Title

The cost-effectiveness of vaccinating pregnant women against seasonal influenza in England and Wales

Authors

Mark Jit[1,*], Deborah Cromer[1], Marc Baguelin[1], Julia Stowe[1,2], Nick Andrews[1], Elizabeth Miller[1]

[1] Centre for Infections, Health Protection Agency, 61 Colindale Avenue, London NW9 6BT, United Kingdom

[2] Institute of Child Health, University College London, 30 Guildford Street, London WC1N 1EH, United Kingdom

* Corresponding author

Telephone: +44(0)2083277803

Fax: +44(0)2083277868

E-mail address: mark.jit@hpa.org.uk

Abstract

We assessed the cost-effectiveness of vaccinating pregnant women against seasonal influenza in England and Wales, taking into account the timing of vaccination relative to both the influenza season and trimester of pregnancy. Women were assumed to be vaccinated in their second or third trimester. Vaccination between September and December was found to have an incremental cost-effectiveness ratio of £23,000 per QALY (95% CI £10,000 - £140,000) if it is assumed that infants are partially protected through their mothers, and of £29,000 per QALY gained (95% CI £14,000 - £200,000) if infants are not protected. If some vaccine protection lasts for a second season, then the ratio is only £15,000 per QALY gained (95% CI £6,000 - £91,000). Most of the benefit of vaccination is in preventing symptomatic episodes, regardless of health care resource use. Extending vaccination beyond December is unlikely to be cost-effective unless there is good protection into a second influenza season. Key sources of uncertainty are the cost of vaccine delivery and the quality of life detriment due to a clinically apparent episode of confirmed influenza. The cost of vaccine purchase itself is relatively low.

Keywords (all MeSH terms)

Influenza, vaccination, cost-effectiveness

Abbreviated title

Cost-effectiveness of influenza vaccine for pregnant women

1. Introduction

Vaccination against influenza is currently recommended in the United Kingdom (UK) for patients at high risk of influenza-related morbidity and mortality. These patients include adults over 65 years old and individuals in clinical risk groups such as those with asthma and diabetes, as well as chronic heart, kidney and lung disease [1]. However, healthy pregnant women are not included in these risk groups. In contrast, both the United States and Canada recommend vaccinating healthy women who will be pregnant during the influenza season [2;3] while Australia recommends vaccination of pregnant women in their second or third trimester during the influenza season [4]. Pregnancy was also listed as one of the risk categories for priority immunisation in the United Kingdom during the 2009 H1N1v swine influenza pandemic. The rationale for vaccinating pregnant women is that they have a higher risk of complications from influenza which increases with stage of gestation [5;6].

The Joint Committee on Vaccination and Immunisation (JCVI), after reviewing these severity data, advised in 2006 that influenza vaccination should be offered to women in their second and third trimester of pregnancy [7]. First trimester women were excluded as the risk-benefit profile was not considered favourable [6]. However, as with other health interventions, implementation of such advice is subject to favourable cost-effectiveness analysis. It is important that any cost-effectiveness analysis takes into account the timing of vaccination, specifically the stage of pregnancy at which women become eligible for vaccination and the extent to which this overlaps with the influenza season. Also, unlike currently vaccinated risk groups, pregnant women will be not be eligible for vaccination each year, (unless a subsequent pregnancy also coincidences with the influenza season). Hence, vaccine protection in the following season may be an additional benefit that is not accrued for those

vaccinated each season. A further benefit of vaccinating pregnant women is that their infants may benefit through passive immunity [8;9].

Although two cost-effectiveness analyses of pregnant women in the United States have been published [10;11], there are no published cost-effectiveness analyses for the UK (or indeed any other part of the world besides the United States). Hence we present the first cost-effectiveness analysis of seasonal influenza vaccination for pregnant women in the UK, which will inform policy making in the UK and be useful for making similar decisions in other developed countries. We also consider issues around timing of vaccination and length of protection not incorporated into previous analyses.

2. Methods

2.1. Decision analytic model

A decision tree model was used to compare outcomes from cohorts of vaccinated and unvaccinated pregnant women, as well as their infants. Women in the model are divided into cohorts based on week of pregnancy for the purpose of vaccination, and vaccinated between the months of September to December as long as they are in the second or third trimester of pregnancy. Vaccine protection is assumed to occur two weeks after vaccination to account for the time taken for protective antibodies to rise to sufficient levels [12]. Once vaccinated, they are assumed to be protected both during their pregnancy and after, until the next influenza season starting the following September. In some scenarios, protection at a lower level is assumed to continue in the following season. All analyses were conducted in R (R Development Core Team, 2010, http://www.R-project.org).

