Vaccine 28 (2010) 2370–2384

Contents lists available at ScienceDirect

Vaccine

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

Vaccination against pandemic influenza A/H1N1v in England: A real-time economic evaluation

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ARTICLE INFO

Article history:
Received 17 November 2009
Received in revised form
17 December 2009
Accepted 6 January 2010
Available online 21 January 2010

Keywords:
Influenza
Vaccination
Mathematical Model

ABSTRACT

Decisions on how to mitigate an evolving pandemic are technically challenging. We present a real-time assessment of the effectiveness and cost-effectiveness of alternative influenza A/H1N1v vaccination strategies. A transmission dynamic model was fitted to the estimated number of cases in real-time, and used to generate plausible autumn scenarios under different vaccination options. The proportion of these cases by age and risk group leading to primary care consultations, National Pandemic Flu Service consultations, emergency attendances, hospitalisations, intensive care and death was then estimated using existing data from the pandemic. The real-time model suggests that the epidemic will peak in early November, with the peak height being similar in magnitude to the summer wave. Vaccination of the high-risk groups is estimated to prevent about 45 deaths (80% credibility interval 26–67), and save around 2900 QALYs (80% credibility interval 1600–4500). Such a programme is very likely to be cost-effective if the cost of vaccine purchase itself is treated as a sunk cost. Extending vaccination to low-risk individuals is expected to result in more modest gains in deaths and QALYs averted. Extending vaccination to school-age children would be the most cost-effective extension. The early availability of vaccines is crucial in determining the impact of such extensions. There have been a considerable number of cases of H1N1v in England, and so the benefits of vaccination to mitigate the ongoing autumn wave are limited. However, certain groups appear to be at significantly higher risk of complications and deaths, and so it appears both effective and cost-effective to vaccinate them. The United Kingdom was the first country to have a major epidemic in Europe. In countries where the epidemic is not so far advanced vaccination of children may be cost-effective. Similar, detailed, real-time modelling and economic studies could help to clarify the situation.

1. Introduction

In March 2009, an outbreak of a novel strain of influenza A/H1N1 (hereafter H1N1v) linked to swine influenza was detected in Mexico. By 12 June 2009, the infection had shown sustained human-to-human transmission across the world, leading the World Health Organisation to declare an influenza pandemic. The first wave of the outbreak of H1N1v in the United Kingdom (UK) appeared to peak around 25 July 2009, but cases began to increase again in September.

Vaccines specific to pandemic influenza have been successfully developed. The UK has a contract with two vaccine manufacturers (GlaxoSmithKline and Baxter) to procure H1N1v vaccines. On 7 August 2009, the Joint Committee on Vaccination and Immunisation (JCVI) recommended that high-risk individuals be prioritised for vaccination [1]. These individuals consist of everyone in the current seasonal influenza vaccine clinical at-risk groups (those with chronic respiratory, heart, kidney, liver neurological disease, diabetes, and immunosuppression), excluding the low-risk elderly but including pregnant women and household contacts of immunocompromised individuals. The vaccination programme was rolled out on 21 October with primary care surgeries receiving the vaccine in the following week [2]. The UK has ordered sufficient doses to cover the entire population, so there is the opportunity to extend

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doi:10.1016/j.vaccine.2010.01.002

these recommendations to lower risk individuals. However, the extent of vaccination is restricted by other considerations including the timeliness of the arrival of vaccine doses, the cost of distribution and likely vaccine uptake among different population groups.

Decisions about extending vaccination to low-risk individuals depend partly on the epidemiological impact and cost-effectiveness of such options. Here we describe how we fit an epidemic model to the estimated number of cases in real-time to predict the impact and cost-effectiveness of a range of vaccination options.

2. Methods

2.1. Epidemiological modelling

An age and risk group structured deterministic transmission dynamic model was used to estimate the impact of vaccination. The model has a modified SEIR structure, meaning that it has compartments for individuals who are susceptible to being infected by H1N1v (S), latently infected (E), infectious (I), and recovered (R). The population is also split into three risk groups – those in a seasonal influenza risk group, pregnant women, and those who are not in a risk group, with random mixing (within an age group) between the groups. The size of these groups is 8.6 million, 0.5 million and 42.3 million respectively. Population data were obtained from the Office for National Statistics (ONS) estimate from England mid 2008 and estimates of the size of each risk group provided by the Department of Health, England (Peter Grove, personal communication).

At the onset of the widespread epidemic (1 June) a small fraction of individuals in each age class were assumed to be infectious, and the remainder susceptible. However, older individuals were assumed to have a lower susceptibility, based on results from recent sero-epidemiological analyses [33]. An individual who became infected in the model was assumed to have natural immunity to further infections of H1N1v throughout the time course of the model (12 months). In addition, a fraction of individuals who were vaccinated were assumed to respond and become immune to infection and therefore disease, while non-responders remained susceptible to infection and disease. Vaccination was assumed to begin in the autumn of 2009 and be spread out over a number of weeks. Protection was assumed to occur on average 2 weeks after vaccination (see Appendix A for details). The model population was subdivided into seven age groups: under 1 year, 1–4 years, 5–14 years, 15–24 years, 25–44 years, 45–64 years and over 64 years.

In order to estimate plausible epidemiological scenarios for a second wave, the model was fitted using maximum likelihood to central estimates from the Health Protection Agency (HPA) of the weekly number of H1N1v cases from 1st June to 18th October 2009 [3]. Key parameters (the initial reproduction number, latent and infectious periods) were sampled from uniform distributions which were wide enough to encompass the range of values suggested in analyses of the initial influenza epidemic [4] (see Appendix A for details). Those combinations of parameters that gave an acceptable fit to the observed data were retained and used to simulate the future incidence of infection and disease with different vaccination programmes in place.

The rates at which individuals from different age groups came into contact with each other was based on the reported frequency of close contacts by UK respondents in the recent POLYMOD study of epidemiologically relevant contact patterns [5]. The method of Hens et al. [6] was used to take into account uncertainty in contact patterns. Two sets of contact patterns were used: one for term-time and one during summer holidays when schools are closed. School holidays were assumed to start 46–52 days after June 1 [7]. Each of these model realisations were compared to the 20 weeks of data by minimising the Poisson deviance between the number of cases each week reported by the HPA, and the model estimate of this. The best-fitting 1% of the realisations were retained to simulate the effect of vaccination. Every vaccination programme evaluated was implemented on each of the retained (i.e. best-fitting) realisations to generate an estimate of the expected impact of vaccination, including epidemiological uncertainty.

A significant fraction of influenza infections are subclinical, or do not result in typical febrile symptoms. Thus, there are likely to have been more influenza infections over the summer and early autumn than the estimate of clinical cases by the HPA predict, requiring the data to be re-scaled to take account of this. The epidemic has grown more slowly in the autumn than occurred in the summer, suggesting that a significant fraction of individuals were infected in the early wave. By rescaling the estimated cases by different factors and comparing the model fits (including the fit to the autumn growth rate) it is possible to estimate by how much the estimated weekly number of clinical cases is less than the number of infections (see Appendix A). A multiplication factor of 10 gives a good overall fit to the data, though multipliers of 7.5 and 12.5 were used in the sensitivity analysis. To check the validity of the multiplication factor and selected model runs, we compared the proportion of children who were infected during the first wave with sero-incidence data collected by the HPA [33], using samples taken in September (a sufficient time after the first wave to allow for a delay in seroconversion). The clearest signal in the sero-incidence data is an increase in the proportion of children under 15 years old who were seropositive between baseline and the first wave, and this corresponded well with our model predictions (see Appendix A).

Fig. 1(a, c, d) shows the predicted size of the first and second waves, using different multiplication factors. In each case, the model predicts that the peak height of the autumn wave will be similar in size to the summer wave (though, on average, if a high multiplication factor is assumed, then a lower second wave results). The epidemic is expected to peak in the first two weeks of November 2009, and epidemic activity is expected to cease around January 2010. Fig. 1(b) shows the results of the model validation exercise. The model was fitted to data on 27 September, and the resulting model projections (blue shaded area) are compared with the HPA's estimated weekly numbers. The pink shaded area shows a similar comparison using data up to 18 October. It can be seen that the model gives accurate short-term projections. For instance, using data up to the end of September the model accurately predicts the height and timing of the peak, 6 weeks later. The uncertainty around the projections is narrowed as more data become available. The good description of the subsequent epidemic suggests that the model provides a sound basis for projecting forward over the forthcoming weeks.

2.2. Economic modelling

Following the guidelines used by the National Institute of Health and Clinical Excellence (NICE) [8], the reference case was a cost-utility analysis performed from the perspective of the health care provider (the NHS) and lifetime time horizon, with future benefits and costs discounted at 3.5% per annum. The burden of disease due to the number of infections predicted by the epidemiological model was estimated, and a proportion of them assumed to result in clinical symptoms. Each clinical case was associated with an age and risk group specific risk of a general practitioner (GP) consultation (either telephone or clinic), National Pandemic Flu Service (NPFS) consultation (either telephone or internet), antiviral delivery, hospitalisation, intensive care and death. Each of these health care or clinical endpoints was then associated with a cost to the health

