Effect of mass paediatric influenza vaccination on existing influenza vaccination programmes in England and Wales: a modelling and cost-effectiveness analysis

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Summary
Background In 2013 England and Wales began to fund a live attenuated influenza vaccine programme for individuals aged 2–16 years. Mathematical modelling predicts substantial beneficial herd effects for the entire population as a result of reduced influenza transmission. With a decreased influenza-associated disease burden, existing immunisation programmes might be less cost-effective. The aim of this study was to assess the epidemiological effect and cost-effectiveness of the existing elderly and risk group vaccination programme under the new policy of mass paediatric vaccination in England.

Methods For this cost-effectiveness analysis, we used a transmission model of seasonal influenza calibrated to 14 seasons of weekly consultation and virology data in England and Wales. We combined this model with an economic evaluation to calculate the incremental cost-effectiveness ratios, measured in cost per quality-adjusted life-years (QALY) gained.

Findings Our results suggest that well timed administration of paediatric vaccination would reduce the number of low-risk elderly influenza cases to a greater extent than would vaccination of the low-risk elderly themselves if the elderly uptake is achieved more slowly. Although high-risk vaccination remains cost-effective, substantial uncertainty exists as to whether low-risk elderly vaccination remains cost-effective, driven by the choice of cost-effectiveness threshold. Under base case assumptions and a cost-effectiveness threshold of £15 000 per QALY, the low-risk elderly seasonal vaccination programme will cease to be cost-effective with a mean incremental cost-effectiveness ratio of £22 000 per QALY and a probability of cost-effectiveness of 20%. However, under a £30 000 per QALY threshold, the programme will remain cost-effective with 83% probability.

Interpretation With the likely move to decreased cost-effectiveness thresholds, reassessment of existing risk group-based vaccine programme cost-effectiveness in the presence of the paediatric vaccination programme is needed.

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Introduction
Individuals at high risk of serious complication after an influenza infection have historically been the target for seasonal influenza annual vaccination programmes worldwide. However, because of the indirect effects of vaccination, termed herd protection, the vaccination of groups who are important for transmission of infection is often also cost-effective. A large proportion of this transmission is attributable to children and adolescents because of the relatively high number of contacts they have with others, the fraction of these contacts that involve touching, and their susceptibility to influenza infection. Some countries have broadened their seasonal influenza vaccine recommendations to immunise healthy children and adolescents every year, for example in the USA and more recently in the UK in 2012.

If paediatric immunisation programmes gain high coverage early enough in the influenza season to interrupt transmission to risk groups, any existing risk group-based vaccine programme becomes less cost-effective. If a national paediatric programme renders elderly and risk group vaccination programmes not cost-effective, then removing annual vaccination from these target groups will allow a large annual saving. Previous analysis in the context of the UK suggests that substantial uncertainty exists regarding the cost-effectiveness of an elderly low-risk programme in the presence of a moderate vaccine uptake of 50% in healthy children and adolescents, with a third of simulations finding the elderly vaccine not to be cost-effective.

To reduce seasonal influenza-associated serious disease in elderly people and in individuals clinically at risk from influenza-related disease, England and Wales are introducing a publicly funded universal funded paediatric vaccination programme, using live attenuated influenza vaccine (LAIV). The LAIV programme began in 2013 and offered the intranasal vaccines to all healthy children aged 2–3 years and to healthy children aged 4 years and those in primary grades 1–6 (children commencing the school year aged 5–10 years) who were enrolled in a pilot study done in seven regions. In 2014–15, the programme extended to all children aged 2–16 years. Mathematical modelling predicts substantial beneficial herd effects for the entire population as a result of reduced influenza transmission. With a decreased influenza-associated disease burden, existing immunisation programmes might be less cost-effective. The aim of this study was to assess the epidemiological effect and cost-effectiveness of the existing elderly and risk group vaccination programme under the new policy of mass paediatric vaccination in England.
Research in context

Evidence before this study
Using a transmission model, our previous study showed that a paediatric vaccination programme can effectively control seasonal influenza because of the substantial herd protection conferred to unvaccinated children and adults. The decision to implement a paediatric vaccine programme in England was initiated after the evidence presented in a later study that combined the previous mathematical model with a cost-effectiveness analysis. Although this study showed paediatric vaccination to be very cost-effective, the study only superficially assessed the effect of this programme on existing target group vaccination.