Women have a risk of acquiring a symptomatic influenza infection, which varies according to the week of the year and their vaccination status. Each infected woman then has a probability of consulting a general practitioner (GP), being hospitalised in a general ward, being admitted to intensive care for influenza-related illness or dying of influenza-related causes (Figure 1). GP clinic attendees have a probability of being prescribed medication. Infants of mothers have a risk of acquiring influenza and of requiring health care or dying as a result. The cost to the health service and number of quality adjusted life years (QALYs) gained in vaccinated and unvaccinated women (and their infants) are then compared to estimate the incremental cost-effectiveness of vaccination. Costs are presented in 2008 £. A time horizon of two years post-vaccination is adopted, with costs and benefits incurred at least 12 months post-vaccination discounted at a rate of 3.5% per annum. A health service perspective is adopted (hence excluding productivity changes) and results are present as incremental costs per QALYs gained, and the cost-effectiveness of vaccination is evaluated according to the threshold of £20,000 - £30,000 per QALY gained, as recommended by the National Institute for Health and Clinical Excellence [13].

2.2. *Data sources*

Population. The average number of maternities in England and Wales in the years 2002-2007 (the years for which these data are available) is 637,585 [14]. These are assumed to be uniformly distributed throughout the year. However, about 10% of the population aged 15-44 years is in a clinical risk group [15], and so would already be eligible to receive vaccination. It is therefore assumed that vaccination would be offered to an additional population of 570,000 pregnant women each year.

Hospitalisations. Most influenza-related hospital admissions are not recorded using an influenza code. The true number of hospitalisations due to influenza was estimated using a regression technique previously used for estimating the burden of rotavirus disease [16] and influenza [17]. Full details of the analysis are given in Supplement S1. Briefly, hospital admissions in 2000 – 2009 for respiratory illness with infectious causes in pregnant women not in clinical risk groups were extracted from Hospital Episode Statistics (HES). In addition, weekly counts of respiratory pathogens in 2000 – 2009 for the 15-44 year old age group were extracted from LabBase2, a surveillance database that records the number of laboratory confirmed samples of various pathogens reported to the Health Protection Agency [18]. The seasonal pattern of laboratory reports was then used to estimate the proportions of hospitalisations in each week of the year that due to various pathogens. An equivalent analysis was performed on infants aged 0-5 months, the age group deemed to be potentially partially protected by maternal antibodies and hence by vaccinating mothers. The risk of hospitalisation for influenza in infants under one month old is very low as most hospitalisations were attributable to other organisms particularly respiratory syncytial virus; hence we removed this group from the analysis.

Intensive care. Comprehensive data on intensive care admissions are not available on the HES database [19]. Hence the risk of a pregnant woman already hospitalised for influenza being admitted to intensive care was estimated from two sources: (i) the placebo arms of published trials of influenza-related interventions [20-23] (assuming that the risk is no different for pregnant women) and (ii) data on intensive care admissions gathered during the 2009 H1N1 pandemic (assuming that the risk is no different for seasonal influenza). The reported risks lie between 2.8% and 17.9% (details in the Supplement S2).

GP consultations. The incidence of GP consultations for lower respiratory tract infections in females aged 15-44 years old from 2001 to 2008 was extracted from the Royal College of General Practitioners (RCGP) Weekly Returns Service [24], an anonymised database with information from approximately 70 sentinel practices in England and Wales. These included consultations with a READ code for pleurisy, pneumonia, bronchitis, laryngitis and influenza-like illness (ILI). Two methods were used to estimate the proportion of these consultations attributable to influenza: (i) multiple linear regression with laboratory reports of respiratory pathogens to estimate the proportion of all lower respiratory tract infections due to influenza (as with hospitalisations), and (ii) using consultations for ILI on their own. The second method assumes that consultations for ILI that are not for influenza are offset by consultations due to influenza not recorded as ILI. The annual risk of having a GP consultation for influenza in this population was estimated to be 1.9% and 2.4% using the first and second method respectively, and 2.2% when both estimates were combined (details in Supplement S3). This is significantly higher than an earlier estimate of 0.72% for the incidence of GP consultations in the population of England and Wales using data from the General Practice Research Database (GPRD) [17], possibly because not all consultations are coded in the GPRD [25].