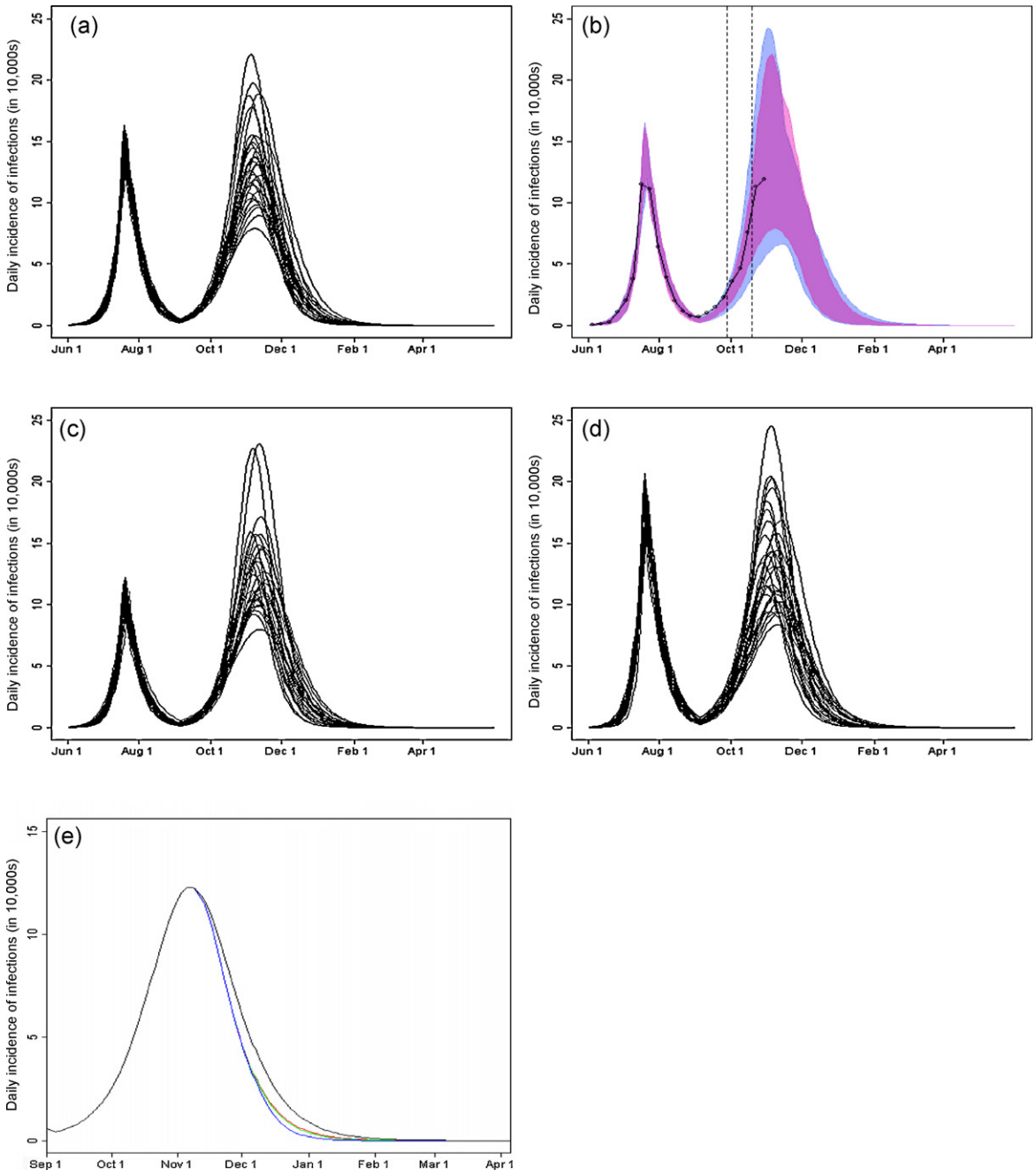

Fig. 1. Projections of the number of infections over time across the best-fitting 1% of model realisations, for the different multipliers of the central estimates of weekly clinical cases (a) 10 times (base case), (c) 7.5 times and (d) 12.5 times, as well as (b) a model validation exercise and (e) the average predicted impact of vaccination on infections. In (b), projections from the 30 best-fitting simulations with a multiplier of 10 are shown: the blue shaded area gives the range of model projections using data up to 27 September (first vertical line), the pink shaded area gives the range of projections using data up to 18 October (second vertical line). The estimated number of infections (re-scaled HPA weekly case estimates) is shown as points joined by a line. Note that data up to 1st November are shown. In (e) the black curve shows the course of the epidemic without vaccination, red with vaccination of high-risk individuals, green with vaccination of risk groups and 0.5–4 year olds, while blue shows vaccination of risk groups of 5–14 year olds.

service and quality of life detriment. The cost-effectiveness of different vaccination options was then estimated by calculating a net incremental discounted cost per quality adjusted life year (QALY) gained. This incorporated the discounted cost of each option (cost of vaccine programme minus treatment costs saved) as well as the number of discounted QALYs gained as a result of averting cases of H1N1v.

All costs are expressed in 2008 prices, and were assumed to occur in the current financial year, although future benefits from deaths averted were discounted at the recommended rate. Unit costs taken from previous years were inflated to £2008 using the Hospital and Community Services Pay and Prices Index [9].

2.3. Estimate of health outcomes and health service utilisation

2.3.1. Symptomatic cases

The clinical definition of ILI is a report of fever and at least one other influenza-related symptom. A review of volunteer challenge studies found that 37% of individuals infected with influenza A/H1N1 had fever [10], so this was assumed to be the proportion of H1N1v cases with symptoms. Thus 37% of infections (on average)

are assumed to result in clinical cases that may then incur costs, and incur a health (QALY) loss.

2.3.2. Calls to the National Pandemic Flu Service (NPFS)

The NPFS is a telephone and internet service that was launched on 23 July 2009 to allow people in England with ILI to obtain antivirals without visiting their GP [11]. The number of assigned unique numbers for receipt of antivirals (equivalent to a prescription) by age up to 29 September 2009 was multiplied by the age-specific proportion positive, using data from 3 August to 26 September. Cases were distributed according to risk groups, using the data available from two separate weeks (23–30 July, and 23–29 September), giving the estimated number of antivirals distributed for H1N1v. Dividing this by the model estimate of the number of symptomatic cases gave the proportion of cases that received antivirals via NPFS. We attributed antiviral prescriptions to a telephone or internet consultation using data from the NPFS.

2.3.3. GP calls and consultations

FluSurvey (www.flusurvey.org.uk) [12] is an internet-based cohort in which participants report the occurrence of respiratory symptoms, as well as contact with health service and usage of medication. The number of cases of influenza-like illness (ILI) reported in FluSurvey was extracted. A respondent was assumed to have ILI if he or she reported a fever and at least one other influenza-related symptom (blocked/runny nose, cough, sore throat, headache, muscle/joint pain, chest pain, stomach ache, diarrhoea, nausea, chills, weakness or eye irritation). The age and risk group dependent ratio of cases reporting calls or office consultations to GPs to total cases was calculated. Between 8 May and 18 September there were 1551 cases recorded in FluSurvey resulting in 476 calls and 145 consultations.

Uncertainty around parameters governing the proportion of cases requiring calls to the NPFS, calls to a GP, GP office visits, hospitalisations and intensive care treatment was estimated by sampling from binomial distributions representing the number of cases among all individuals reporting ILI (for the FluSurvey database) or confirmed pandemic influenza (for the Regional Microbiology Network (RMN) database). This was multiplied by similar binomial samples representing uncertainty in the age and risk group breakdown of cases.

2.3.4. Hospitalisations

The age-specific hospitalisation rate was estimated using information collected by the Regional Influenza Centre via the FluZone database during the containment phase of the epidemic. Out of the 7564 people with confirmed swine flu 129 were hospitalised. Risk group specific rates were estimated using the distribution of hospitalised cases in a study of laboratory-confirmed pandemic influenza cases admitted to hospitals, reported through the Regional Microbiology Network (RMN). Data were available for 456 patients of whom 203 were in a risk group. Empirical distributions were used for sampling since the long tail made fitting to standard parameterised distributions (gamma or lognormal) difficult. Distributions were adjusted for age and risk group according to the ratios in the data set. The proportions of risk group and non-risk group patients admitted to intensive care, paediatric intensive care and intensive treatment units were also recorded. No cases were recorded as being admitted to high dependency units.

2.3.5. Deaths

The case-fatality ratio was estimated using two methods. First, we used the likely number of deaths due to H1N1v in two Southern Hemisphere countries (Australia and New Zealand), where the pandemic wave is believed to be largely ended [13]. Data from other Southern Hemisphere countries were not used since they were either extremely small (French Polynesia, New Caledonia) or were in different income levels from the UK as defined by the World Bank. This number was then inflated by the ratio of the population size to the size of the UK population, and divided by the total number of H1N1v cases predicted by real-time modelling. Second, the cumulative number of confirmed deaths due to pandemic influenza on 16 September was divided by the estimate of the cumulative number of symptomatic pandemic influenza cases on 16 September [3]. As a form of sensitivity analysis, the ratio was recalculated after assuming that deaths occurred several weeks after the case was assumed to have occurred, as highlighted in a previous estimate of the case-fatality ratio of H1N1v [14]. Four scenarios (instantaneous deaths, one week after case, two weeks after case, and three weeks after case) gave very similar case-fatality due to the slow rate of growth in cumulative cases after mid-August. The mean of the three estimates (one each using Australian, New Zealand and UK data) was thus obtained. The overall rate was then combined with a risk and age group dependent multiplier which was calculated using data from 59 of the 66 reported deaths with risk group information. The estimated mortality rate was assumed to have a normally distributed error term, with standard error calculated from the three estimates used to estimate the mean. Uncertainty around age and risk group information was estimated from sampled binomial distributions representing the number of individuals in particular groups among the 59 reported deaths with risk group information.

The differential life-expectancy for those in influenza risk groups was calculated from the MSGP4 survey of 500,000 individuals in general practices in England and Wales [15], using a previous analysis used to estimate the benefit of pneumococcal vaccination [16]. This assumes that those who did not consult over the period of the study (1 year) for any of the risk conditions were not in the risk group, and that the relative mortality risk has not changed since 1991–1992 (even though overall life-expectancy has improved). The resulting age group specific relative risk (compared to the general population) was multiplied by the current (2008) age-specific risk of death to calculate the age- and risk group specific life-expectancy. Pregnant women were assumed to have the same life-expectancy as the low-risk group. The age and risk group specific discounted life-expectancy was used to estimate the (discounted) life-years lost per case. Life-expectancy was assumed to be higher for those in the low-risk group.

2.3.6. QALY loss

To estimate the health related quality of life loss from non-fatal cases of H1N1v, we contacted individuals with confirmed H1N1v infection in the first and second week of June. These individuals were identified using an electronic reporting system of suspected H1N1v cases, which contained information on all detected and confirmed, rejected and presumed cases outside London and the West Midlands for the first two and a half months of the pandemic (the survey was not conducted among individuals from London and the West Midlands) [17]. Only cases that had occurred in the previous eight days were sent the questionnaire, to minimise recall bias. Confirmed H1N1 cases and controls (investigated for ILI, but found not to have H1N1v) were sent a questionnaire about their age, pre-existing risk conditions and the symptoms of their recent illness. In addition they were asked to complete the EQ-5D questionnaire (a generic health status instrument) [18] for the worst day of illness and for the day of receipt of the questionnaire. They were followed up two weeks later to obtain baseline data (i.e. their health status after recovery), as well as data on the duration of symptoms. Children (11 years or over) received a child-friendly version of the questionnaire (using slightly modified language). Parents or guardians were asked to fill out the questionnaire on behalf of younger children. A total of 647 questionnaires were sent

out and 288 (45%) returned. The results suggested that the mean QALY loss per episode in children was 0.0074 (SD = 0.00085) and 0.0082 (SD = 0.00081) in adults. Although the differences were not significant we used these differential age-based QALY losses in the later analysis. A QALY loss of 0.008 is equivalent to losing 2.9 days of full health. We assumed that this QALY loss described cases not requiring hospital treatment. For hospitalised cases we assumed a QALY loss 2.17 times greater, based on the ratio of QALY loss between hospitalised and uncomplicated influenza cases used in a previous economic evaluation of interventions during an influenza pandemic [19].

