Health and economic impact of the seasonal influenza vaccination programme in England

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\section*{A R T I C L E   I N F O}

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\section*{A B S T R A C T}

\textbf{Background:} The seasonal influenza vaccination programme in England targets individuals over 65 years old and in clinical risk groups.

\textbf{Methods:} A model of influenza transmission and disease was fitted to weekly primary care consultations due to influenza in a typical pre-pandemic season (2006/2007). Different scenarios were constructed about influenza severity and how well vaccines match circulating strains to assess the impact and cost-effectiveness of the current vaccination programme.

\textbf{Results:} A well-matched vaccine may reduce the incidence of laboratory-confirmed influenza illness from 8.2\% (95\% range 4.3--13\%) to 5.9\% (95\% range 2.9--9.7\%), with 56--73\% of this due to indirect protection. The programme is likely to be cost-effective unless both low severity and poor matching is assumed.

\textbf{Conclusion:} The current seasonal influenza vaccination programme appears to substantially reduce disease burden and provides good value for money.

\section*{1. Introduction}

Annual seasonal influenza vaccination is recommended for people most at risk of infection and its complications in many high-income countries [1]. In England, vaccination is recommended for individuals aged 65 years and over, health care workers, pregnant women and those in clinical risk groups (people of all ages with chronic respiratory, heart and renal diseases, diabetes and immunosuppression due to disease or treatment).

However, the age and clinical risk groups considered most at risk of infection and hence targeted by vaccination differ widely between countries [1]. The impact and economic rationale of country-specific recommendations is not always well established, and indeed was recently debated in the United Kingdom. Some economic models have examined the impact of extending recommendations to other groups such as children under 12 years or adults 50--64 years [2,3]. However, most of these are static models that do not realistically model infection transmission, and hence indirect protection in non-vaccinated individuals such as household members of vaccinated children. Some models have tried to estimate the magnitude of such indirect protection based on household secondary attack rates in household studies [4,5], but these estimates will inevitably have limited validity outside the study population.

Any model considering the health and economic impact of options for influenza vaccination would first need to establish the burden of influenza in the absence of vaccination, then the (direct and indirect) benefit of vaccination. The burden of influenza-related disease in the absence of vaccination largely depends on the pre-existing level of immunity in the population (as a result of vaccination or infection in previous years), the rate at which influenza is transmitted between different groups in the population and the severity of disease caused by the circulating strains. The impact of vaccination depends on the coverage of the vaccine in a non-linear way because of the effect of indirect protection (herd immunity). Disentangling the effect of the vaccination programme and estimating how many cases and deaths might have occurred had the programme not been in place is therefore not straightforward and subject to considerable uncertainty.

Here we assess the impact and cost-effectiveness of the existing seasonal influenza vaccination programme in England, in the period 2000--2009 with relatively high influenza vaccine coverage. We use as an exemplar the 2006/2007 epidemic year, a "typical" recent (post-2000) year, which has a relatively low level of influenza infection and one type of strain circulating.
2. Methods

2.1. Transmission dynamic modelling

A previously described [6] age-structured dynamic model of influenza transmission was adapted to describe the dynamics of influenza transmission, disease and vaccination during the 2006/2007 influenza season in England (population 51 million). To capture the uncertainty around the natural history and transmission of influenza, key model parameters were determined by randomly sampling from their plausible probability distributions to generate 600 epidemic time series (weekly number of infections by age and risk group). These parameters are the latent and infectious period of influenza, contact rate between people of different ages, proportion of people who are immune to influenza at the start of the influenza season, initial reproduction number at the start of the influenza season and timing of the epidemic peak. We assume that people in risk groups do not differ from people not in risk groups in terms of their contact behaviour. The epidemic time series are combined with the proportion of individuals with serologically confirmed influenza who consult a general practitioner (GP) to generate 30,000 possibilities for the time series of clinical influenza in the population.

The model was then used to evaluate vaccination of clinical risk groups and those at least 65 years old, but not of pregnant women (who were not recommended for vaccination until 2010) or health care workers (due to low uptake and lack of data). For each epidemic time series, a fraction of the population in each age and risk group was assumed to be vaccinated, based on weekly vaccine uptake data for 2006/2007 (from Health Protection Agency reports and publications [7]). Vaccine wastage of 10%, and a 2-week delay between vaccination and immunity onset was assumed. Vaccine efficacy was assumed to be 70% in vaccinees under 65 years and 46% in older vaccinees, when the vaccine is well matched to the circulating strain [8]. While this may overestimate protection in young children, vaccine coverage in these children with the existing risk-based strategy is low (3% of under 15s). If the vaccine is poorly matched, efficacy was scaled down by 40% to reflect the ratio of efficacy in studies with poorly matched and well-matched vaccines reported in a systematic review [9].

