate the vaccine uptake rates from 1995 to 2014. Therefore, there is a need for updated optimal vaccine strategy recommendations.

In this study we evaluate whether, in light of new age-specific data on influenza incidence, the current LAIV pediatric influenza program in England and Wales should be altered. We determine the cost-utility of seven vaccine strategies at varied coverage levels by modeling counterfactual scenarios over the period 1995/1996–2013/2014. The seven proposed strategies are focused on school age divisions, specifically preschool, primary school, and secondary school. A historical counterfactual was used because the current pediatric vaccination program in the UK is still in phased implementation. Our expansion on the study by Baguelin et al. [3] includes updates to the surveillance and epidemiological data, additional age specific stratification, and vaccine uptake rates per month from 2009 to 2014.

2. Methods

We parameterized our dynamic model with the season- and strain-specific joint posterior distributions to recapitulate 19 historical influenza seasons in England and Wales between 1995/1996 and 2013/2014. Using this model, we then evaluated the potential impact of seven vaccination pre-school and school-based programs. Finally, we integrated these results into an economic framework to determine the optimal pediatric influenza vaccine program. The mean QALY loss and mean cost over the 19 seasons were used to evaluate the Incremental Cost-Effectiveness Ratio (ICERs) in order to compare each strategy.

2.1. Mathematical model

To determine the direct and indirect vaccine effects on seasonal influenza incidence under each alternative vaccination strategy we used a previously described transmission model called 'fluEvidenceSynthesis' [5]. The model was calibrated to multiple surveillance metrics from England and Wales over the 19 year period [5]. The latest version of the 'fluEvidenceSynthesis' package uses a modified Susceptible-Exposed-Infectious-Recovered (SEIR) differential equation model which simulates influenza infections, influenza-related complications, and resultant healthcare costs for individuals in a series of age and risk classes [5]. The previous study by Baguelin et al. used seven age groups, which we expanded to eleven age groups on the following intervals: 6 months-<1,1, 2–4, 5–11, 12–14, 15–16, 17–24, 25–44, 45–64, 65–74, 75+ years. Two risk strata for simulating high and low risk groups were included in each age stratum. The final SEIR model contains 22 separate age-risk strata. The model simulated outcome metrics for three influenza strains: A/H1N1, A/H3N2, and B.

2.2. Model calibration and data sources

The analysis was coded in R (version 3.5.0) [6], using R Studio (version 1.1.453) with the R package 'fluEvidenceSynthesis' [7]. The R package 'fluEvidenceSynthesis' model (version 1.0.0) has been revised from the developmental version previously used by Baguelin et al. and the previous package published on Github by van Leeuwen [5,7]. Independent model trajectories for each of the 19 (1995/6–2013/4) influenza seasons and three strains were fit by Markov chain Monte Carlo (MCMC) for each of the three strains (A/H1N1, A/H3N2, B). Each season used two chains for a total 38 calibrations per strain. Chain convergence was determined with the Gelman-Rubin diagnostic test [8] with a potential scale reduction factor adjusted for sampling variability threshold of 1.2 or below for the five parameters of interest. Any season that did not converge based on the Gelman-Rubin diagnostic was restarted with the last value of the previous Markov chain and the two chains were run for an additional 200,000 iterations. For most seasons approximately 1.4 million iterations were needed to achieve convergence.

Unknown model parameters estimated by MCMC were the ascertainment probability (ϵ_i), virus transmissibility (q), the probability of become infected outside of the main epidemic (ϕ), age-group specific susceptibility (σ_i), and a coefficient for the initial number of infections each season per strain (I_0). Prior distributions for these five unknown parameters and the four assumed known epidemiological parameters are shown in Table S1 [34–37].

The likelihood distribution for the MCMC summarized surveillance data from two sources: the number of weekly influenza-like-illness (ILI) age-specific General Practitioner (GP) consultations, and the number of virologically-confirmed cases per week. For the period 2009/2010–2013/2014, we used a custom inference function in the R package to add the extra age classes from the data to the binomial and hypergeometric likelihood. All code is available at https://github.com/tajwenzel/UKfluwork.

2.2.1. Respiratory virus Royal College of General Practitioners research and surveillance centre (RCGP)

During weeks of potential influenza activity, the RCGP takes samples from patients with an ILI and records the weekly incidence of consultations among sentinel general practices across England [9]. We obtained the size of the monitored population in the sentinel network, and the total number of patients who consulted General Practitioners for an ILI. Additionally, we obtained the number of laboratory samples tested for suspected ILI cases, and the number of lab positives for influenza strains A/H1N1, A/H3N2, and B.

2.2.2. Social mixing between groups

Social mixing parameters among the additional age groups were estimated using data from a pan-European survey of contact structure known as POLYMOD [10]. Survey data from the Great Britain cohort was sampled with replacement to generate multiple 11×11 contact rate matrices, where each cell describes the interaction frequency between age groups [3]. Further details are described in earlier papers [5,11].

2.2.3. Inactivated vaccine coverage

For the period 1995/1996–2003/2004 coverage by age and risk group was taken from Joseph et al. [12] Coverage for the 65+-year age group from 2004/2005 onwards was taken from the Health Protection Agency/Department of Health (HPA/DH) annual reports on the influenza program [13]. Uptake rate and total achieved coverage by age and risk group for the period 2004/2005–2013/2014 was taken from end of season summaries from Public Health England [14–16]. We calculated a time-varying immunization rate (i.e. the rate at which vaccination provides protection against influenza in the SEIR model) for each age and risk group by combining these vaccination coverages, the vaccine efficacy by strain, and the rate at which vaccination was delivered to each group. Therefore each

calculated immunization rate was unique to the age and risk group, influenza season, and time within the season. This immunization rate was used as a parameter in the SEIR model to simulate movement for the Susceptible, Exposed, or Infected state into the Vaccine state.