2.3.7. Costs

Unit costs of a clinic and telephone consultations, hospitalisations, stays on intensive care and antivirals were taken from standard or published sources. The cost of an NPFS telephone consultation was assumed to be equal to that of an NHS Direct consultation [20]. Internet-based consultations are assumed to be free (that is the sunk costs of setting up the NPFS website are ignored). In the base case, the cost of the vaccines is also assumed to be sunk. This is because the vaccines were ordered at the start of the pandemic and the cost of the vaccines cannot be readily recovered. Delivery costs of £5.25 per dose are assumed [21]. Transport and other costs are assumed to be small, and are ignored. The costs of the vaccine are varied in the sensitivity analysis. Unit costs and their sources are given in Table 1.

2.4. Vaccination assumptions

In the base case, a two dose strategy for children under 10 years old and one dose for all others was assumed, based on advice by the Joint Committee on Vaccination and Immunisation (JCVI) [22]. The efficacy of Pandemrix® (the main H1N1v vaccine used in the United Kingdom) against clinical endpoints has yet to be determined, although it short-term safety and immunogenicity has been established in clinical trials [23]. Seasonal influenza vaccines have been found to have a clinical efficacy of over 70% [24], and Pandemrix®, whose trials have demonstrated very good serological responses in adults, may be expected to have better clinical efficacy due to its novel adjuvant. Hence we investigated two scenarios for clinical efficacy in individuals 10 years and over: a base case scenario with single dose clinical efficacy of 70%, and a more optimistic scenario with efficacy of 85%. For children under 10 years old, only half the usual adult dose is given, so we assumed 35% efficacy after a first dose and 70% after a second dose (or 42.5% and 85% for the optimistic scenario). We also investigated the possibility that a single half-dose of vaccine in these children would provide the same efficacy as in older individuals (70% or 85%). In these scenarios, it was assumed that these children would only be given a single vaccine dose. Vaccine uptake was assumed to be 70% in risk groups and 40% in other groups.

The schedule over which doses are expected to be procured puts constraints on the vaccination programmes that can be implemented over the autumn. It was assumed that high-risk groups are vaccinated first (as decided by the JCVI in August [1]), and that the first dose of the vaccine is delivered between October 26 and November 8 [2]. Children under 10 years old were assumed to receive the vaccine 3 weeks after the first dose. We then explored the possibility of extending vaccination to low-risk groups in any of four age categories (6 months – 4 year olds, 5–14 year olds, 6 months – 14 year olds and 65+ year olds). In the base case, it was assumed that vaccination of low-risk groups would begin on November 16, that it would take two weeks for the first dose to be given and that children under 10 years would receive the second dose after 3 weeks. We also explored the effect of delays in vaccinating the low-risk groups.

Since there are likely to be large operational constraints to vaccinating significant numbers of individuals in a very short space of time, we assume that these strategies are mutually exclusive: that is, vaccination can be extended to one of these low-risk groups. We ignore policies involving vaccination of low-risk adults aged 15–64 years old, since they would have to wait until the epidemic was largely over before sufficient doses would be available to start vaccinating.

2.5. Sensitivity analyses

Parametric sensitivity analyses were conducted in order to quantify the impact of uncertainty around parameters governing the incidence of different levels of severity of illness, costs and quality of life weights. These were sampled across the distributions given in Table 1. For each of the 600 accepted realisations from the epidemic model 20 simulations were produced, sampling randomly over the parameter space in the economic model, to give a total of 12,000 samples. Hence the sensitivity analyses incorporated uncertainty in both epidemiological and economic parameters. The number of simulations performed represented a compromise between computational effort and validity of findings. The results of the base case model were checked using a larger sample (120,000 simulations) and were found to be very similar to those shown (data available on request).

Regression analysis was used to assess the key drivers of the cost-effectiveness results. Variables that were found to be multicollinear with other variables were excluded. The influence of each non-multicollinear variable on cost-effectiveness was shown as a tornado graph. A net benefit approach was used by assuming that the marginal societal willingness to pay for a QALY gained was £20,000. This approach was taken to ensure that the error terms were well behaved.

3. Results

Fig. 1(e) shows the estimated impact of the different vaccination programmes on number of infections during the second wave of the H1N1 epidemic. The impact of vaccination is attenuated by the fact that vaccination can only occur late in the epidemic. Table 2 shows the estimated number of cases and deaths prevented, QALYs gained and treatment costs averted for the different vaccination strategies, compared with the no vaccination alternative. Vaccination of the high-risk groups is estimated to avert about 45 deaths (80% credibility interval 26–67), and save 2910 QALYs (80% credibility interval 1579–4471). Extending vaccination from the risk groups to low-risk individuals is estimated to have a modest impact on deaths averted as few deaths occur in the low-risk individuals, and vaccination is assumed to start later in these groups. The impact on cases is greater, particularly if vaccination is extended to low-risk school children.

Fig. 2 shows the range of values for the incremental cost-effectiveness ratios for the different strategies across all realisations of the model. Each realisation of the model is a single set of model parameter values sampled over the entire distribution of possible values that they can take. The horizontal lines represent £20,000 and £30,000 per QALY gained, the thresholds used by the National Institute for Health and Clinical Excellence as a guide to determine if a policy is cost-effective [8]. Hence realisations below the two thresholds are likely to be deemed cost-effective, realisations above the thresholds are unlikely to be deemed cost-effective, and there is less certainty about decisions regarding realisations located between both thresholds.

The largest incremental benefit is obtained by vaccinating risk groups compared to not vaccinating anybody. Such a strategy is

Table 1
List of parameters used in the model as well as distributions representing uncertainty around them used in sensitivity analysis.

Parameter	Estimate	Uncertainty distribution	Source
Vaccination parameters			
Days between vaccination and vaccine protection	14	Triangular on [7, 21]	Assumption
Incidence and risk estimates			
Proportion of infected cases with symptoms	0.37	Triangular on [0.25, 0.51]	Review of volunteer studies [10]
Proportion of ILI cases calling GP			FluSurvey [12]
Low-risk 0–14 years	0.35	Bootstrap sample from binomial (np = 26, n = 74)	
Low-risk 15–64 years	0.29	Bootstrap sample from binomial (np = 285, n = 969)	
Low-risk 65+ years	0.28	Bootstrap sample from binomial (np = 30, n = 107)	
High-risk 0–14 years	0.13	Bootstrap sample from binomial (np = 2, n = 16)	
High-risk 15–64 years	0.36	Bootstrap sample from binomial (np = 124, n = 343)	
High-risk 65+ years	0.22	Bootstrap sample from binomial (np = 9, n = 42)	
Proportion of ILI cases visiting GP			FluSurvey [12]
Low-risk 0–14 years	0.11	Bootstrap sample from binomial (np = 8, n = 74)	
Low-risk 15–64 years	0.08	Bootstrap sample from binomial (np = 74, n = 969)	
Low-risk 65+ years	0.06	Bootstrap sample from binomial (np = 7, n = 107)	
High-risk 0–14 years	0.12	Bootstrap sample from binomial (np = 2, n = 16)	
High-risk 15–64 years	0.13	Bootstrap sample from binomial (np = 45, n = 343)	
High-risk 65+ years	0.21	Bootstrap sample from binomial (np = 9, n = 42)	
Proportion of ILI cases calling NPFS			NPFS [11]
Low-risk 0–14 years	0.12	Data-derived; 95% interval [0.09,0.17]	
Low-risk 15–24 years	0.16	Data-derived; 95% interval [0.11,0.22]	
Low-risk 25–44 years	0.11	Data-derived; 95% interval [0.08,0.16]	
Low-risk 45–64 years	0.07	Data-derived; 95% interval [0.04,0.10]	
Low-risk 65+ years	0.02	Data-derived; 95% interval [0.00,0.07]	
High-risk 0–14 years	0.26	Data-derived; 95% interval [0.18,0.36]	
High-risk 15–24 years	0.09	Data-derived; 95% interval [0.06,0.12]	
High-risk 25–44 years	0.07	Data-derived; 95% interval [0.05,0.09]	
High-risk 45–64 years	0.11	Data-derived; 95% interval [0.07,0.16]	
High-risk 65+ years	0.01	Data-derived; 95% interval [0.00,0.04]	
Proportion of ILI cases calling NPFS			NPFS [11]
<1 years	0.32	Bootstrap sample from binomial (np = 682, n = 2134)	
1–4 years	0.65	Bootstrap sample from binomial (np = 13970, n = 21642)	
5–14 years	0.64	Bootstrap sample from binomial (np = 30734, n = 48116)	
15–24 years	0.53	Bootstrap sample from binomial (np = 47620, n = 89207)	
25–44 years	0.50	Bootstrap sample from binomial (np = 72162, n = 143619)	
45–64 years	0.59	Bootstrap sample from binomial (np = 36380, n = 61344)	
65+ years	0.80	Bootstrap sample from binomial (np = 10522, n = 13088)	
Proportion of ILI cases admitted to hospital			RMN, FluZone
Low-risk 0–4 years	41.8 per 1000	Bootstrap sample from binomial (np = 64, n = 82) × binomial (np = 21, n = 414)	
Low-risk 5–14 years	5.6 per 1000	Bootstrap sample from binomial (np = 55, n = 91) × binomial (np = 31, n = 3514)	
Low-risk 15–64 years	11.5 per 1000	Bootstrap sample from binomial (np = 132, n = 260) × binomial (np = 69, n = 3585)	
Low-risk 65+ years	24.4 per 1000	Bootstrap sample from binomial (np = 2, n = 23) × binomial (np = 8, n = 51)	
High-risk 0–4 years	214.4 per 1000	Bootstrap sample from binomial (np = 18, n = 82) × binomial (np = 21, n = 414)	
High-risk 5–14 years	67.1 per 1000	Bootstrap sample from binomial (np = 36, n = 91) × binomial (np = 31, n = 3514)	
High-risk 15–64 years	63.2 per 1000	Bootstrap sample from binomial (np = 128, n = 260) × binomial (np = 69, n = 3585)	
High-risk 65+ years	324.8 per 1000	Bootstrap sample from binomial (np = 21, n = 23) × binomial (np = 8, n = 51)	
Proportion of hospitalised cases requiring intensive care			
Low-risk	41.4 per 1000	Bootstrap sample from binomial (np = 6, n = 145)	
High-risk	70.0 per 1000	Bootstrap sample from binomial (np = 7, n = 100)	
Case-fatality ratio	0.112 per 1000	Normal (μ = 0.112/1000, σ = 0.0121/1000)	Pandemic influenza death register, Southern Hemisphere countries [13]
Proportion of deaths by age and risk group			Pandemic influenza death register
Low-risk 0–14 years	0.039	Bootstrap sample from binomial (np = 2, n = 51)	
Low-risk 15–64 years	0.098	Bootstrap sample from binomial (np = 5, n = 51)	
Low-risk 65+ years	0.020	Bootstrap sample from binomial (np = 1, n = 51)	
High-risk 0–14 years	0.20	Bootstrap sample from binomial (np = 10, n = 51)	
High-risk 15–64 years	0.67	Bootstrap sample from binomial (np = 34, n = 51)	
High-risk 65+ years	0.14	Bootstrap sample from binomial (np = 7, n = 51)	
Costs			
GP telephone consultation	£22	None	Costs of Health and Social Care [9]
GP clinic consultation	£37	Lognormal (normal μ 37, normal σ 8.4)	
NPFS call	£17		Harris et al. [20]
Antiviral (oseltamivir) course including delivery	£16		British National Formulary [31]
Hospital admission	£840	Lognormal (normal μ 839, normal σ 192.1)	
Intensive care (0–14 years)	£1600	Triangular (vertices 1197, 1680, 1900)	NHS Reference costs [18]