Added value of this study
In this Article, we assess the epidemiological effect and cost-effectiveness of the existing elderly and high-risk group vaccination in the presence of paediatric vaccination. Our study suggests that a mass paediatric vaccination programme will not affect the existing recommendation of risk group vaccination in England. However, the continued cost-effectiveness of a low-risk elderly vaccination programme is uncertain.

Methods

Epidemiological effect of paediatric vaccination
For this cost-effectiveness analysis, to predict the direct and indirect effects of seasonal influenza vaccine programmes, we use a previously described transmission model of seasonal influenza in England and Wales that is calibrated to 14 seasons of data.15,16 Using this calibrated model, we assessed the influenza incidence in two groups: the high-risk population (individuals older than 6 months who have a diagnosed clinical disorder that puts them at risk of complications after influenza infection); and the low-risk elderly population (individuals older than 64 years who are not categorised as high risk). We assess the influenza incidence with and without low-risk elderly and high-risk vaccination, in the presence of three different paediatric programmes: (1) preschool age (2–4 years) only; (2) preschool and primary school age (2–10 years); and (3) preschool, primary, and secondary school age (2–16 years). Because children are known to be epidemiological drivers for seasonal influenza transmission, the speed at which children are vaccinated will probably affect the disease burden of the rest of the population. Therefore, we considered three administration speeds: (1) slow (uptake achieved between Jan 1 and Jan 31); (2) linear (uptake achieved between Oct 1 and Jan 31); and (3) fast (uptake achieved between Oct 1 and Oct 31). We also assessed the effect of different paediatric vaccine coverages on the effectiveness of the low-risk elderly and high-risk vaccine programmes.

Transmission model and LAIV assumptions
We use an age-specific and risk-specific mathematical model that captures seasonal influenza transmission in England and Wales. The model is calibrated to the number of influenza-like illness consultations and the frequency of virological confirmations from 1995 to 2009. The calibrated model is parameterised with data on vaccination coverage, vaccine uptake speeds, and vaccine effectiveness data for elderly and high-risk inactivated influenza vaccination (IIV) in the absence of any paediatric vaccination. We calibrated the model using a Bayesian evidence synthesis approach, which captures uncertainty in the model parameters and is able to generate a distribution of model outcomes consistent with available data. The model captures the
Economic evaluation assumptions
To calculate the cost-effectiveness of the elderly programme and high-risk programmes, we integrated the transmission model into an economic evaluation. The economic evaluation tracks the number of general practitioner consultations, hospital admissions, and deaths for each year for the three strains. QALYs lost are assumed for febrile cases to have a mean of $7.49 \times 10^{-3}$, and for cases admitted to hospital, to be normally distributed with a mean of $0.018$ (SD $0.0018$). Vaccine costs associated with vaccine price reimbursement and administration were triangularly distributed ($\£10.00$, $\£15.05$, $\£20.00$). General practitioner and hospital treatment costs are assumed to be normally distributed with mean prices $\£37.00$ (SD $\£8.40$) and $\£839.00$ (SD $\£192.10$). Further details of the specific health economic values used, including the health burden of each of the associated health outcomes has been previously published. No discounting was applied because the economic evaluation results report the uncertainty in the cost per QALY gained over a single year.

Statistical analysis
The analysis was run in R, using R Studio with the R package fluEvidenceSynthesis. Plots were drawn using Mathematica version 10.3.0.0.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. KEA, MB, JP-G, EvL, RP, and MR had access to the raw data. The corresponding author had full access to all of the data in the study and the final responsibility for the decision to submit for publication.

Results
As a universal paediatric programme expands to older ages (ie, from preschool age [2–4 years] to primary age [children commencing the school year aged 5–10 years] to secondary age [adolescents commencing the school year aged 11–15 years]), the number of cases of influenza averted by an elderly or high-risk vaccination programme diminishes (figure 1). Importantly, however, as the paediatric programme expands, and there are concurrent drops in influenza incidence in the elderly and high-risk populations, the speed at which the paediatric programme is implemented becomes important. A rapid implementation each year of any vaccination programme of preschool, primary school, and secondary school children, even in the absence of an elderly vaccine programme, would avert a similar number of cases as the same paediatric programme implemented gradually over the influenza season in the presence of an elderly programme.