The RCGP data do not provide information on pregnancy status, so the increased risk of an influenza-related GP consultation in each trimester of pregnancy compared to non-pregnant women in the same age group was estimated using data from the GPRD instead. The GPRD contains medical records for about 2000 representative general practitioners in the United Kingdom [26]. All consultations for ILI occurring between 1 January 1992 and 30 June 2007 for individuals aged 15-44 years with at least 2 years of continuous follow up were extracted.

For each individual, ILI episodes were regarded as separate if they occurred more than 28 days apart. A total of 35,706 records of ILI for analysis in 29,606 women were extracted from the GPRD database. For these women, READ codes indicating a delivery were used to determine whether a birth occurred, and if so, its date. The relative incidence of ILI at different stages of pregnancy was then estimated using the self controlled case-series method, which automatically adjusts for individual level confounding [27].

Medication. A population-based study using consultations for influenza-like illness in the GPRD found that 45.3% of patients aged 15-64 years old were prescribed antibiotics, and 17.7% were prescribed antipyretics or analgesics [28]. Other categories of drugs were rarely prescribed. It is likely that antibiotic prescribing rates have decreased since the study was conducted (1991-1996). As a rough estimate, it was assumed that the total number of prescriptions for drugs for influenza was 50% of the number of GP visits for influenza.

Deaths. The HES database recorded 28 deaths between 2001 and 2008 in pregnant women hospitalised for respiratory disease with no underlying health condition. Multiplying the deaths in each month by the proportion of respiratory hospitalisations attributed to influenza in that period gives an estimated 0.97 deaths due to influenza in pregnancy per year, with a risk of dying of 0.0029% per case. The risk of death in non-pregnant adult women was adjusted using the reduction in the risk of hospitalisation after pregnancy. The coefficient of variation for influenza deaths was assumed to be the same as that for hospitalisation. The average age of pregnancy was assumed to be 29 years [29], with the quality-adjusted life years lost due to influenza calculated using mortality rates by age group and health-related quality of life scores from the general population [30]. Hence we estimated that the death of an infant and a pregnant mother result in 20.0 and 23.8 QALYs lost respectively. The risk of

death in infants was taken from the estimated annual number of deaths due to influenza A and B from a regression analysis on respiratory disease data from the Office for National Statistics [17].

Attack rate for confirmed clinically apparent influenza. The incidence of confirmed influenza accompanied by clinical symptoms in adults was estimated using data from the placebo arms of clinical trials of influenza prophylaxis (vaccines or antiviral drugs). Since there were no data for pregnant women, it was assumed that healthy pregnant women had the same risk of clinical influenza as other healthy adults. Five studies [31-35] were identified as being relevant as they were published after 1990, actively followed a cohort of healthy adults for clinical respiratory symptoms and incorporated laboratory confirmation of influenza infection (see Table 1). All five were based in the United States. The attack rates in placebo recipients from the five studies based were then combined using a random effects model to give a pooled estimate of 5.9%. Weekly counts for influenza A and B isolates extracted from the LabBase2 database were used to determine the seasonality of these episodes of influenza. For infants, because of lack of data, we conservatively estimated that all symptomatic influenza episodes are captured by the incidence of hospitalisations.

Vaccine characteristics. A recent Cochrane review pooled results from several randomised studies of seasonal influenza vaccine efficacy using a random effects model. Efficacy was reported as 80% (95% CI 56% – 91%) against strains that matched the circulating strain [36]. Data are lacking on vaccine efficacy in pregnant women, so it was assumed that the vaccines equally efficacious in this population. Vaccination with a poorly matched strain [36;37] or a previous year's strain [38;39] has lower efficacy compared to vaccinating with a well-matched current strain of influenza. Additionally, immunogenicity against clinical endpoints

following vaccination has been found to wane over a period of months, even within the same influenza season [40;41]. Hence in scenarios where vaccine protection lasted a second season, vaccine efficacy was assumed to be half of that in the first season (i.e. 40%).

Two studies suggest that vaccinating mothers would protect their infants. A randomised study in Bangladesh found a 63% (95% CI 5 – 85) reduction in laboratory-confirmed influenza in infants under 24 weeks old whose mothers had received influenza vaccines, compared to a control group whose mothers received a pneumococcal vaccine [8]. A case-control study in a Connecticut hospital found a 79% (95% CI 25 – 94) reduction in infants under 6 months old [9]. We combined both results with equal weight to estimate the protective effect of vaccinating mothers on their children under six months old.