2.3. LAIV interventions

Using the 19 annual posterior distributions of the calibrated model, we modeled influenza incidence in England and Wales in the presence of seven vaccination programs targeted at school-age cohorts. We compared the effectiveness and health outcomes in each counterfactual vaccine scenario to each other and the actual metrics from 1995/1996–2013/2014 using a cost-effectiveness analysis. The effectiveness of each alternative program was assessed by measuring the Quality-Adjusted-Life-Years (QALYs) lost, number of febrile/symptomatic cases, and infection-related mortality prevented by one vaccine dose. In addition to a status quo strategy, we analyzed 21 alternative strategies. These alternatives included the seven basic strategies given below with final coverage of the target age group at increments of 30%, 55%, and 70%, representing the lower bound, average level, and upper bounds of empirical coverage. LAIV vaccination programs were simulated starting on September 1st, the usual start of the fall session, and ending on December 12, a week before the Christmas holiday.

1. **SQ** (Status Quo): Low-Risk 65+ year olds and high risk individuals 6 months-65+ year olds vaccinated with annual trivalent inactivated influenza vaccine (TIV), or Quadrivalent Influenza Vaccine (QIV) at empirical coverage rates.
2. **V2-4y:** Low-risk 2–4 year olds (Preschool) vaccinated with LAIV at 30%, 55%, 70% coverage in addition to SQ.
3. **V5-11y:** Low-risk 5–11 year olds (Primary School) vaccinated with LAIV at 30%, 55%, 70% coverage in addition to SQ.
4. **V12-16y:** Low-risk 12–16 year olds (Secondary School) vaccinated with LAIV at 30%, 55%, 70% coverage in addition to SQ.
5. **V2-11y:** Low-risk 2–11 year olds (Preschool & Primary School) vaccinated with LAIV at 30%, 55%, 70% coverage in addition to SQ.
6. **V2-4y/12-16y:** Low-risk 2–4 & 12–16 year olds (Preschool & Secondary School) vaccinated with LAIV at 30%, 55%, 70% coverage in addition to SQ.
7. **V5-16y:** Low-risk 5–16 year olds (Primary & Secondary School) vaccinated with LAIV at 30%, 55%, 70% coverage in addition to SQ.
8. **V2-16y:** Low-risk 2–16 year olds (Preschool, Primary School, & Secondary School) vaccinated with LAIV at 30%, 55%, 70% coverage in addition to SQ.

2.3.1. LAIV efficacy

Influenza vaccine efficacy (VE) is dependent on two factors: (1) the degree of matching between vaccine strain and circulating strain that season, and (2) the quality of immune response generated in the host. High risk groups such as the immunocompromised and elderly subgroups are known to have increased susceptibility to disease and a poor immune response to the influenza vaccine resulting in low efficacy. Each age stratum was divided into individuals at low or high risk of complications associated with influenza (e.g. individuals with chronic conditions). We assumed the proportion of people in a high risk group was constant from 1995 to 2014, but that the proportion of high risk people varied by age group (Table S2). Following National Health Service (NHS) 2018/2019 guidelines, our model assumed high risk individuals aged 6 months-2 years old and adults 18–64 years old received QIV [17]. Individuals aged 65+ years received TIIV.

We use two average VE estimates from the Cochrane collaboration [18] to emulate strain matching between the vaccine and wild-type strain during poor and well-matched years. When the vaccine was well-matched with the annual circulating strain VE was fixed at 70% in the general population and 42% in the clinical high risk and 65+ year old group. During poorly matched years we assigned 40% VE for the general population and 28% VE in the high risk and elderly group. We did not make specific allowances for differences in vaccine efficacy between the three vaccine types: LAIV, QIV, and TIIV. We assumed the 'all-or-nothing' mechanism of vaccine efficacy with a maximum protection period of one year. Similarly, disease derived immunity was assumed to last for one year maximum.

For the 1995/6–2008/9 period strain-matching information was taken from Public Health England (PHE, then Health Protection Agency) [13]. The degree of matching between the circulating and vaccine strains for the 2009/2010–2013/2014 seasons were obtained from PHE estimates (Table S4). We considered each influenza strain independently and calculated its cumulative clinical and economic effects as it is currently unknown how influenza strains interact within-host and within-population.

2.3.2. Health outcomes

This analysis was conducted from the perspective of the NHS using a one-year time horizon recurring on September 1st. The discount rate, reflecting the fact that people prefer to receive benefits and save costs in the present relative to the future, were calculated annually at 3.5% as recommended by the National Institute for Health and Care Excellence (NICE) [19]. Additionally we conducted a one-way sensitivity analysis at discount rate levels 0%, 1.5%. The estimated number of health outcomes and the commensurate QALYs were calculated per influenza season and averaged across 19 seasons (1995–2013) during the subsequent cost-effectiveness analysis.

To account for uncertainty in the estimated number of different health outcomes attributable to influenza per year, we sampled the normal distributions from Cromer et al.'s regression analysis (Table S2) [20]. Health outcomes examined included number of infections, number of symptomatic infections, influenza-related GP consultations, hospitalizations and mortality. We did not control for non–influenza-related complications or other confounding variables such as income, education, ethnicity, and number of comorbidities.

The primary health-related quality of life measure for the analysis were QALYs. Individuals with symptomatic influenza experienced an age-specific reduction in QALYs. Similarly, individuals infected with influenza who were hospitalized experienced a commensurate age and risk-specific quality of life loss. Fatal influenza infections were assumed to lose an age and risk-group specific discounted quality-adjusted life expectancy. Age-specific quality of life weights for respiratory illnesses were taken from Kind et al., using the EQ-5D rating scale (Table S3) [21]. Average weights for children less than 18 years did not exist, therefore we estimated their average health-related quality of life weight as 0.9 based on estimates from the 18–20 years old group [4].