Because of the high morbidity and mortality in the high-risk group, vaccination of these individuals remains cost-effective in the presence of all paediatric strategies.
with an ICER of less than £15 000 per QALY gained for all simulations (figure 2). By contrast, the presence of paediatric vaccination produces a qualitative shift in the ICER for low-risk elderly vaccination.

Under the 70% vaccine coverage base case, we find that although low-risk elderly vaccination is likely to maintain an ICER of less than £30 000 per QALY (83% of simulations), the ICER itself has increased by £9982 per QALY relative to no paediatric programme. Compared with no paediatric programme, the low-risk elderly programme has a much higher chance of falling between £20 000 per QALY and £30 000 per QALY (29%, compared with 12%) or more than £30 000 per QALY (17%, compared with 1%; figure 2). Conversely, with a cost-effectiveness threshold of £15 000 per QALY, the elderly programme is no longer cost-effective, with a mean ICER of £22 000 per QALY, and 80% of simulations providing ICER estimates of greater than £15 000 per QALY.

To assess the effect of paediatric uptake speed, we calculated the cost-effectiveness of elderly vaccination under a possible scenario in which the target coverage (70% vaccine uptake) was reached by the beginning of November (figure 2) compared with the present scenario, in which school-based administration increases gradually from October through December; achievement of the target coverage earlier (ie, by the beginning of November) resulted in a reduction in the cost-effectiveness of elderly vaccination and an increase in the ICER by £479 per QALY.

Our model suggests that changing the cost-effectiveness threshold across a reasonable range determines whether the low-risk elderly vaccination remains cost-effective. For example, even under optimistic conditions of fast delivery by the beginning of November and a coverage of 90% for the 2–16 years paediatric programme, the probability that elderly vaccination is cost-effective at £30 000 per QALY is still 68%. However, if the cost-effectiveness threshold falls to £15 000 per QALY under likely base case conditions, the elderly programme will cease to be cost-effective, with only 5% of simulations falling below the threshold (figure 2).

We also assessed the effect of a reduced whole-season direct effectiveness of LAIV relative to the IIV that is currently given to elderly and high-risk individuals (figure 3). Under base case assumptions, the probability that the elderly programme is cost-effective increases as the whole-season LAIV direct effectiveness decreases. Under the conservative threshold of £15 000 per QALY, reducing LAIV effectiveness to half of IIV effectiveness increases the probability that the elderly programme is cost-effective from 42% to 65%

Discussion
We used a previously described calibrated mathematical model of seasonal influenza transmission in England and Wales to assess the likely epidemiological and economic effect of a paediatric programme, which is currently being rolled out across England, on the existing seasonal influenza vaccine programme. We found that under reasonable assumptions of vaccine coverage achieved in the pilot schemes, uncertainty exists about the continuing cost-effectiveness of the low-risk elderly vaccination programme that is available to all individuals with no underlying chronic disorders. The uncertainty surrounding these results stems primarily from the cost-effectiveness threshold assumed. We found that vaccinating high-risk individuals was always cost-effective. Our analysis shows the potentially large effect of additional vaccination programmes on the cost-effectiveness of existing schemes. Particularly, the
analysis highlights the importance of the assessment of existing influenza vaccination policies in the presence of increased herd protection after paediatric vaccination. Although our results suggest that vaccinating high-risk individuals will always be cost-effective over all plausible outcomes of the paediatric vaccination programme, the decision to maintain low-risk elderly vaccination is not so straightforward. As the new paediatric programme in England and Wales increases its scope from preschool-age children only to also include school-age children, with uptake consistent with other school-based programmes, significant uncertainty will probably arise concerning the cost-effectiveness of a low-risk elderly vaccination programme. Our analysis suggests three important questions for policy makers in countries wishing to introduce a paediatric programme (panel).