Vaccination coverage was assumed to be 45%, approximately based on reported coverage of the seasonal influenza vaccination among high risk individuals under 65 in 2007/8 [42].

Quality of life detriment due to influenza. An analysis of patient-reported health state valuations in placebo-controlled trials of oseltamivir reported that 4.27 (95% CI 1.28 – 7.04) quality adjusted life days were lost per episode of symptomatic influenza [43], corresponding to a QALY loss of 0.0117 (95% CI 0.0035 – 0.019). During the 2009 influenza pandemic, a questionnaire-based study among individuals with confirmed influenza resulted in an estimate of 0.0082 (95% CI 0.0066 – 0.0098) QALYs lost per influenza episode [15]. Combining both estimates with equal weight gives an overall QALY loss per episode of 0.010 (95% CI 0.0012 – 0.019).

For hospital and ICU admissions, quality of life weights of 0.65 and 0.52 respectively were used, based on an expert consultation convened by the Institute of Medicine [44]. Given the lack of information about uncertainty around these estimates, they were varied over symmetrical triangular distributions up to a maximum quality of life weight of 0.87 (the average quality of life for someone aged 20-39 years old [30]. The estimated length of stay for influenza hospitalisations was 3.68 days (95% CI 2.91 - 4.45), using admissions for influenza-like respiratory illnesses in HES regressed against respiratory pathogens in LabBase2 (see Supplement S1). The quality of life weights were multiplied by the average length of hospital stay for influenza to obtain the additional quality of life detriment incurred by patients admitted to acute care, on top of the usual detriment for symptomatic influenza.

Adverse events following vaccination. There is no evidence that influenza immunisation is associated with any serious adverse events in pregnant women or their children [5], although immunisation is associated with a raised risk of mild adverse events in adults [36]. It was assumed that these events had no significant quality of life implications. In a previous cost-effectiveness analysis [43], systemic adverse reactions to vaccination were assumed to occur in about 1% of vaccinated individuals and be equivalent to having influenza for a single day. However, this may be an overestimate, since reported adverse events following vaccination are typically far milder than actual influenza [6].

Health care costs. NHS reference costs for a non-elective admission for unspecified acute lower respiratory infection with complications and comorbidities (code DZ22B) were used to estimate the cost of a hospital episode for influenza in a pregnant woman. For intensive care admissions, the cost of an episode of adult critical care with one organ supported (code XC06Z) was used. The cost of an intensive care admission is in addition to the cost of the

hospitalisation that resulted in the time in intensive care. A GP consultation was costed on the basis of a clinic consultation of 17.2 minutes, including qualification and direct care staff costs [45]. The cost of prescriptions for influenza was based on the price to the health service of three drugs commonly prescribed for influenza-like illness in pregnant women (penicillin, erythromycin and paracetamol) [46].

The British National Formulary holds details on twelve seasonal influenza vaccines indicated for use in the United Kingdom. The cost per dose of the vaccines ranges from £4.40 to £9.05 with an average of £6.04 [46]. In addition, a 10% vaccine wastage rate was assumed. Vaccine administration costs of £7.51 per person vaccinated were assumed based on the item of service payment to GPs for vaccination. This was varied between £5.50 (ten minutes of client contact time for a band 5 practice nurse) to £10.33 (ten minutes for a midwife, i.e. a band 7 advanced nurse).

2.3. Sensitivity analysis

The influence of all epidemiological and economic parameters on the incremental cost-effectiveness ratio was jointly explored using probabilistic sensitivity analysis. Monte Carlo sampling was conducted on the joint distribution of the parameters (see Table 2), with 50,000 samples drawn. The relative influence of each parameter on the cost-effectiveness of vaccination was explored using a multivariate linear regression model, with parameter values as predictors and the incremental cost-effectiveness ratio as outcome. To correct for heteroskedasticity and reduce the influence of non-linearities at extreme values, robust standard errors were used and the most extreme 5% of outcomes were excluded. The regression coefficient for each parameter was multiplied by the endpoints of the parameter's

corresponding 95% credibility interval to obtain a predicted range for the incremental cost-effectiveness ratio when the parameter is varied. In addition, univariate sensitivity analysis was conducted on two key parameters (attack rate and QALY loss associated with clinically apparent influenza). Lastly, two scenarios about the efficacy of vaccination in the second season (i.e. beyond the September following vaccination) were explored; one in which the vaccine continued to provide full protection and another in which the vaccine no longer protected.