Table 1 (*Continued*)

Parameter	Estimate	Uncertainty distribution	Source
Intensive care (15–65 years)	£1400	Triangular (vertices 1192, 1410, 1607)	NHS Reference costs [18]
Vaccine (per dose)	£10	None	Assumption
Vaccine delivery costs	£5.25	None	Department of Health [21]
Utilities			
QALY loss for non-hospitalised children	0.0074	Normal (μ 0.0074, σ 0.00085)	EQ-5D study
QALY loss or non-hospitalised adults	0.0082	Normal (μ 0.0082, σ 0.0018)	EQ-5D study
QALY loss for hospitalised children	0.016	Normal (μ 0.016, σ 0.00082)	Siddiqui and Edmunds [19]
QALY loss for hospitalised adults	0.018	Normal (μ 0.018, σ 0.0018)	Siddiqui and Edmunds [19]

Table 2
The estimated number of cases and deaths prevented, QALYs gained and treatment costs averted for the different strategies, instead of no vaccination, for base case assumptions[†].

Groups to vaccinate	Only risk groups	Risk groups and 0–4 year olds	Risk groups and 5–14 year olds	Risk groups and 65+ year olds	Risk groups and 0–14 year olds	Risk groups and 0–14 and 65+ year olds
Number of cases prevented						
Mean	452,990	486,532	558,168	458,954	573,355	576,503
Median	422,175	448,900	511,930	427,119	524,127	526,817
10th centile	234,274	243,375	267,800	236,046	272,628	273,636
90th centile	710,252	777,693	908,364	721,682	938,357	944,056
Number of deaths prevented						
Mean	45	46	48	45	48	49
Median	43	44	46	43	46	46
10th centile	26	26	27	26	27	27
90th centile	67	68	72	67	73	73
Number of hospital admissions prevented						
Mean	10,386	10,808	11,398	10,460	11,604	11,645
Median	9,569	9,927	10,456	9,629	10,631	10,662
10th centile	5,225	5,349	5,565	5,246	5,627	5,640
90th centile	16,547	17,377	18,430	16,688	18,830	18,911
Total QALYs saved						
Mean	2,910	3,065	3,396	2,938	3,466	3,481
Median	2,733	2,855	3,147	2,757	3,202	3,215
10th centile	1,579	1,619	1,732	1,587	1,753	1,757
90th centile	4,471	4,779	5,380	4,526	5,517	5,546
Treatment costs avoided (£m)						
Mean	13.4	14.0	15.1	13.5	15.4	15.5
Median	12.3	12.8	13.8	12.4	14.0	14.1
10th centile	6.7	6.9	7.2	6.7	7.3	7.3
90th centile	21.5	22.7	24.7	21.7	25.2	25.3

[†] Vaccine efficacy of 70% after 1 dose in ≥10 s and 2 doses in <10 s, vaccine efficacy of 35% after 1 dose in <10 s, no vaccine purchase costs (administration cost of £5.25 only), 70% vaccine coverage in high-risk groups, 40% vaccine coverage in low-risk groups and vaccination of low-risk groups beginning on November 16.

also very likely to be cost-effective, since most model realisations lie below the £20,000 per QALY gained threshold. Extending vaccination to low-risk groups as well is relatively less costly than vaccinating high-risk groups, partly because uptake among these groups is assumed to be lower. However, such strategies also achieve lower incremental benefits, and are less likely to be cost-effective. Of the strategies involving extending vaccination beyond high-risk individuals, extending vaccination to the low-risk adults over 64 years appears least likely to be cost-effective. Vaccinating either 0–4 year olds or 5–14 year olds appears to be more cost-effective than vaccinating older adults, with vaccinating 5–14 year olds having a more attractive cost-effectiveness profile. Choosing to vaccinate all children under 15 year old would prevent more cases than vaccinating 5–14 year olds only, but would be less cost-effective because many of the 0–4 year olds would be protected due to herd immunity as a consequence of vaccinating older children.

Table 3 shows the effect of varying key assumptions in the model around the size of the epidemic, effectiveness of vaccination, speed of vaccine roll out and likely vaccine uptake. The proportion of model realisations that are cost-effective are shown for two strategies. The first is vaccination of high-risk groups only compared to no vaccination. The table shows that vaccinating high-risk individuals remains almost certain to be cost-effective across most changes in assumptions. Only if vaccine cost is not treated as a sunk cost is the cost-effectiveness profile of this strategy affected. Even so, with an assumed cost per vaccine dose of £10 (seasonal influenza vaccines cost about £6 per dose), vaccinating risk groups may still be cost-effective at a threshold of £30,000 per QALYs gained. Since this strategy is almost always cost-effective, we also show the cost-effectiveness of extending vaccination to the next most cost-effective group to vaccinate. This is always low-risk children from 5 to 14. This strategy is more sensitive to model assumptions. In particular, delays in the programme by just a few weeks are likely to cause a large part of the benefit of vaccination to be lost, and hence the strategy to be deemed not cost-effective. Extending vaccination from this group to children under 5 or adults over 64 is highly unlikely to be cost-effective across all the scenarios considered (not shown in the table).

Fig. 3 is a tornado diagram that shows the most influential parameters driving the cost-effectiveness of vaccinating high-risk individuals, as well as the effect of varying them across their likely range. The most influential parameter is the overall size of the epidemic without vaccination (which is a measure of the uncertainty within the epidemiological model). Other key parameters for cost-effectiveness are the QALY loss per case, hospitalisation rates and costs, and case-fatality ratios.

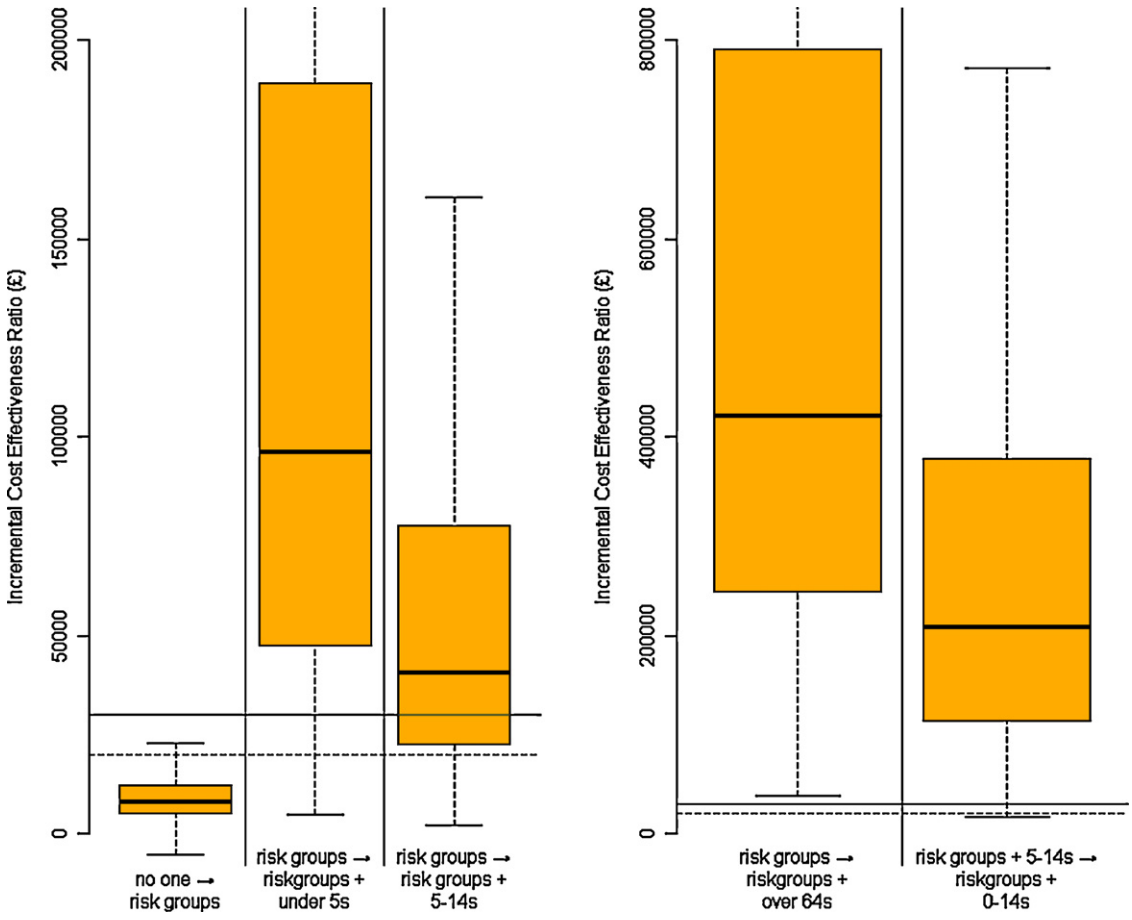

Fig. 2. Incremental cost-effectiveness ratio of the base case model across different realisations of the model, assuming £5.25 administration costs per dose of vaccine. Vaccination high-risk individuals only is compared to no vaccination, while low-risk group vaccination strategies are compared to vaccinating risk groups only. Horizontal dotted and straight lines respectively show the £20,000 and £30,000 per QALY thresholds used by NICE for decision making. Note the change in scale on the right-hand panel.

Table 3
Proportion of model realisations that indicate that either (i) vaccinating risk groups or (ii) extending vaccination from risk groups to low-risk 5–14 year old children, is likely to be cost-effective, when model assumptions are altered.