In England, the LAIV school-based pilot programme aimed at children aged 5–10 years reached a coverage of 52% in the first season of introduction and 57% in the second. However, national school-based administration of vaccines usually reaches much higher coverage. For example, at present, the first dose uptake for the human papillomavirus vaccine in England for girls aged 12–13 years is 89%, and for the 3-in-1 Tetanus-Diphtheria-Polio in Scotland for students aged 15–16 years is 88%. Although the human papillomavirus and 3-in-1 vaccines are usually administered through the entire school year, influenza vaccines must achieve the target coverage in a short timeframe, typically before the Christmas holidays. As such, once the LAIV programme is established, a school-based administration of LAIV will probably achieve much higher coverage than the coverage that exists at present, but not as high as the coverage achieved by other school-administered vaccines. Unlike the timings for preschool, elderly, and high-risk vaccine administration, which are patient-led, the timing for a school-based vaccine administration would be determined by the regional National Health Service.
We reassess the cost-effectiveness of the elderly vaccination policy in England because it was one of the first countries to introduce a publicly funded programme of paediatric influenza vaccination. With results suggesting that this is a highly cost-effective health policy, other countries will probably also follow a similar route. We would therefore recommend that decision makers consider the following three questions before adapting and renegotiating their influenza vaccination policies:

1. Are they willing to pay the same per vaccine dose for an elderly influenza vaccination programme in the presence of a national paediatric programme? In our base case scenario in the English context, the mean incremental cost-effectiveness ratio thresholds are considered: £30 000 per QALY (red, cost-effective), £20 000 per QALY (blue, very cost-effective under current protocol), and £15 000 per QALY (green, cost-effective under proposed protocol). A relative direct effectiveness of 1 corresponds to the LAIV having the same whole-season direct effectiveness as the IIV (base case value), and a relative direct effectiveness of 0 corresponds to the LAIV having no effect on influenza epidemiology and is therefore equivalent to the cost-effectiveness of the elderly programme with no paediatric coverage. LAIV=live attenuated influenza vaccine. QALY=quality-adjusted life-year. IIV=inactivated influenza vaccine.

Panel: Policy considerations for countries wishing to introduce a paediatric influenza vaccination programme

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2. How quickly would the vaccines be available and administered via a preschool-based and school-based programme? Our results show that swift paediatric vaccination can negate the requirement for elderly vaccination, whereas slow uptake wastes vaccine doses by protecting children too late to have any effect on the reduction of transmission.

3. Would a focus on the achievement of a high coverage across all paediatric groups be more cost-effective than maintaining a historically low elderly coverage? When combined with previous results, we conclude that the per dose cost-effectiveness of a paediatric (2–16 years) vaccine is higher than that for an elderly vaccine, such that expansion of the paediatric programme as much as possible will always be economically advisable.
can be reduced. The accuracy of the model predictions are also contingent on the disease burden data to which the model is calibrated. Although the modelling approach is able to convey uncertainty in the predictions, robust age-specific influenza surveillance information is key for accurate model predictions.

With substantial uncertainty around the cost-effectiveness of an elderly vaccination in the presence of a paediatric programme in England, other developed countries with a large fraction of the population older than 65 years might wish to reassess their funded elderly programme. In 2014, 9.5 million individuals were older than 65 years in England, 17-6% of the total population and the same number of those aged 2–16 years. Assuming an elderly vaccine uptake of 70% and a dose and administration cost of about £16 per vaccine, discontinuing elderly vaccination would save more than £106 million annually.

Most developed countries have an ageing population as a result of a decreasing birth rate and an increasing life expectancy. These demographic shifts will not only increase the scale of an age-targeted programme, but they will also affect their cost-effectiveness through changes in age-specific social mixing patterns that affect the level of herd protection accrued. Frequent reassessment of policy decisions is essential to ensure these changes are accounted for.

The evidence needed to withdraw a funded vaccine programme might be different to that needed to initiate one. Should a decision be under consideration to remove a long-standing vaccination programme as a result of improved public health measures elsewhere, it might be wise to offer a scaled-back programme rather than completely remove an established policy. How such a scaled-back programme would be implemented depends on the details of the at-risk groups. For example, 55% of the high-risk population are themselves older than 65 years. Alternatively, extenuating circumstances might exist that take precedent over low probabilities of cost-effectiveness. Moreover, our results suggest that in countries that currently have no funded influenza vaccination programme in place, it is necessary to consider a suite of age-group and risk-group based strategies concurrently to optimise any national influenza programme.

**Contributors**
KEA, MB, JP-G, and Evl conceived the study. DH did the data analysis. KEA wrote the manuscript, which was revised by MB, RP, MR, Evl, and JP-G.

**Declaration of interests**
KEA reports personal fees from Sanofi Pasteur, outside the submitted work. MR reports grants from GlaxoSmithKline and Pfizer, outside the submitted work. All other authors declare no competing interests.

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