2.3.3. Costs

Two elements of costs were included in the analysis. The first cost element was use of health services during the influenza season for the whole population of England and Wales. This was based on the calculated number of annual clinical cases, the number of general practitioner consultations, and the number of inpatient hospitalizations. The second element was the total cost per dose of vaccine acquisition, service, and provider reimbursement. We calculated the costs of influenza vaccine delivery through pharmacies, GPs, and school-based programs from the NHS perspective. A sum-

mary of economic costs appears in Table 1 expressed in 2018 British Pounds Sterling. If costs were not available for the current year, costs from previous years were updated to 2018 British Pounds Sterling using the Consumer Price Index for Health Costs [22]. We assumed that services for waste disposal and sharps removal for all delivery methods–except school-based vaccination–were managed and paid for directly by the NHS with no additional cost. Productivity losses were not incorporated into the analysis.

Units of vaccine administration costs were obtained from previously published studies and from PHE/NHS budget documents when available (Table S6). Differences in vaccine deployment costs were dependent on the age group targeted by the specific strategy and the coverage achieved. For example, in strategy V2-11y, Preschool and Primary school children are targeted for vaccination. Low-risk preschool aged children would receive LAIV from their GP and incur the GP delivery cost, while low-risk primary school children receive school-based LAIV delivery and incur the school-delivery cost. Total Costs per vaccine dose administered were calculated as the sum of NHS vaccine service payment, the vaccine purchase payment, and dependent on the method of administration a delivery fee, the Sonar reporting system fee, and disbursement fee. The Sonar system is a clinical records database used by pharmacists and the NHS to synchronize and record patient vaccinations details. Further discussion on the vaccine cost derivation is in supplemental Section 3.4.

2.3.4. Cost-Effectiveness analysis

For alternative strategies the mean QALYs and mean cost over the 19 seasons were used to evaluate the Incremental Cost-Effectiveness Ratio (ICERs). The ICER for each strategy was calculated using the formula:

$$ICER = (C_C - C_S)/(Q_C - Q_S)$$

where C_S is the predicted total of health care and vaccination costs and C_C the same total for its comparator. The predicted QALY losses for a strategy and its comparator are denoted as Q_S and Q_C. The comparator of a strategy is the next non-dominated strategy with the next lower incremental cost. Using the average estimate of costs and QALYs, strategies for which an alternative strategy would avert more QALYs at equal or lower cost were considered 'strongly dominated' and excluded. Strategies with a mean ICER that is higher than the mean ICER of a more costly strategy were deemed weakly dominated and excluded. ICERs for the remaining strategies were then recalculated accordingly. We used the remaining strategies to define the cost-efficiency frontier of the cost-effectiveness plane.

We also calculated the Cost-Effectiveness Acceptability Curve, which indicates the probability that an intervention is cost-effective compared with an alternative strategy for a range of willingness to pay values [23]. Costs and effects for each strategy were derived from 2500 parameter sets drawn from the joint posterior distribution over a willingness-to-pay (WTP) range of £1–£30,000 per QALY.

To determine the optimal strategy, we conducted a probabilistic sensitivity analysis using a net health benefits (NHB) approach. The incremental net health benefit is calculated by first assuming a willingness to pay threshold, then converting monetary benefits in 2018 British Pounds Sterling into QALYs:

$$NHB = \Delta E - \Delta C/\lambda$$

where λ = decision-maker's willingness-to-pay per QALY gained; ΔE = annual incremental QALYs gained by a vaccination strategy and ΔC = incremental vaccination costs less any savings in other healthcare costs due to influenza cases avoided. This process is repeated in 2500 model simulations to estimate the probability a strategy is optimal. The optimal vaccination strategy was determined based on the proportion of parameter sets with the highest incremental NHB across a willingness-to-pay range of £1–£30,000 per QALY. The optimal strategy may vary from simulation to simulation as a consequence of parameter uncertainty.

3. Results

Our results suggest strategies that including primary school LAIV vaccination (Strategy V5-11y) are more likely to be associated with cost-effectiveness. The incremental analysis demonstrated Strategy V5-11y (Primary School) was the most cost-efficient strategy compared incrementally against the others. The Incremental Cost-Effectiveness Ratio (ICER) for V5-11y was estimated at £639 spent to gain 1 QALY (Net Benefit: 404 M£ [95% Credible Interval: 155, 795]), well below the current NHS Willingness-To-Pay (WTP) threshold (£20,000 per QALY gained) (Table 2). In fact, all strategies had a 100% probability of being cost-effective at the £20,000/QALY WTP threshold (Fig. 1, Panel B). Strategies V5-11y, V2-11y, V5-16y, and V2-16y were 100% likely to be cost-effective at £8000/QALY, while Strategy V2-4y (Preschool vaccination) was the least likely to be cost-effective reaching 100% at a cost of £16,000/QALY. However, the incremental analysis between strategies also demonstrated V2-4y/12-16y (Preschool & Secondary School)–was

Table 1
Economic parameters used to estimate intervention costs and costs to the National Health Service as a result of influenza infection. Here 'GP' denotes General Practitioner. Inflation adjustments for medical services sourced from King et al. [22].

	Item	Estimate	Uncertainty	Inflation Adjustment	Source
Cost of vaccination					
	School-Delivery (per dose)	£20.14	Triangle(a = 17, b = 25, c = 20.14)	None	Derived (Table [tab: vcost])
	Pharmacy Delivery (per dose)	£17.29	Triangle(a = 14, b = 22, c = 17.29)	None	Derived (Table [tab: vcost])
	GP Delivery (per dose)	£19.66	Triangle(a = 17, b = 25, c = 19.66)	None	Derived (Table [tab: vcost])
Healthcare Costs					
	Hospital cost (per episode)	£911	Lognormal (normal μ = 911, normal σ = 215)	1.085	[3]
	GP cost (per consultation)	£39	Lognormal (normal μ = 39, normal σ = 8.6)	1.046	[3]
Healthcare Provider Costs					
	NHS Nurse Salary (per hour)	£36	None	None	[32]
	NHS Band 1 Driver (per hour)	£9.88	None	None	[33]

Table 2
The Incremental Cost-Effectiveness Ratios (ICER) where the comparator is the strategy with the next highest cost. All net outcomes were calculated at a discount rate of 3.5% and final coverage uptake of 55% among the targeted age group for each strategy. Of the proposed interventions all were associated with cost-effectiveness at the £20,000 Willingness-to-Pay, however strategy V2-4y/12-16y was strongly dominated meaning another strategy, V5-11y, was less expensive and more effective. All costs are expressed in 2018 British Pounds Sterling.