2.4. Optimal period for vaccination

The optimal period in the year in which to administer seasonal influenza vaccination to pregnant women was explored. It was assumed that the new season's vaccines would be available from September, and that women are vaccinated only during their second or third trimester of pregnancy. The cheapest option (apart from no vaccination) would be to vaccinate all women in their second or third trimester in September. The incremental cost-effectiveness of the second cheapest option, vaccinating all women in their second or third trimester in September and October, was compared to a September-only option, and so on.

3. Results

The incremental cost-effectiveness ratio is £23,000 per QALY gained (95% CI £10,000 - £140,000) under base case assumptions (infants partially protected through their mothers, and no efficacy after the first season). If infants are not protected, this rises to £28,000 per QALY gained (95% CI £13,000 - £200,000). However, if mothers and infants are protected for a second season, this drops to only £15,000 per QALY gained (95% CI £6,000 - £93,000).

A total of 200,000 women are expected to be vaccinated each season. Under base case assumptions, vaccination is expected to prevent 3,200 (2,100 – 4,100) GP consultations, 290 (180 – 420) hospitalisations, 18 (8 – 30) ICU admissions and 0.33 (0.24 – 0.42) deaths in that vaccinated cohort. A total of 9,000 (6,600 – 10,000) episodes of influenza are estimated to be prevented and 96 (16 - 180) QALYs saved. The cost of the programme is estimated to be £2.2 million (£1.4 - £3.0 million), but reduce expenditure on primary and acute care by £590,000 (£280,000 - £1.1 million).

Figure 2 shows corresponding cost effectiveness acceptability curves. With a threshold of £30,000 per QALY gained, 69%, 54% and 87% of Monte Carlo samples are considered cost-effective for the base case scenario, scenario without infant protection and scenario with second season protection respectively. With a more stringent threshold of £20,000 per QALY gained, the corresponding proportions are 38%, 20% and 70%. This indicates that vaccination could be regarded as borderline cost-effective without second season protection, and very cost-effective with such protection, based on the criteria used by the National Institute for Health and Clinical Excellence.

The most influential parameters affecting the incremental cost-effectiveness ratio are shown as a tornado plot in Figure 3. Figure 4 shows how the incremental cost-effectiveness ratio changes when two key parameters (QALY loss due to clinically apparent influenza and administrative cost of the vaccine) are varied. Assuming infant protection and no protection beyond the first season, a QALY loss of about 0.007 per episode of influenza (instead of 0.01) is enough to push the incremental cost-effectiveness of vaccination above £30,000 per QALY gained. Similarly, a vaccine administration cost of about £11 per dose (instead of

£7.51) will make vaccination cease to be cost-effective at a threshold of £30,000 per QALY gained.

Figure 5 shows the incremental cost-effectiveness vaccination of extending a vaccination programme starting in September, to different months of the year. With a willingness to pay threshold of £30,000 per QALY gained, vaccination should be carried out between September and December. However, if vaccine protection lasts beyond a first season then vaccination would be cost-effective under that threshold up to May.

4. Discussion

Vaccinating pregnant women against seasonal influenza may be cost-effective, with an incremental cost-effectiveness ratio of around £23,000, assuming protection for a single season and some benefit to infants.

This analysis uses a regression-based technique to determine the proportion of health care attendances that may be attributable to influenza. Recently, the assumptions used by such ecological models have been questioned by Gilca and co-workers [47]. The method we have used here takes into account many of the issues they raise, which have been ignored by some previous models, including differential rates of disease reporting by organism, variation of circulating organisms by age group and secular trends in disease incidence (such as the occurrence of epidemic seasons at different times each year). While we have not considered changes in reporting rates over time, when there is indication of a long-term variation in reporting rates (such as for GP consultations for LRTI), we have used several models including ones which incorporate a term for year of reporting. All the models give broadly

similar conclusions for the proportion of consultations attributable to influenza, so we have achieved some degree of internal validation and thus have some confidence in the robustness of our results.

Our findings appear less optimistic than those in the study of maternal influenza immunisation in the United States [10], which estimated that vaccination would be cost-effective from a third party payer perspective as long as the overall attack rate was over 2.5% (compared to 5.9% used in our model). However, the American model did not consider the timing of vaccination and seasonality of influenza, and hence the possibility that a woman would not be vaccinated in time to be protected throughout the influenza season.