Threshold (£ per QALY gained)	Proportion of model realisations deemed cost-effective			
	No one → Risk groups		Risk groups → Risk groups + 5–14 s	
	£20,000	£30,000	£20,000	£30,000
Base case[†]	93%	98%	20%	37%
Vaccinating low-risk groups begins on November 23 (1 week delay)	93%	99%	7%	16%
Vaccinating low-risk groups begins on November 30 (2 week delay)	93%	99%	2%	6%
Vaccinating low-risk groups begins on December 7 (3 week delay)	93%	99%	0%	2%
Vaccinating low-risk groups begins on December 14 (4 week delay)	93%	98%	0%	0%
50% vaccine coverage in high-risk groups	81%	94%	31%	48%
20% vaccine coverage in low-risk groups	93%	98%	5%	15%
Vaccine efficacy of 85% after 1 dose in ≥10 s, 2 doses in <10 s	96%	100%	18%	34%
Vaccine efficacy of 70% after 1 dose in all (no second dose given)	95%	99%	45%	61%
Vaccine efficacy of 85% after 1 dose in all (no second dose given)	95%	99%	41%	57%
Cost of vaccine £10 per dose + £5.25 administration cost	15%	43%	0%	1%
Lower first wave incidence	96%	100%	34%	51%
Higher first wave incidence	91%	98%	19%	35%

[†] Vaccine efficacy of 70% after 1 dose in ≥10 s and 2 doses in <10 s, vaccine efficacy of 35% after 1 dose in <10 s, no vaccine purchase costs (administration cost of £5.25 only), 70% vaccine coverage in high-risk groups, 40% vaccine coverage in low-risk groups and vaccination of low-risk groups beginning on November 16.

4. Discussion

The model suggests that a significant fraction of individuals were infected in the first wave of the epidemic, and that the peak height of the autumn wave is likely to be similar to that observed in summer (subsequent data confirmed this model prediction, see Appendix B). As the risk of serious consequences following infection is much higher in the risk groups, it appears that vaccinating these groups is likely to be effective at reducing deaths and cost-effective, when compared to widely used norms. Extending vaccination to low-risk groups is likely to be much less effective at reducing deaths and QALYs lost, partly because of the lower risk in these individuals, and partly because the programmes must start later in the epidemic, to allow for stocks of vaccine to become available. Furthermore, the effect and cost-effectiveness of such an extension is highly dependent on its timing.

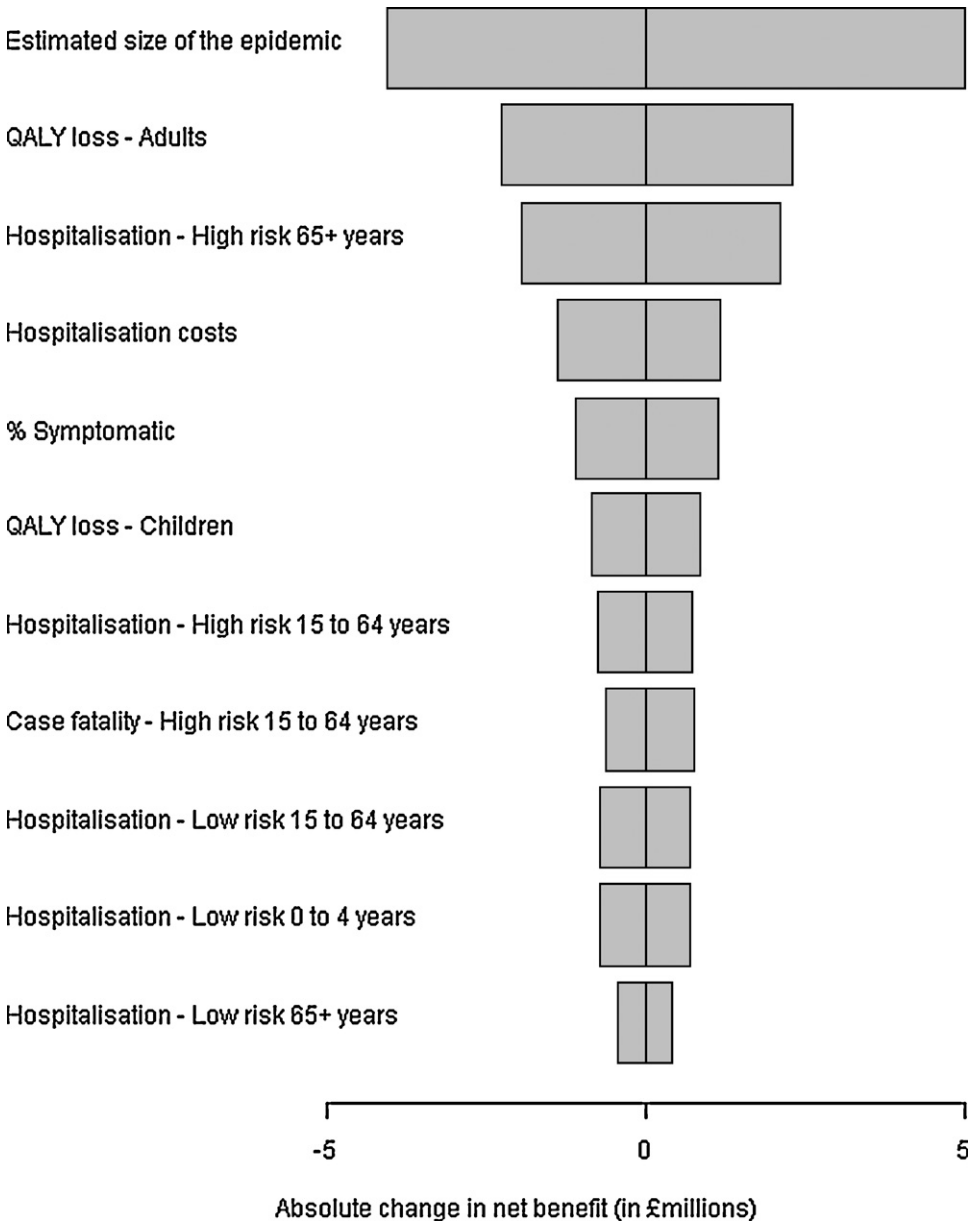

Fig. 3. Tornado diagram showing the influence of the most important parameters on the incremental cost-effectiveness ratio of vaccinating high-risk groups. Each bar shows the change in the ratio from its baseline figure of £19,600 when each variable is varied between its 25% and 75% endpoints.

The main strength of the paper is that the epidemiological model is fitted to the data, well describing the particular double-peaked epidemic observed in England. This represents a significant advance over previous assessments of H1N1v vaccination policy [e.g. 25,26], as the model is specifically fitted to the emerging epidemic data in real-time, which should greatly improve the validity of the projections and findings. As the model well describes the unfolding epidemic, it provides a sound basis for estimating future infections as well as an assessment of the uncertainty around these predictions. We have combined this information with economic and health outcome data (including a bespoke study of the impact of H1N1v on health related quality of life) to estimate the potential impact and cost-effectiveness of vaccination options. Importantly, our key finding that vaccination of the high-risk groups is probably both effective and cost-effective, is robust to uncertainty in epidemiological, outcome and economic parameters.

The model used was relatively simple. The model was a deterministic mass-action type transmission dynamic model with no spatial structure assumed. The model had to be transmission dynamic in nature in order to assess the impact of vaccinating the key transmitters (children) and compare this to other strategies (such as vaccinating the elderly or risk groups). It was also clearly necessary to structure the model by age and risk group. No further stratifications were necessary to evaluate the policy options, and it was thus the simplest model that could be chosen. Its simplicity enabled the model to be fitted in real-time. Fitting a stochastic, individual based model, for instance, would have been far more computational demanding, with no additional benefit for policy evaluation.

The model provides an estimate of the underlying number of individuals infected in the population and how this changed over time. By comparing this with the estimated case numbers we could derive a multiplication factor (which we estimated to be 10 times). This is partly because we are comparing estimated infections (some of which would be subclinical) with estimated clinical cases. It is possible that this factor could have changed over time. However,

in order to estimate changes in this factor, it would have been necessary to have data on changing health seeking behaviours and/or changes in the sero-incidence over time. These data were not available in sufficiently large samples sizes to infer whether this ratio was changing over time. A constant ratio also fitted the data very well (Fig. 1), and was therefore used.

One weakness is the lack of information on key parameters surrounding vaccination. For example, vaccine efficacy data used for licensing were based on H5N1 strains instead of H1N1v strains, and only provided immunogenicity rather than efficacy endpoints. Clinical trials of actual H1N1v vaccines are underway, but again these will only provide immunogenicity endpoints in the short-term. Consequently we based our assumptions about vaccine efficacy on experience with seasonal influenza vaccines. It is quite possible that H1N1v vaccines will have better efficacy than this. If this is the case, scenario analyses suggest that vaccinating low-risk children will be substantially more cost-effective than our base case indicates. In addition, it is possible that the vaccines will have differential impacts against infection and clinical disease. In the absence of any data on the action of the vaccine, we have taken the simplest assumptions – that it provides complete protection in those that respond.

There is also considerable uncertainty in the level of vaccine uptake in different age and risk groups. We assumed that 70% of the risk groups would accept vaccination, on the basis of a targeted vaccination programme being aimed at them early in the second wave of the epidemic. There is no experience of vaccinating low-risk groups routinely in the UK (except for the low-risk elderly), and recent attitudinal surveys in other countries suggest that uptake is likely to be low in these groups [27,28]. It is unavoidable that there will be these gaps in our knowledge, since we are evaluating new vaccines aimed at a novel infection, and no similar vaccination programme has been attempted in the past. In the time since submission of this paper, it seems that the coverage in the high-risk group has been lower than anticipated here, and it has taken longer to vaccinate them. The impact on the incidence of disease will therefore be lower than anticipated here (see Appendix B for an updated analysis) and the cost-effectiveness of the high-risk strategy will be lower than is presented in the results.

Lastly, there is uncertainty about the long-term benefit of vaccination. We have assumed that benefits of vaccination only last for the duration of pandemic (assumed to be from June 1 2009 to May 31 2010). However, it is likely that H1N1v will be one of the circulating seasonal strains in 2010 [29], albeit with some antigenic drift, and it is possible that the adjuvanted vaccine will provide some degree of protection a year or more after vaccination [30]. If this is the case, then the benefit of vaccinating even in December 2009 would be greater than our model currently suggests

Vaccinating school children is the most cost-effective option after vaccination of high-risk individuals. Such an option is far more cost-effective if the vaccines can be made available by mid-November, but by mid-December would have little effect and is almost certainly not cost-effective. Such a rapid roll out of sufficient doses of vaccine may be difficult for operational reasons, since such an extension can only begin when high-risk individuals have been vaccinated. This suggests that vaccine uptake in high-risk groups needs to be closely monitored. Once this appears to have saturated, making any remaining doses available to low-risk groups as promptly as possible could be beneficial. Such a move would benefit high-risk groups as well, since they would be indirectly protected through herd immunity.

Decisions on how to control a novel infection in a rapidly evolving situation necessarily have to be made on the basis of incomplete information. In particular, the long manufacturing lead-time means that decisions about ordering vaccines had to be made before detailed information on the severity of this strain were available. As information has become available decisions about how to use this stockpile can be refined. Mathematical and economic models are well suited to this task as they synthesise information from different sources and provide projections under different scenarios. The modelling work presented here has highlighted that England had a much larger epidemic in the summer than was previously thought, and that the second wave will be of a similar size. This means that vaccination of children and other low-risk groups during the latter part of the autumn is likely to have a modest impact. This is not necessarily the case elsewhere, where the epidemic is not so far advanced. Similar, detailed, real-time modelling and economic studies could help to clarify the situation in other countries.