Intervention Strategy	V2-4y	V5-11y	V12-16y	V2-11y	V2-4y/12-16y	V5-16y	V2-16y
Age Groups Vaccinated	Low-Risk 65+, High risk 6 months-65+, 2–4 year olds	Low-Risk 65+, High risk 6 months-65+, 5–11 year olds	Low-Risk 65+, High risk 6 months-65+, 12–16 year olds	Low-Risk 65+, High risk 6 months-65+, 2–11 year olds	Low-Risk 65+, High risk 6 months-65+, 2–4 & 12–16 year olds	Low-Risk 65+, High risk 6 months-65+, 5–16 year olds	Low-Risk 65+, High risk 6 months-65+, 2–16 year olds
Targeted School-Age Cohort	Preschool	Primary School	Secondary School	Preschool, Primary School	Preschool, Secondary School	Primary School, Secondary School	Preschool, Primary School, Secondary School
(a) 3.5% Discount, 55% LAIV Coverage (Reference Scenario)							
ICER	2419	1772	2699	2055	2576	2088	2267
Net-Benefit in Millions (£GBP)	120.1	404.4	203.7	500.4	326.3	599.0	693.5
NB Lower	42.0	154.8	71.7	189.2	112.5	218.3	260.5
NB Upper	241.3	795.3	406.1	984.6	676.8	1157.8	1387.6
(b) 1.5% Discount, 55% LAIV coverage							
ICER	2308	1672	2535	1945	2402	2003	2169
Net-Benefit in Millions (£GBP)	125.1	424.1	214.9	528.1	349.1	622.2	723.4
NB Lower	43.8	169.4	81.7	201.6	127.6	237.0	269.5
NB Upper	254.0	827.6	416.4	1018.2	696.7	1240.4	1380.1
(c) 0% Discount, 55% LAIV coverage							
ICER	2163	1578	2420	1846	2283	1884	2044
Net-Benefit in Millions (£GBP)	132.1	454.0	226.7	556.6	367.7	665.0	716.3
NB Lower	51.7	179.7	82.9	216.7	139.4	266.9	316.0
NB Upper	258.1	872.9	442.6	1122.8	720.3	1280.0	1433.2
(d) 3.5% Discount, 70% LAIV coverage							
ICER	2367	1891	2778	2276	2508	2315	2607
Net-Benefit in Millions (£GBP)	154.1	487.2	250.0	589.5	417.0	698.2	783.2
NB Lower	57.4	181.4	87.8	202.2	149.4	255.8	277.3
NB Upper	312.7	936.5	515.3	1172.9	824.7	1433.9	1543.1
(e) 3.5% Discount, 30% LAIV coverage							
ICER	2173	1456	2416	1630	2272	1668	1794
Net-Benefit in Millions (£GBP)	68.3	255.4	120.3	323.3	192.8	388.4	450.6
NB Lower	25.6	96.2	42.4	119.4	67.8	154.3	167.0
NB Upper	137.4	481.0	242.0	641.8	382.4	754.9	875.0

strongly dominated by Strategy V5-11y which was both less expensive and more effective (Fig. 2).

Although Strategy V5-11y was the most cost-effective in the incremental analysis, Strategy V2-16y was determined to be the optimal strategy–the strategy that maximizes the net health benefits–in 44% of the simulations (Fig. 1, Panel A). The next closest strategy was V5-16y which was optimal for 26% of simulations. Strategies V2-4y, V5-11y, and V12-16y were optimal for less than 10% of simulations suggesting these strategies are cost-effective but rarely optimal. No changes in the optimal order were observed for WTP > £20,000 per QALY. For less than £20,000 per QALY the status quo strategy was a contender for optimal strategy until WTP = £5250/QALY where it fell below 1% probability of being optimal (Fig. 1, Panel A).

Simulation outcomes (e.g. NHB) for each proposed strategies compared to the current program are presented in the seven right hand columns of Table 3 ordered by net cost.

3.1. Cost outlay for vaccination programs

The total cost outlay –the sum of the vaccine purchase and the vaccine administration– of each strategy increased with the level of coverage and the size of the target vaccine population (Supplemental Section 3.6). For example, strategy V2-4y (Preschool) is the least expensive intervention and V2-16y (Preschool, Primary, Secondary) is the most expensive. The cost-outlay for interventions which included school-based delivery among ages 5–11 years old, or 12–16 years old were more expensive than those that included 2–4 year olds. School-based vaccine administration was the most expensive delivery method at £20.14 per LAIV dose. Aside from strategy V2-4y/12-16y, more expensive interventions that distributed more vaccine were more effective in reducing incidence and associated costs than the cheaper strategies. For example, strategy V2-16y had the lowest annual GP and hospitalization costs, and had the highest net-benefit among the interventions due to the large number of averted cases and deaths (Table S8). Although school-age children were the target of vaccination, the majority of QALY gains compared to the status quo occurred in the 25–44 year old and 65+ age groups (Supplemental Section 3.6).