Further details about model structure, the way the prior distributions of its parameters were constructed and the way it was fitted to data are provided in Supplemental Appendix 1.

2.2. Clinical disease

The proportion of individuals infected with influenza that gives rise to clinical disease was determined from a review of the proportion of such individuals who have ILI symptoms [10].

A proportion of these people are assumed to consult a GP. The weekly incidence of influenza-like illness (ILI) consulting in general practice in 5 age groups (1–4, 4–14, 15–44, 45–64 and 65+ years) in 2006/2007 reported by the Royal College of General Practitioners (RCGP) Weekly Returns Service was multiplied by the viral positivity of samples in each age group [8] to obtain the incidence of strain-confirmed GP consultations for ILI. However, GP consultations with influenza may not necessarily be classified as ILI. Hence, the 50 clinical time series from the transmission model which fitted data on ILI consultations multiplied by a variable factor were chosen, with this factor representing the proportion of all GP consultations for influenza that were recorded as ILI.

The proportion of influenza-attributable ILI that results in hospitalisations and deaths is poorly characterised. We developed two approaches for estimating these figures.

(a) Low severity scenario. The number of deaths by age and risk group was estimated by multiplying the number of GP consultations due to clinical diagnoses of influenza or influenza-like illness by the fraction of these that are expected to die within 30 days estimated from a study of the General Practice Research Database (GPRD) [11]. The number of hospitalised cases per GP case was estimated from the ratio of expected influenza related hospitalisations and GP consultations by age from that study. The relative risk of complications by risk group and age in the GPRD-based study [11] was used to attribute hospitalisations to risk group.

The above procedure gives an estimate of GP consultations, hospitalisations and deaths by age and risk group. The overall burden estimated by this method was lower than has been published previously. In particular, estimated number of deaths is very low (particularly in the elderly) using this method. For instance, the method estimates 179 deaths in the 65+ age group which compares with estimates from a burden of disease study by Pitman et al. [12] of 9200 deaths from influenza A annually in the same age group (albeit from a slightly earlier time period). For this reason, we derived a high severity scenario.

(b) High severity scenario. We assumed that 10% of cases with ILI due to influenza consult GPs, based on data from an internet-based cohort (Flusurvey) from 2010/2011 [13], and applied the ratios of hospitalisations and deaths to GP consultations for acute respiratory illness in the Pitman study, rather than from the previously mentioned GPRD-based study [11]. This gives a median estimate of approximately 8600 deaths annually (incidence 0.11%) in the elderly. However, the proportion of hospitalisations in risk groups was still determined from the GPRD-based study [11].

2.3. Economic modelling

Health and economic parameter distributions used were taken from our previous cost-effectiveness evaluation of pandemic influenza vaccination [6], and are summarised in Table 1. Loss of quality adjusted life years (QALYs) as a result of an influenza death was estimated from the average age-specific life expectancy in 2009 (using data from the Office for National Statistics), adjusted by age-specific quality of life norms [14] and discounted by 3.5% per annum as recommended by the National Institute for Health and Clinical Excellence (NICE) [15]. All other benefits from one season’s vaccination are assumed to occur in a single year, so any other discounting is unnecessary. Costs are given in 2008 pounds. Uncertainty in epidemiological parameters governing influenza natural history and epidemiology was combined with uncertainty in economic parameters by Monte Carlo sampling from their joint distributions. Separate sensitivity analyses were conducted for the high/low severity scenarios and the well-matched/poorly matched vaccine scenarios described above.

3. Results

The model suggests that without vaccination, the incidence of influenza-attributable ILI over the course of a single season may range from a median of 17% (95% interval 6–21%) in 15–24 year olds to 3% (95% interval 2–6%) in 65+ year olds. Based on English coverage and population figures, around 20% of the population (10.5 million individuals) are vaccinated against influenza annually (3% of under 15 s, 13% of 15–65 s and 74% of over 65 s). The model estimates that such a large fraction of the population being vaccinated, mostly before the annual influenza season, results in substantial direct and indirect (herd) protection. Around 1000–2700 cases per 100,000 people prevented annually depending on how well the vaccine is matched, of which 56–73% are due to indirect protection.

Given a well-matched vaccine, the incidence of influenza-attributable ILI falls to a median of 13% (95% interval 5–20%) for the 5–14 years age group and 2% (95% interval 1–3%) for the 65+
years age group. Overall incidence may fall from 8.2% (95% interval 4.3–13%) to 5.9% (95% interval 2.9–9.7%). This means that around 1.2 million cases of influenza are prevented, 73% of them by indirect protection. Even if the vaccine is not well matched, 0.4 million influenza cases will be prevented, 56% of them by indirect protection. The clinical attack rate in adults (7% in 15–24 year olds and 6% in 25–44 year olds) compares to a confirmed attack rate of 5–7.5% in healthy adults over one season in the control arms of vaccine and antiviral clinical trials [16].