The favourable cost-effectiveness of vaccination depends on several assumptions. The cost of delivering vaccination is important because the actual cost of purchasing the vaccine is comparatively low. The base case administration cost is based on the item of service payment to GPs; however, this is an internal transfer cost which does not take into account the cost of actual clinician time. Hence the way the vaccine is delivered is crucial. Our model suggests that vaccination will need to be delivered largely by practice nurses during routine antenatal appointments to be clearly cost-effective. If midwives deliver vaccines, then vaccination may be marginally cost-effective. If a separate appointment for vaccination needs to be made, or if vaccination is delivered by GPs themselves (for whom ten minutes of client contact time is estimated to cost £30.50), then vaccination is highly unlikely to be cost-effective regardless of other assumptions made.

Another key assumption is the estimate of the QALY loss due to influenza, which was obtained from a study that combined health state valuations on a disease-specific Likert scale

from the placebo arm of four clinical trials of oseltamivir, and transformed the outcomes into quality of life weights [43]. There is substantial uncertainty around the resulting estimate, both due to variability in the results from primary data sources (reflected in the large confidence intervals around the distribution of possible QALY loss values), as well as uncertainty about the validity of the mapping process. The second estimate is from direct measurements of patients with laboratory confirmed influenza using the EuroQol EQ-5D instrument. However, the study was conducted during the 2009 influenza pandemic so its validity outside a pandemic situation is not established. This highlights the need for a study to obtain valuations from patients with seasonal influenza using the EQ-5D. A further issue is that the health state valuations were done in the general adult population rather than in pregnant women. It is not known whether pregnancy may induce a different quality of life detriment as a result of influenza (apart from the greater risk of GP consultations and hospitalisations in pregnant women with influenza). However, a comparison of symptoms in pregnant and non-pregnant individuals of reproductive age with H1N1v influenza found no significant differences in symptoms apart from shortness of breath [48]. Furthermore, any differential in the quality of life detriment is more likely to indicate that pregnancy worsens the impact of influenza rather than ameliorating it, hence making vaccination more cost-effective.

Vaccinating pregnant women is likely to be more cost-effective than vaccinating the wider adult population for several reasons. Firstly, pregnant women are at a higher risk of influenza-related GP consultations and hospitalisations compared to non-pregnant women of the same age [5]. Nevertheless, such cases still contribute to only a very small proportion of all clinically apparent influenza cases, since the incidence of influenza patients using health care resources (GPs, hospitals and intensive care units) is low compared to the overall burden

of clinically apparent influenza. We estimate that pregnant women with influenza have only a 14% risk of influenza-related GP consultation and 2.2% risk of influenza-related hospitalisation. Consequently, the increased cost-effectiveness of vaccinating pregnant women compared to other healthy adults is mainly due to potential vaccine protection for infants of vaccinated mothers, and potential persistence of vaccine protection beyond the first influenza season (which is not relevant to other seasonal vaccination programmes since individuals are revaccinated every influenza season). If these benefits are not included, then the cost effectiveness of vaccinating pregnant women is expected to be only slightly better than that of vaccinating the entire healthy adult population. However, it is not clear whether and how the incidence of seasonal influenza will change after the H1N1 pandemic of 2009 which has the potential to displace strains of influenza that were predominant prior to the pandemic. Such changes are likely to affect the cost-effectiveness of vaccinating both pregnant women and the wider adult population. Also, if there is a means of prolonging the efficacy of the vaccines (perhaps by using adjuvanted vaccines) then vaccinating pregnant women would become more cost-effective.

Acknowledgments

We thank Pauline Kaye, Colin Campbell, Jonathan van Tam and Ahmed Hashim for supplying information from data sources on the risk of intensive care admission in patients hospitalised for influenza during the 2009 H1N1v pandemic. In particular, Pauline Kaye supplied data from the Regional Microbiology Network laboratories, Colin Campbell supplied data from the Chief Medical Officer's hospitalisation dataset, while Jonathan van Tam and Ahmed Hashim supplied data from FLU-CIN. We thank Doris Otomewo for extracting data from LabBase2. We also thank John Edmunds for helpful discussions. DC, MB and JS were funded by the Policy Research Programme in the Department of Health, England (grant number 039/0031). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

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Caption for supplemental material (submitted in a separate file)

Technical details of calculations used to estimate the burden of disease due to influenza in pregnant women.