3.2. Sensitivity analysis

We used a one-way sensitivity analysis to determine how robust each proposed strategy would be to changes in the discount

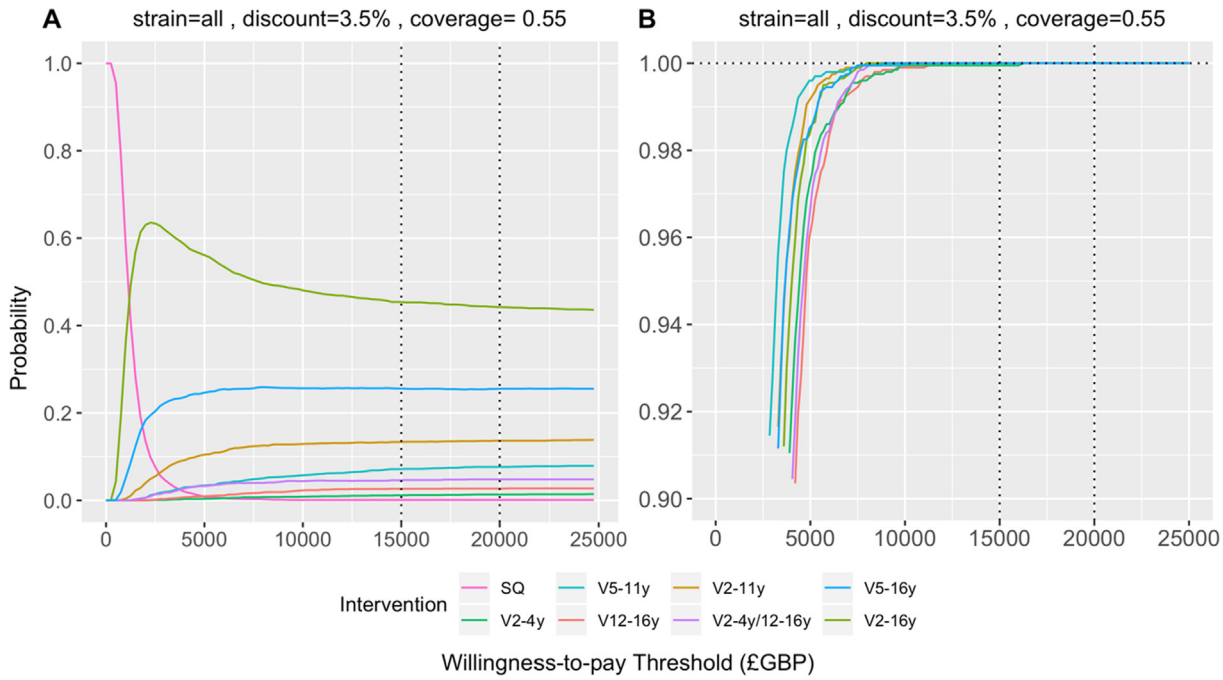

Fig. 1. In panel A, each curve depicts the probability that a strategy would confer the greatest net health benefit across a range of cost-effectiveness thresholds, estimated by the proportion of simulations in which that strategy was optimal at each threshold. In panel B, each curve demonstrates the probability a strategy is merely cost-effective when compared to the each WTP threshold. A strategy such as V2-16y that vaccinates all school-age children has a high probability of being optimal as it distributes the most vaccine, and confers large net health benefits. However the large cost of the vaccine distribution makes V2-16 less likely to be cost-effective. A strategy that is cost-effective is not necessarily optimal.

rate and total achieved coverage. We compared intervention strategies side-by-side at 30%, 55%, and 70% total coverage, and at discount levels 0%, 1.5% and 3.5% (Table 3). Increasing the discount rate from 0% to 3.5% and holding coverage at 55% resulted in increased cost per QALY gained and minor decreases to the overall net benefits (Table 2).

At all levels of coverage (30%, 55%, 70%), all strategies had a 100% probability of being cost-effective at the current NHS WTP and at the more conservative WTP of £15,000/QALYs gained (Figure S9). However, uncertainty around cost-effectiveness became more pronounced when coverage levels were varied. For example, the acceptability curve for strategies V2-4y and V12-16y were insensitive to changes in total coverage, whereas increasing coverage for strategies V2-11y, V2-16y, and V5-16y resulted in a more expensive WTP threshold to achieve the same probability (Fig. 3). Strategies that contained the Primary school age group such as V5-11y and V5-16y achieved 100% probability of being cost-effective at WTP £7250/QALY at coverage levels of 55% and 70% (Fig. 3). Similarly, strategies V2-11y and V2-16y achieved 100% probability at WTP £7500/QALY gained. At 30% total coverage, where fewer vaccines were purchased and distributed, strategies had a higher probability of being cost-effectiveness at lower costs per QALY gained. Across seven strategies 70% coverage was determined to be the optimal strategy in 50% of simulations at WTP £20,000/QALY.

The probability a strategy was optimal, and its subsequent rank order in terms of the optimal strategy were generally insensitive to the change in discount rate. Under all coverage and discount levels the optimal strategy was consistently V2-16y (Fig. S11). Strategy V2-16y was very sensitive to increases in coverage. It gained an additional 20–25% probability of being optimal when coverage was increased from 30% to 55% and 55% to 70%. Conversely, V5-16y remained constant with 21–22% probability of being optimal when total coverage was increased from 30% to 70%. The probability any of the remaining strategies were optimal decreased as coverage increased.

3.2.1. Strain-specific differences

Under 55% achieved coverage each strain demonstrated a strain-specific cost-efficiency frontier (Fig. 2). This indicates some strategies were more effective for some strains than others. The A/H3N2 cost-efficiency frontier most-resembled the frontier created from the sum of all three strains. Influenza strain A/H3N2 incurred the greatest health care costs and QALYs lost regardless of which intervention strategy was used (Fig. S8). Prevention of A/H3N2-related health care and economic outcomes with any of the new strategies rendered every intervention cost-effective with a probability of 99% at £15000 WTP at every discount and coverage level considered. Strains with lower severity like A/H1N1 rendered it the strain least likely to be associated with cost-effective estimates with an average 10% of simulations failing at £15000 willingness-to-pay threshold (Fig. S9). Interestingly, among the three strains, strain B incurred the greatest number of GP consultation fees with an average £15.3 million spent annually at 55% coverage.