Competing interest

WJE's partner works for GlaxoSmithKline and therefore he declares a possible competing interest. He has no other competing interests. All other authors declare that the answer to the questions on your competing interest form are all No and therefore have nothing to declare.

Acknowledgements

We thank Elizabeth Miller for many helpful discussions, Elizabeth Miller, Pauline Kaye and Rashmi Malkani for providing data from the follow up of cases confirmed by the HPA Regional Microbiology Network (RMN); Elizabeth Miller, Katja Hoschler, Pia Hardelid and Elaine Stanford for data on the H1N1v serological survey; Shirley Cole, Anthony Underwood and other members of the HPA Immunisation, Hepatitis & Blood Safety Department for contributing to the EQ-5D study; the EU FP7 EPIWORK grant 231807 for the flusurvey data; Alessia Melegaro for data about the mortality in risk groups; Ruth Chapman for analysing data on laboratory-confirmed hospitalisations; Andre Charlett for estimates of the number of pandemic influenza cases; Guy Walker for useful discussions and analysis around imputing Southern Hemisphere data to estimate influenza mortality rates and Peter Grove for data on the size of risk groups for vaccination.

Financial support for this study was provided by a grant from the Policy Research Programme of the Department of Health, England (reference number DOH 039/0031). PJW thanks the MRC. The authors' work was independent of the funders, who had no role in the study design, analysis of data, writing of the manuscript or decision to submit for publication.

Appendix A.

A.1. Epidemiological model (1): transmission

An age and risk group structured deterministic transmission dynamic model was used to estimate the impact of vaccination. The model has a modified SEIR (susceptible-exposed-infected-recovered) structure. The population is split into seven age groups (<1, 1–4, 5–14, 15–24, 25–44, 45–64, 65+) and three clinical groups (those in a seasonal influenza risk group (excluding the low-risk elderly), pregnant women, and those who are not in a risk group) with random mixing (within an age group) between the clinical groups. The size of these groups is given in Table A1. To allow the latent and infectious periods to be gamma-distributed, we assume that there are two classes of each (hence SEEIIR structure), with the same rate of loss of latency (γ_1) and infectiousness (γ_2) in both groups. Hence the average latent period is $2/\gamma_1$ and average infectious period $2/\gamma_2$. The equations are as follows (in which time

Table A1
Estimated population size by age and risk group. Based on ONS estimate from England mid 2008 and HPA estimates of the size of the risk groups.

Age	Population England	Non-risk groups	Risk groups	Pregnant women
0	667,600	633,080	34,520	–
1–4	2,461,800	2,334,505	127,295	–
5–14	5,904,100	5,598,811	305,289	–
15–24	6,862,500	5,804,137	930,514	127,849
25–44	14,417,400	12,042,866	1,997,843	376,691
45–64	12,847,800	11,147,800	1,700,000	–
65+	8,285,200	4,785,200	3,500,000	–
Total	51,446,400	42,346,400	8,595,460	504,540

dependencies have been dropped for clarity):

$$\begin{cases} \dfrac{dS_{ik}}{dt} = -\lambda_i S_{ik} - \displaystyle\sum_{p=1}^{z} v_{ikp} S_{ik} \\ \dfrac{dE^1_{ik}}{dt} = \lambda_i S_{ik} - \gamma_1 E^1_{ik} \\ \dfrac{dE^2_{ik}}{dt} = \gamma_1 (E^1_{ik} - E^2_{ik}) \\ \dfrac{dE^1_{ik}}{dt} = \gamma_1 E^2_{ik} - \gamma_2 I^2_{ik} \\ \dfrac{dE^2_{ik}}{dt} = \gamma_1 E^1_{ik} - \gamma_2 I^2_{ik} \\ \dfrac{dR_{ik}}{dt} = \gamma_2 I^2_{ik} + \displaystyle\sum_{p=1}^{2} v_{ikp} S_{ik} \end{cases}$$

where S_{ik} represents the number of susceptibles of age group i and risk group k, E^1_{ik} and E^2_{ik} represent exposed, but not yet infectious individuals, I^1_{ij} and I^2_{ij} represent infectious individuals, R_{ik} represents immune individuals of age class i and risk group k, and λ_i is the age group specific force of infection, given by:

$$\lambda_i = \sigma_i \sum_{j=1}^{7} \sum_{k=1}^{3} \beta_{i,j} (I^1_{jk} + I^2_{jk})$$

where β_{ij} is the rate at which individuals in age group i make effective contact with those in age group j and σ_i is the susceptibility of age group i; v_{ikp} is the rate of immunisation of risk group k in age group i under programme p (see details below).

We assume that at the outset of the widespread epidemic (1st June) a small fraction of individuals in each age class are infectious, and the remainder are susceptible. However, not everyone is equally susceptible. We assume that older individuals have a lower susceptibility based on recent sero-epidemiological analyses. Thus the incidence $Z_{ik}(n)$ of infection in individuals in age group i and risk group k at day n is:

$$Z_{ik}(n) = \int_{n-0.5}^{n+0.5} \gamma_1 E^2_{ik} dt$$

where $Z_{ik}(n)$ is the incidence among age group i and risk group k at day n.

A.2. Epidemiological model (2): vaccination

We assume that natural infection results in permanent immunity (within the time scale of the model). We further assume that a fraction of individuals who are vaccinated respond and become permanently immune to infection and therefore disease, the non-responders remain susceptible to infection and disease. We assume that vaccination will be rolled out beginning in the autumn of 2009.

The translation of vaccination to protection is modelled by taking into account both the delay resulting from the spread of uptake (by default two weeks but a four week long uptake is considered in the sensitivity analysis) and the delay taken by an individual to acquire protection once vaccinated. The uptake is modelled by a uniform spread between t^{start}_{ikp} and t^{end}_{ikp} with density $1/(t^{\text{end}}_{ikp} - t^{\text{start}}_{ikp})$ and protection by a triangular distribution starting after one week, peaking at two weeks and ending after three weeks. The rate v_{ikp} at which vaccinated individuals pass from S (susceptible) to R (immune) on following the start of the vaccination programme is given by the convolution product of the two functions multiplied by the coverage and efficacy in the age and risk group. Fig. A1 show profiles for an uptake of 2 weeks (base case) and 4 weeks.

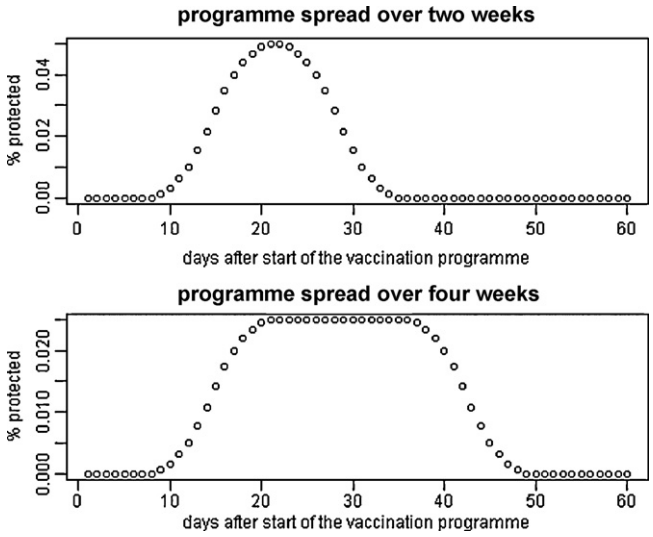

Fig. A1. Profiles of the rates at which susceptibles get protected (moving from the susceptible to the immune class) after the start of the vaccination programme as a result of both the spread of uptake and time to achieve immunity.

Under the base case of the model, children are vaccinated through two dose programmes, while adults are immunised following one dose, $v_{ik2} = 0$ for $i > 3$, for age group 3 (5–14 year old), the efficacy had to be reworked to match the recommendation by JCVI to give one dose for children older than 9 years.

A.3. Parameterisation

In order to estimate plausible epidemiological scenarios for a second wave, we fit the model to HPA estimates of the weekly number of H1N1v cases allowing key unknown epidemiological parameters to vary. Those combinations of parameters that gave an adequate fit to the observed data were retained and used to simulate the future incidence of infection and disease with different vaccination programmes in place (see below). The model was run for 12 months.

The epidemiological model was fitted to the central HPA estimate of the weekly number of H1N1v cases by age group from June 1st to October 18th 2009 using maximum likelihood.

Age-specific contact rates from the Great British arm of the POLYMOD survey (a diary-based survey of daily contacts in eight European countries) [5] were used, using data on close contacts. To account for uncertainty in the contact patterns, 10,000 bootstrap contact matrices were obtained for term-time and during holiday periods, following the method of Hens et al. [6]. Each term-time contact matrix was multiplied by a randomly selected age-specific

susceptibility profile (σ_i) and the transmission coefficient, q, to give a next generation matrix. The value of the transmission coefficient that results in a reproduction number of one (i.e. for which the eigenvalue of this resulting next generation matrix equals one) was then found. This matrix is then multiplied by the reproduction number at the beginning of the epidemic, R_{ini}, which is also sampled across a range (see below). The result is 10,000 bootstrapped next generation matrices that incorporate variation in the susceptibility profile and variation in the estimate of the reproduction number at the outset of the epidemic. Each of the term-time contact matrices is paired with one of the randomly selected bootstrapped holiday period matrices. During the summer holidays the holiday contact matrices replace the term-time ones. The date of school closure is allowed to vary uniformly from between July 17th and July 23rd. Schools all re-open on September 3rd. Other key parameters were sampled from uniform distributions (see below), and the whole model was run 60,000 times. Each of these model realisations were compared to the 20 weeks of data by minimising the Poisson deviance, which is given by:

$$DEV = 2\sum_{w=1}^{20}\sum_{i=1}^{7}(C_{wi}(\ln C_{wi} - M_{wi}) + M_{wi} - C_{wi})$$

where C_{wi} is the estimate of the number of infections in age group i week w, and M_{wi} is the model estimate of the number of infections in age group i in week w. The best-fitting 1% of the realisations were retained to simulate the effect of vaccination. Every vaccination programme evaluated was implemented on each of the retained (i.e. best-fitting) realisations to generate an estimate of the expected impact of vaccination, including epidemiological uncertainty.

The epidemiological parameters that were used and ranges over which they were sampled were:

- The initial reproduction number, R_{ini} [1–1.5]
- The latent period, $2/\gamma_1$ [0.1–2.1] days
- The infectious period, $2/\gamma_2$ [0.4–2.1] days
- The day (after June 1st) on which school holidays are assumed to result in a change in contact patterns [46–52] days
- The 10,000 susceptibility profiles were constructed by sampling uniformly from the lowest and highest proportion susceptible by age group, as determined by different microneutralisation test thresholds (dilution between 20 and 80) from HPA serological results [33].