Table 1. Attack rate of confirmed influenza with clinical symptoms reported from the placebo arm of five influenza prophylaxis trials in healthy adults.

First author	Intervention	Case definition	Attack rate (placebo arm)	Sample size
Bridges [31]	Influenza vaccination	Clinical symptoms and culture confirmation	7.3%	274
Monto [32]	Antivirals	Clinical symptoms and culture confirmation	6.1%	554
Hayden [33]	Antivirals	Clinical symptoms and culture confirmation	4.8%	519
Wilde [34]	Influenza vaccination	Clinical symptoms and serological confirmation	7.0%	358
Powers [35]	Influenza vaccination	Clinical symptoms and serological confirmation or viral isolation	12.5%	24

Table 2. Distributions used for the parameters in the model.

Parameter	Mean	Distribution	Source
Epidemiological parameters			
Probability that a pregnant woman is hospitalised with influenza in the ... first trimester … second trimester … third trimester	 0.089% 0.11% 0.20%	 Normal with μ=0.089%, σ=0.0091% μ=0.11%, σ=0.011% μ=0.20%, σ=0.020%	Hospital Episode Statistics, laboratory reports (see Supplement S1)
Probability that any adult woman is hospitalised with influenza	0.0051%	Normal with μ = 0.0051%, σ = 0.0014%	[17] (see Supplement S1)
Probability that any infant aged 1-6 months is hospitalised with influenza	1.25%	Normal with μ = 1.25%, σ = 0.22%	HES, LabBase2 (see Supplement S1)
Probability that someone hospitalised for influenza is admitted to intensive care	10%	Triangular with min=3%, max=17%, mode=10%	[20-23]; data on file from the 2009 influenza H1N1 pandemic (see Supplement S2)

Probability that any pregnant woman consults a GP with influenza in the … first trimester … second trimester … third trimester	 2.46% 2.70% 2.33%	 Normal with μ=2.46%, σ=0.35% μ=2.70%, σ=0.45% μ=2.33%, σ=0.39%	RCGP Weekly Returns Service [24], GPRD [26] (see Supplement S3)
Probability that any adult woman consults a GP with influenza	2.2%	Normal with μ = 2.2%, σ = 0.35%	RCGP Weekly Returns Service [24], GPRD [26] (see Supplement S3)
Probability that GP consultation for a pregnant woman with influenza results in a prescription	50%	Triangular with min=37%, max=63%, mode=50%	[28]
Probability of death for a pregnant woman with influenza	0.0029%	Normal with μ = 0.0029%, σ = 0.00029%	[19]
Probability that any infant dies of influenza	0.00074%	Normal μ = 0.00074%, σ = 0.00017%	[17]
Attack rate (incidence of confirmed clinically apparent influenza)	5.9%	Normal with μ = 5.9%, σ = 0.0060%	[31-35] (see Table 1)

Outcomes			
QALYs lost due to influenza episode	0.010	Normal with μ = 0.010, σ = 0.0044	[43]
Quality of life detriment during influenza hospital episode	0.35	Triangular with min=0.13, max=0.57, mode=0.35	[30;44]
Quality of life detriment during influenza intensive care episode	0.48	Triangular with min=0.13, max=0.83, mode=0.48	[30;44]
Length of hospital stay for influenza (days)	3.68	Normal with μ = 3.68, σ = 0.39	Hospital Episode Statistics, laboratory reports (see Supplement S1)
Costs (in £)			
Hospitalisation	1446	Lognormal with μ = 7.2, σ = 0.35	[49]
Intensive care	983	Lognormal with μ = 6.8, σ = 0.40	[49]
GP consultation	52	Lognormal with μ = 3.7, σ = 0.68	[45]

GP prescription	1.62	Triangular with min=1.18, max=1.89, mode=1.78	[46]
Dose of vaccine	6.04	Triangular with min=4.4, max=9.1, mode=4.62	[46]
Administration cost	10.33	Triangular with min=5.67, max=18, mode=7.32	[50]
Vaccine characteristics			
Vaccine efficacy	80%	Lognormal with μ = 80%, σ = 56%	[36]
Influenza risk reduction in children aged 1-6 months of vaccinated mothers	71%	Triangular with a = 63%, b = 79%, c = 71% (mean=71%)	[8;9]
Vaccine wastage	10%	Fixed	Assumed

Figure captions

Figure 1. Decision tree for vaccination of a pregnant woman. The probability of each branch in the tree depends on the month of conception and the incidence of influenza in a given month. Note that a patient may have more than one health care use outcome, although this is not shown in the tree.