Fixing coverage at 70% and examining all three discount levels revealed that for strain B and A/H1N1 less expensive strategies focused on one group such as V2-4y, V5-11y, and V12-16y were associated with favorable cost-effectiveness outcomes. More expensive strategies focused on vaccinating all school ages (V2-16y) were often weakly dominated by V5-11y, V2-11y, or V5-16y (Supplemental Section 3). Strategy V2-4y/12-16y was strongly dominated in every sensitivity scenario except under strain A/H3N2 at 1.5% discount rate and 70% coverage.

4. Discussion

After examining seven counterfactual scenarios for the period 1995/1996–2013/2014 where school-age vaccine strategies were implemented instead of status quo, we conclude the most efficient way of reducing seasonal influenza-attributable morbidity and mortality in the UK is to use strategies that include the key

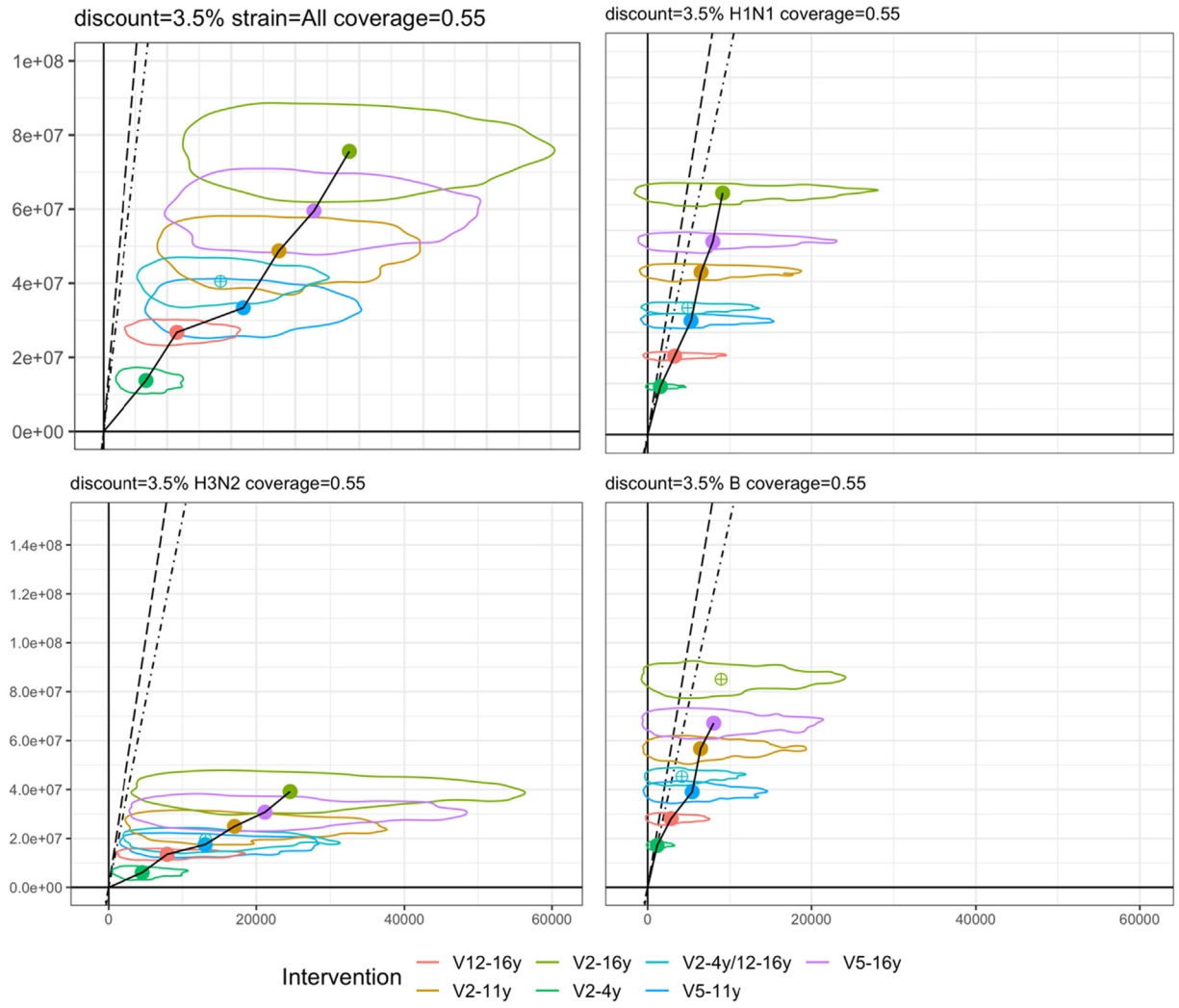

Fig. 2. Incremental analysis with displaying average costs and quality-adjusted life years (QALYs) gained across all strains and stratified by strain. The graphs depict the estimated change in costs and QALYs gained over the reference strategy (Status Quo). Each contour line represents 90% of the Monte Carlo simulations with the coloured point inside being the mean outcome of the scenario. The two diagonal lines represent £15,000 (long-dash) and £20,000 (dash-dot) per QALY gained. Unfilled points indicate strategies that are dominated by others. The black line segments represent the cost efficiency frontier.

Table 3
Incremental Cost-effectiveness ratios where the comparator is the Status Quo intervention and net benefits with associated 95% credibility range calculated under different discount rates for Quality-Adjusted Life Years (QALYs), and different total coverage for the LAIV strategy. All costs are expressed in 2018 British Pounds Sterling. Please note, the ICERs given above are for simulation comparison purposes only and were not used in the cost-effectiveness analysis.