However, there are large uncertainties around estimates of the number of deaths prevented, ranging from a median of 0.03 per 100,000 (under a low severity scenario with a poorly matched vaccine) to 5 per 100,000 (under a high severity scenario with a well-matched vaccine). The higher figures amount to over 2700 deaths a year. The median numbers of hospitalisations and GP consultations prevented range between 0.73–9.2 and 22–260 per 100,000 respectively, or 370–4700 and 11,000–130,000 in absolute numbers, depending on scenario.

Although the impact of vaccination on health care use due to influenza varies widely between scenarios, vaccination is still estimated to prevent a substantial number of cases, and therefore result in large QALY gains from morbidity avoided, particularly in years when the vaccine strains are well matched. Thus the vaccination programme appears likely to be deemed cost-effective at a threshold of £20,000–30,000 per QALY gained used as a threshold for cost-effectiveness in England [15], and “very cost-effective” according to the threshold of gross domestic product per capita (about £23,000 in 2011) recommended by the World Health Organization [17]. This is true even in low incidence years, provided the vaccine is well matched to the circulating strains (Fig. 1a). The most important determinants of vaccine cost-effectiveness are the strain severity and match to vaccine, as well as the QALY loss associated with each influenza-attributable ILL episode (Fig. 1b).

Tables showing more details on the impact of vaccination are given in Supplemental Appendix 2.

4. Discussion

Seasonal influenza vaccine uptake in England has been increasing since the 1990s [7], and now covers 20% of the population every year, with 90% of doses given before December. Our model suggests that the level of coverage combined with a low reproduction number typical of influenza may have led to substantial reductions in clinical cases. Direct protection is shown to be important in the vaccinated groups (older adults and risk groups), but other members of the population benefit from substantial indirect protection. Our model predictions are consistent with the observation that GP attendances for ILL have declined in parallel with the increase in vaccine uptake [18]. Hence evaluations using static models (which only capture direct protection) may substantially underestimate the benefits of vaccination.
There is uncertainty around the model estimates of influenza-related mortality, which is estimated to be as high as 8600 deaths a year. This figure is more in line with Health Protection Agency estimates of annual mortality based on excess deaths (deaths above the seasonally expected), which for the last 5 years have ranged from zero in 2006/2007 to over 10,000 in 2008/2009 [19]. The uncertainty around the mortality estimates suggests that there are many deaths associated with influenza in individuals who are not diagnosed by a GP as having ILI either because they did not attend a GP surgery or were not recorded as having ILI. These deaths may account for the large difference between mortality in the low and high severity scenarios.

A number of simplifying assumptions were used in the analysis (in common with most other cost-effectiveness evaluations of seasonal influenza vaccination). Firstly, the model was parameterised with data from 2006/2007, which was a year with low incidence of influenza-attributable disease and only a single circulating strain. Secondly, we do not explicitly model immunity, although natural immunity is implicitly incorporated into the influenza attack rate. For vaccine-induced immunity, we assume that it does not last beyond the current season. In principle this would underestimate the benefits of vaccination, so it will not change the conclusion that the vaccination programme is cost-effective when the vaccine is well matched. However, multi-year influenza dynamics are complex and difficult to predict because of interactions such as strain dynamics, cross-immunity between strains, degree of matching between vaccine and prevailing strains as well as development of natural immunity. Hence an ideal evaluation would use inferential methods to reconstruct the epidemics and their underlying transmission mechanisms over a certain number of years, taking into account the different subtypes circulating in humans (A/H1N1, A/H3N2, B) and immunity towards them.

Thirdly, only indirect estimates of the distribution of the burden of influenza risk and non-risk groups are available. Given that much of the influenza burden is concentrated in risk groups, a better understanding of distribution of morbidity and mortality risk would improve estimates of the impact of extending the programme to non-risk groups. Better data to quantify the true incidence of influenza-attributable clinical illness supported by serological investigation [20] would also improve model estimates.

Despite the limitations of the available data, this is one of the few cost-effectiveness evaluations of seasonal influenza vaccination that uses a transmission dynamic model. It provides a retrospective evaluation of an existing vaccination programme for which no formal cost-effectiveness analysis has yet been published. It is hence a good basis by which to consider the incremental cost-effectiveness of changes to the seasonal influenza immunisation programme.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2012.03.019.

References