The model tracks the total number of infections, but is fitted to data on clinical cases. In addition, initial attempts to fit the model to the data suggested that the HPA's estimated weekly number of cases may have been significantly less than the number of infections, since the slow growth rate of the epidemic in the autumn suggested that a significant number of infections had occurred over the summer, yet the cumulative number of cases reported by the HPA in, for instance, the worst-affected age group (children) was only about 1% of the size of that group. To account for the differential between the estimated number of cases and the number of infections, the weekly age-specific estimate of cases was multiplied up by a factor which we varied, and the model re-fitted to these re-scaled data. However, it was not possible to estimate both the multiplication factor and the fraction of infections symptomatic at the same time. Hence, we compared the estimate of the number of infections after taking into account the multiplication factors (which represented both potential case under-ascertainment as well as the proportion of infections that were clinically apparent) with the model estimates of the same. After fitting, the number of cases was generated by multiplying the estimated number of infections by the fraction of individuals infected with (seasonal) H1N1 that develop influenza-like illness, as estimated in a recent review [10].

Applying the multiplication factor to the data increases the deviance, so the deviance was re-scaled by dividing by the multiplication factor, so that the best-fitting multiplication factor could be estimated. In addition, a range of other summary statistics from

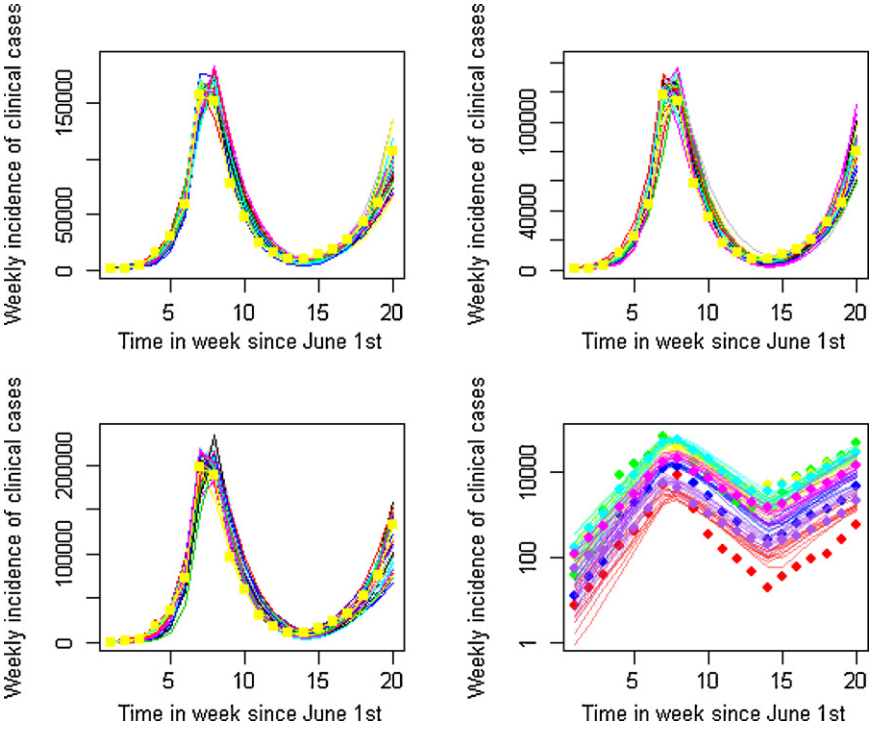

Fig. A2. Comparison of model result for 30 best-fitting realisations to re-scaled data on infections for different scaling factors (10 times, 7.5 times and 12.5 times, a–c, respectively), and comparison of the best-fitting 10 realisation to the age-specific re-scaled weekly data (using base case multiplication factor).

Table A2
Comparison of goodness of fit of model (average of best-fitting 600 runs) to a range of different indicators for a range of different multipliers to the HPA case estimates.

Multiplier	5	6	7	8	9	10	11	12	13	14	15
Initial R	1.24	1.26	1.27	1.30	1.31	1.34	1.35	1.36	1.38	1.39	1.39
First wave serological attack rate in <15 s	0.07	0.09	0.10	0.12	0.13	0.15	0.16	0.18	0.19	0.21	0.23
Recent growth rate	0.48	0.47	0.46	0.45	0.44	0.44	0.43	0.42	0.41	0.40	0.39
Scale free deviance	5.63E+04	5.51E+04	5.67E+04	5.71E+04	5.91E+04	6.16E+04	6.35E+04	6.73E+04	7.14E+04	7.67E+04	8.24E+04

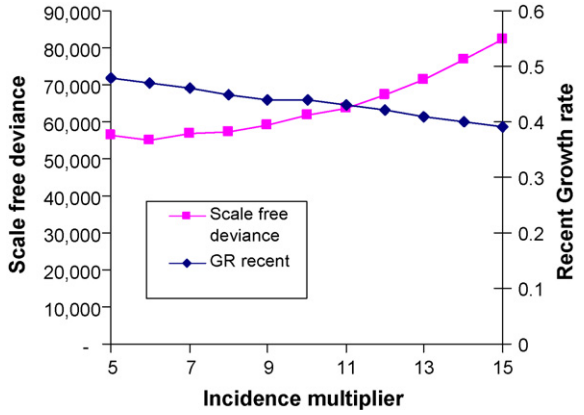

Fig. A3. Re-scaled deviance and autumn growth rate versus the multiplication factor for incidence. Average results of best-fitting 600 realisations shown.

the model were generated and compared to existing data, including the overall growth rate observed during the autumn wave of the epidemic (0.39 per week), and the fraction of children estimated to have sero-converted over the first wave (around 18%, [33]).

Fig. A2 shows the fit of the model to the re-scaled data, while Table A2 compares summary statistics for the models to the re-scaled data and other indicators. It can be seen from Table A2 and Figs. A2 and A3 that multiplying the HPA weekly estimate of cases by 10 to estimate the number of infections gives a reasonable fit to both epidemic waves, as well as a reasonable estimate of the autumn growth rate, and fraction of children who seroconvert. For this reason, this was taken as our base case, but multiples of 7.5 times and 12.5 times were used in sensitivity analyses. Comparing the model to the age-specific data (Fig. A2d), suggests that a good fit is obtained for all age groups except the youngest (<1 years). In this age group the model consistently overestimates the number of infections, perhaps because a fraction of the under 1 s are protected by maternally-derived antibodies, which we have not accounted for in the model. Fig. A4 presents the posterior distribution of the latent and infectious periods and the initial reproductive ratio.

Appendix B. Update of model and further comparison to data

This section outlines the updates and modifications to the model made subsequent to the submission of the paper. For the primary update the model was fitted to data up to 15th November (a second update was also performed using data up to the end of the first week of December). Half-term was implemented by reverting to the holiday contact matrix for a fraction of the population over a period of two weeks starting from 19th October (15% the first week and 85% the second to take account of differences in half-term over the country). Comparing the model results to the data, a better fit was observed if the half-term contact rates were assumed to be a weighted average of the summer and normal contact patterns (75% summer and 25% normal). Delays from onset to death were estimated by fitting a gamma distribution to the data on deaths up to 20 November 2009 for which HPA has detailed information (roughly 75% of cases). Furthermore, only data from England was used to calculate the risk of death (since we now have sufficient data from England; in the main paper we combined data from England with information from Australia and New Zealand).

Adjustments to the vaccine uptake were also made, as coverage appears to be less than anticipated. We now assume an overall coverage of 50% in the risk groups and that it takes 6 weeks to achieve this. The adjusted model was simulated over the course of the epidemic and the cases and deaths were estimated by age and risk group.

B.1. Results

Fig. B1(a and b) show projections for the number of infections and compares these to the estimated weekly number of cases. In Fig. B1a the model is fitted to data until 15th November, and is in good agreement with the subsequent data points (after verti-

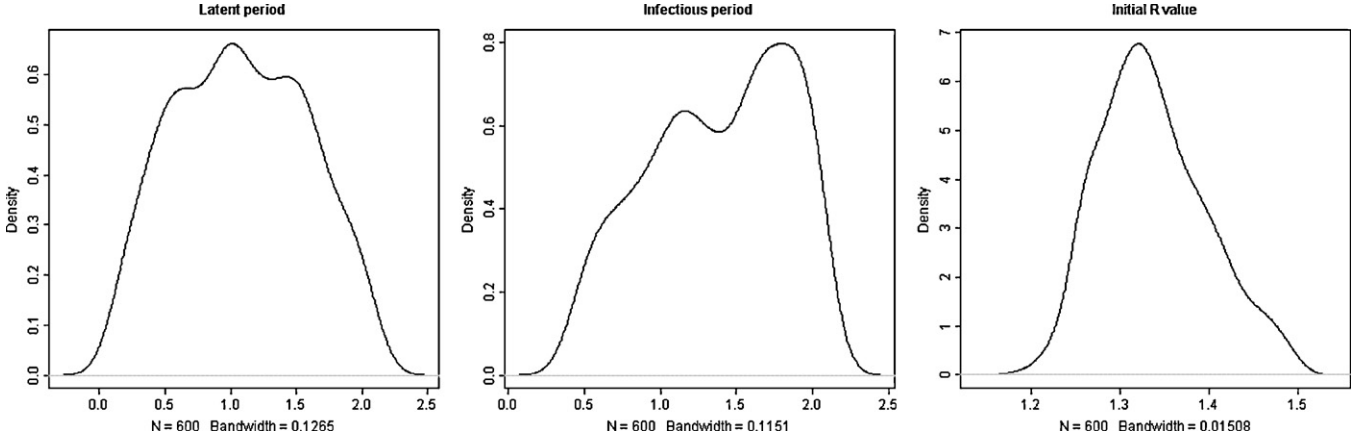

Fig. A4. Posterior distributions of the latent and infectious periods and of the initial reproductive ratio.