Incremental Cost-Effectiveness Ratios							
Intervention Strategy	Target Age-Group (Years)	Net Cost (£GBP Million)		Net QALY Difference		Incremental Comparison	
		Mean	95% Confidence Interval	Mean	95% Confidence Interval	Mean	95% Confidence Interval
V2-4y: Preschool School	Low-Risk 65+, High risk 6 months – 65+	13.8	(10.1, 16.7)	6697	(2800, 12715)	2054	(825, 3282)
V12-16y: Secondary School	Low-Risk 65+, High risk 6 months – 65+, 12–16 years old	26.7	(23.1, 30.0)	11,520	(4939, 21719)	2693	(2640, 2746)
V5-11y: Primary School	Low-Risk 65+, High risk 6 months – 65+, 5–11 years old	33.4	(25.2, 40.3)	21,890	(9480, 41089)	639	(-389, 1666)
V2-11y: Preschool & Primary School	Low-Risk 65+, High risk 6 months – 65+, 2–11 years old	48.7	(37.9, 56.8)	27,456	(11972, 51960)	2761	(1723, 3799)
V5-16y: Primary & Secondary School	Low-Risk 65+, High risk 6 months – 65+, 5–16 years old	59.5	(48.6, 69.2)	32,925	(13961, 60995)	1972	(1468, 2476)
V2-16y: Preschool & Primary & Secondary School	Low-Risk 65+, High risk 6 months – 65+, 2–16 years old	75.6	(62.2, 86.8)	38,452	(16754, 73144)	2909	(1968, 3850)
Interventions ruled out by Dominance or Extended Dominance							
V2-4y/12-16y: Preschool & Secondary School	Low-Risk 65+, High risk 6 months – 65+, 2–4 years old, 12–16 years old	40.5	(33.9, 46.1)	18,340	(7728, 35924)	Dominated by: Primary School (5–11 year olds)	

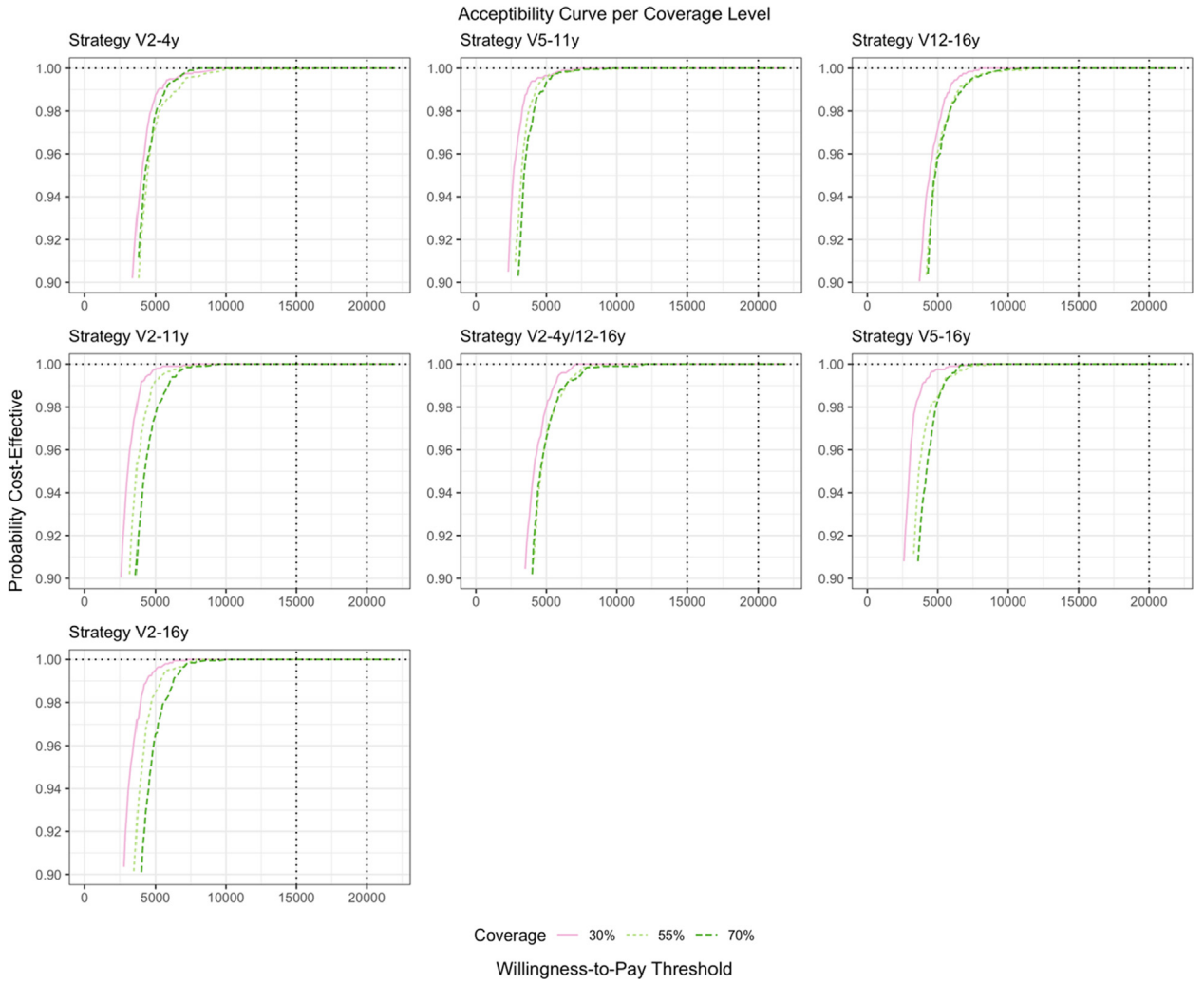

Fig. 3. The utility of increasing coverage from 30% to 55% to 70% for each proposed strategy. Each acceptability curve delineates the probability that a vaccination strategy is cost-effective at a range of willingness-to-pay (WTP) thresholds. All strategies are cost effective at current NHS WTP guidelines, however some strategies (e.g. V2-11y) are more sensitive to changes in coverage than others. The probability a strategy is cost-effective was estimated by the proportion of 2500 simulations that are less than or equal to the proposed threshold (Y-Axis).

school-age cohort: Primary School children (5–11 year olds). Vaccination of only the 5–11 year old age group was cost-effective at the NHS willingness-to-pay threshold of £20,000/QALY, however strategies that were most cost-effective combined vaccination of this cohort with an age group directly above or below it. Depending on the resources available the NHS should consider priority groups for seasonal influenza vaccination as follows:

1. Adults aged 65 or older and persons aged 2–64 years with underlying chronic medical conditions (including pregnant women).
2. Children aged 5–11 years old via school-based vaccine delivery.
3. Children aged 12–16 years old via school-based vaccine delivery.
4. Children aged 2–4 years old via GP based vaccine delivery.

In the 2019/2020 influenza season school-based vaccine delivery will expand to include 11 year olds, remaining in the 5–11 year old age range. Our recommendation for the ongoing pediatric vaccination program is that school-based vaccine delivery continue its phased introduction among 5–11 years old up to and including 12–16 year olds. Simultaneously recommending LAIV vaccination of 2–4 year olds should be phased out.

Strategy V5-16y–vaccinating children in primary school and secondary school–decreased QALYs lost from all sources to a level comparable to that of the 2–16 year old strategy (Figures S6, S7, S8). This strategy was also robust to variation in coverage rate remaining cost-effective at well below £15,000 per QALY gained for coverage as low and high as 30% and 70%. Strategy V5-16y has the advantage of reducing the implementation cost and complexity of a more expensive interventions like V2-16y while delivering an equivalent amount of QALYs gained. The 2–4 year old age-group under interventions where 5–11 year olds were vaccinated with LAIV (strategy V5-11y and V5-16y) had indirect protection equivalent to strategies where 2–4 year olds had direct protection as the vaccine target. The conclusions of our study are consistent with seasonal influenza studies from other countries [24–26] and previous research in the UK [4,27–29], which concluded that pediatric vaccination is effective at reducing morbidity and mortality in the wider population. School-age children have high rates of viral transmission due to little pre-existing immunity and increased exposure potential within their contact network.

School-based delivery of LAIV vaccine was calculated to have the highest cost per dose among the available delivery methods (Supplemental Section 3.6). Up front contributors to the increased cost of school delivery were the inclusion of waste disposal, trained

staff salaries, and travel costs. Despite the initial increase in cost to implement the school program, we predict the total cost will slightly decrease over time as vaccine services (e.g. vaccine administration, waste disposal) are streamlined and integrated into the common practice of the NHS. Additionally fast LAIV uptake from school-delivery would reduce the total number of vaccine doses needed in a community. By inducing immunity in children earlier in the influenza season they indirectly dampen transmission in the wider population [30]. Administration of LAIV to 5–16 year old children also decreases the chance of any adverse vaccine events, and 5–16 year old children are less likely to be absent from school. In contrast, two to four year old children receive LAIV at GP offices, which may result in slower vaccine uptake during the critical period between the start of the school season and the start of the influenza season. Administration of LAIV among 5–16 year old children using the school-based delivery would allow for greater oversight and a swift, regimented schedule of distribution in the available time window.

Finally, increasing research and therapeutic interventions for individuals diagnosed with influenza A/H3N2 may produce further cost-savings for the NHS in the long-term. We also considered the cost-savings of changing the LAIV sprayer size because only 30% of the total sprayer holds vaccine (Supplemental Section 3.5.1). However, waste disposal is a minor fraction of the total cost per dose, and any expense reduction from sprayer size was already captured in the lower bound of the LAIV cost per dose distribution.

One limitation is that, although we have conducted extensive sensitivity analysis, substantial changes to influenza epidemiology may render the examined strategies suboptimal during future seasons. Our model is calibrated for seasonal influenza strains, meaning the final recommended strategy may not be optimal for the high transmission intensity of pandemic influenza strains (e.g. A/H5N1) or other pandemic respiratory viruses (e.g. COVID-19). Influenza viruses undergo antigenic changes, and the benefits of vaccination are dependent on the seasonal components of vaccine efficacy. End-of-season results for 2017/2018 vaccine effectiveness against laboratory confirmed influenza estimated an all strain LAIV effectiveness among low-risk 2–17 year olds as 26.9% [31]. Vaccine effectiveness is generally lower than vaccine efficacy, meaning that our point estimate of 42% for poorly matched years may be an overestimate for some poorly matched years.

The sensitivity of cost-effectiveness recommendations to variation in social contact patterns has not been well-established. Given the small margins between the considered interventions, variation in contact rates, costs, or population age structure could render a strategy that was dominated in Great Britain cost-effective elsewhere. We caution against explicit mapping of the United Kingdom pediatric vaccination program to another setting without adjusting the cost and social contact parameters.

The LAIV pediatric program remains an innovative strategy for tackling seasonal influenza virus by exploiting its dependence on children as key spreaders and should continue deployment. In anticipation of the demands the LAIV pediatric program will put on the NHS at full capacity we have conducted a cost-effectiveness analysis to determine which school age groups should be prioritized in pediatric vaccine distribution. We recommend continuing the vaccination of high risk groups (e.g. chronic conditions) and 65+ year olds in tandem with any school-delivery strategy that includes Primary school (5–11 year old) aged children. Our cost-effectiveness analysis for England and Wales concluded that an intervention targeted at 5–16 year old children would maximize QALYs gained for the lowest cost, allowing 2–4 year old children to be phased out. It remains to be seen if there are further age groups within the Primary school age cohort that should be prioritized during seasonal influenza vaccination in England and Wales.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.10.007.

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