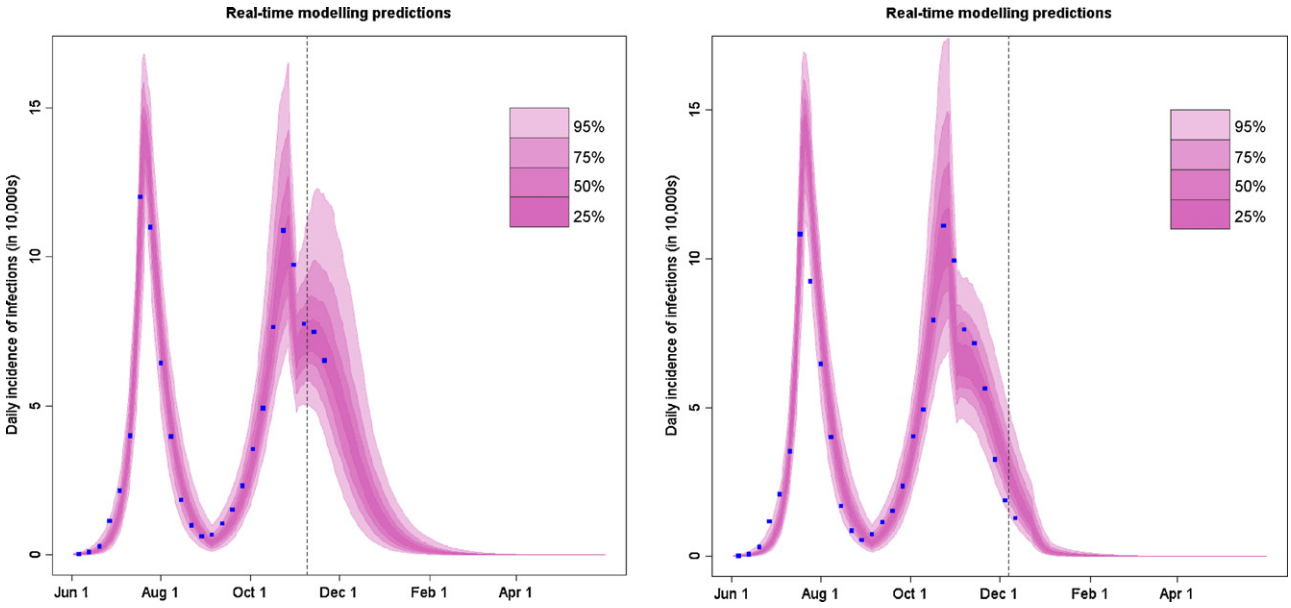

Fig. B1. Predictions of the number of infections in England using a real-time model parameterised using HPA case estimates until the 15th November (a) and 3rd December (b). Shades of colours represent areas including a certain percentage of realisations (25%, 50%, 75% and 95%) by the model and thus give an idea of the uncertainty of the predictions. The blue squares are the weekly data from HPA (to which the model is fitted until 15th November; so the model makes a good prediction of the two data points after 15th November).

Table B1
The estimated number of clinical cases and deaths by age and risk group, and the fraction of the total that has been observed by 1st December 2009.

Age group	Clinical cases			Deaths		
	Total number	% Risk group	% Observed by 1st December	Total number	% Risk group	% Observed by 1st December
<1	50,032 (30,245–73,284)	5%	88%	2 (1–3)	62%	69%
1–4	285,194 (206,373–374,321)	5%	88%	12(8–18)	62%	69%
5–14	968,513 (749,106–1,199,456)	5%	88%	42(28–59)	62%	69%
15–24	582,545 (421,255–768,185)	15%	88%	48(34–65)	81%	69%
25–44	1,005,822 (753,400–1,281,690)	16%	88%	84(61–110)	82%	69%
45–64	443,658 (314,470–593,812)	13%	88%	36(25–49)	80%	69%
65+	131,197 (79,334–192,626)	43%	88%	30(18–44)	95%	69%

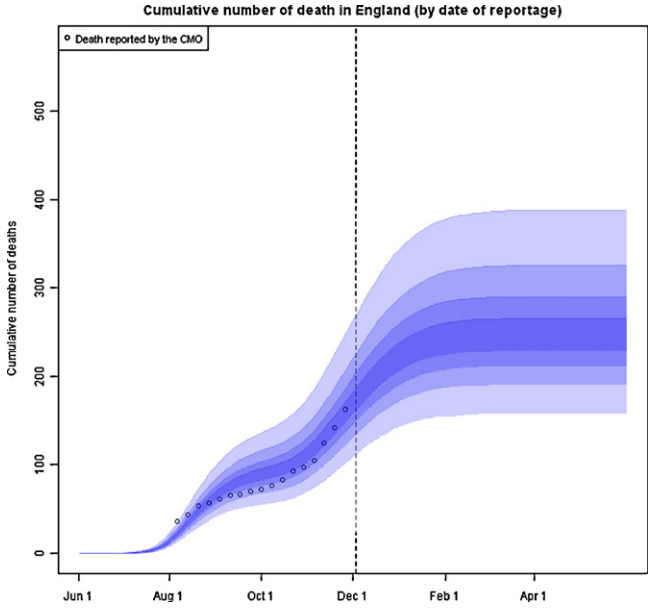

Fig. B2. Predictions of the number of deaths recorded in England using data on cases up to 15th November. The open circles are the weekly reported deaths. The dotted line represents the time of the analysis. The death rates were estimated using data up to 15th September.

cal dotted line) to which it is not fitted. Half-term is expected to have had a significant impact, with many simulations resulting in a modest rebound after this. The epidemic in England is expected to be over by mid January. Using data up until December and implementing Christmas holidays in the same way as half-term, then the model projections suggest that very few cases would be expected from January onwards (Figure A2.2b). Figure A2.2 shows the cumulative number of deaths expected over the course of the epidemic and compares this with those reported by the Chief Medical Officer [32]. Although the model is not fitted to the death data beyond the middle of September, it is clear that it gives a good description of the overall trend. The projected number of deaths over the course of the epidemic is expected to be around 250 (upper limit around 350). Table B1 gives the expected number of cases and recorded deaths by age and risk group over the course of the epidemic, and the fraction of them expected to be recorded by December 1st 2009. Due to the delays between onset and death, and then the recording of deaths, around 30% of deaths are expected to be recorded after December 1st, even though almost 90% of cases are expected to have occurred before this date.

References

[1] Department of Health. Advice from the Joint Committee on Vaccination and Immunisation on swine flu vaccination. Friday 7 August 2009. Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_104372.pdf. (Accessed 30-10-09).

[2] Department of Health. More than 11 million people in England will be offered it first. Available from: http://nds.coi.gov.uk/content/detail.aspx?NewsAreaId=2&ReleaseID=407719&SubjectId=16&AdvancedSearch=true. (Accessed 30-10-09).
[3] Health Protection Agency. HPA weekly national influenza report. www.hpa.org.uk.
[4] Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of Influenza A (H1N1): early findings. Science 2009;(May).
[5] Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 2008;5(March (3)):e74.
[6] Hens N, Ayele GM, Goeyvarts N, et al. Estimating the impact of school closure on social mixing behaviour and the transmission of close contact infections in eight european countries. BMC Infect Dis 2009.
[7] Directgov. Directgov: Find out school term dates. Available from: http://local.direct.gov.uk/LDGRedirect/index.jsp?LGSL=36. (Accessed 30-10-09).
[8] National Institute for Health and Clinical Excellence. Updated guide to the methods of technology appraisal. June 2008. London: National Institute for Health and Clinical Excellence.
[9] Curtis L. Unit Costs of Health and Social Care 2008. Kent: Personal Social Services Research Unit, University of Kent at Canterbury. Available from: http://www.pssru.ac.uk/uc/uc2008.htm. (Accessed 12-09-09).
[10] Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol 2008;167(April (7)):775–85.
[11] Kmietowicz Z. England to launch special flu service next week to take pressure off primary care. BMJ 2009;339:b2932.
[12] Flusurvey. www.flusurvey.org.uk. (Accessed 16-12-09).
[13] Baker MG, Kelly H, Wilson N. Pandemic H1N1 influenza lessons from the southern hemisphere. Eurosurveillance 2009;14(October (42)), pii:19370.
[14] Garske T, Legrand J, Donnelly CA, et al. Assessing the severity of the novel influenza A/H1N1 pandemic. BMJ 2009;339:b2840.
[15] McCormick A, Fleming D, Charlton J. Morbidity Statistics from General Practice, Fourth National Survey 1991-92, MB5. London: HMSO.
[16] Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales. Eur J Epidemiol 2004;19(4):365–75.
[17] Health Protection Agency Epidemiology of new influenza A (H1N1) virus infection, United Kingdom, April-June 2009. Euro Surveill 2009 Jun 4;14(22).
[18] Department of Health. NHS reference costs 2008. Department of Health; 2008.
[19] Siddiqui MR, Edmunds WJ. Cost-effectiveness of antiviral stockpiling and near-patient testing for potential influenza pandemic. Emerg Infect Dis 2008;14(February (2)):267–74.
[20] Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. Vaccine 2007;25(May (20)):3962–70.
[21] Department of Health. GP deal on swine flu vaccination: Department of Health - Public health. Available at: http://www.dh.gov.uk/en/Publichealth/Flu/Swineflu/DH_105132. (Accessed 30-10-09).
[22] Department of Health. H1N1 Swine Flu Vaccination Programme: Information materials and vaccine schedule information. 22 October 2009. Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_107752.pdf. (Accessed 30-10-09).
[23] GlaxoSmithKline. GSK: Results Summaries: Compounds. H1n1 Pandemic Influenza Vaccine. Available from: http://www.gsk-clinicalstudyregister.com/result_comp_list.jsp?compound=H1n1+Pandemic+Influenza+Vaccine. (Accessed 10-10-09).
[24] Demicheli V, Di Pietrantonj C, Jefferson T, Rivetti A, Rivetti D. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2007;2:CD001269.
[25] Yang Y, Sugimoto JD, Halloran ME, Basta NE, Chao DL, Matrajt L, Potter G, Kenah E, Longini Jr IM. The transmissibility and control of pandemic influenza A (H1N1) virus. Science 2009;326(October (5953)):729–33. Epub 2009 September 10.
[26] Medlock J, Galvani AP. Optimizing influenza vaccine distribution. Science 2009;325(September (5948)):1705–8. Epub 2009 August 20.
[27] Maurer J, Harris KM, Parker A, Lurie N. Does receipt of seasonal influenza vaccine predict intention to receive novel H1N1 vaccine: evidence from a nationally representative survey of U.S. adults. Vaccine 2009;27(September (42)):5732–4.
[28] Henrich N, Holmes B. The public's acceptance of novel vaccines during a pandemic: a focus group study and its application to influenza H1N. Emerging Health Threats J 2009;2:e8.
[29] World Health Organisation. Experts advise WHO on pandemic vaccine policies and strategies. Pandemic (H1N1) 2009 briefing note 14. Available at: http://www.who.int/csr/disease/swineflu/notes/briefing_20091030/en/index.html. (Accessed 10-10-09).
[30] Galli G, Hancock K, Hoschler K, et al. Fast rise of broadly cross-reactive antibodies after boosting long-lived human memory B cells primed by an MF59 adjuvanted prepandemic vaccine. Proc Natl Acad Sci USA 2009;106((May) 19):7962–7.
[31] British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary 58. September 2009 edition. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2006.
[32] Donaldson LJ, Rutter PD, Ellis BM, Greaves FEC, Mytton OT, Pebody RG, Yardley IE. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 2009;339:b5213, doi:10.1136/bmj.b5213.
[33] Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon, M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. Lancet 2010; doi:10.1016/S0140-6736(09)62126-7.