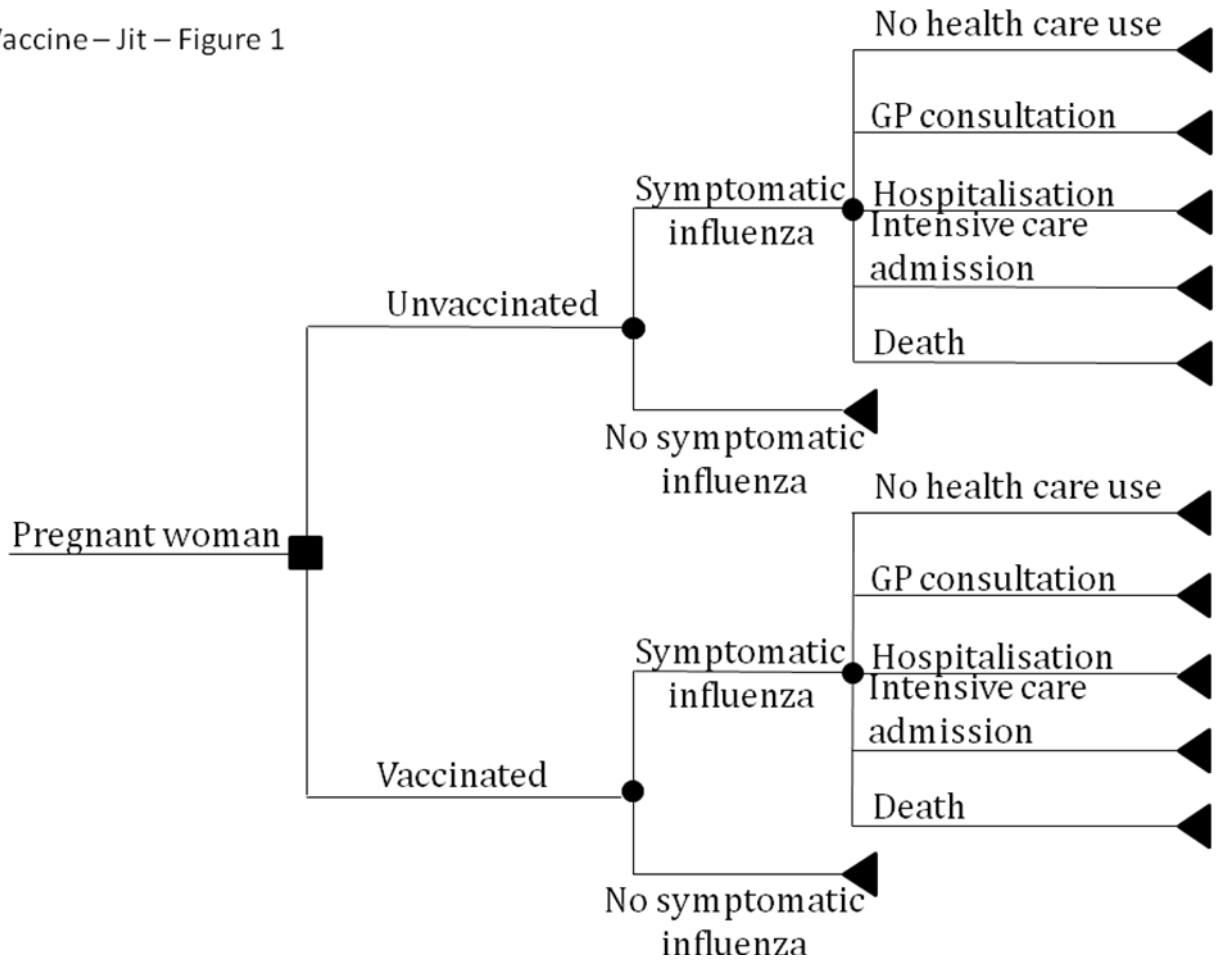
Figure 2. Cost-effectiveness acceptability curve for the programme of vaccinating pregnant women against seasonal influenza, with and without assuming that their infants are also partially protected. Shaded bars indicate the region £20,000-£30,000 per QALY gained.

Figure 3. Tornado graph showing the ten most influential parameters on the incremental cost-effectiveness ratio. Shaded bars indicate the region £20,000-£30,000 per QALY gained.

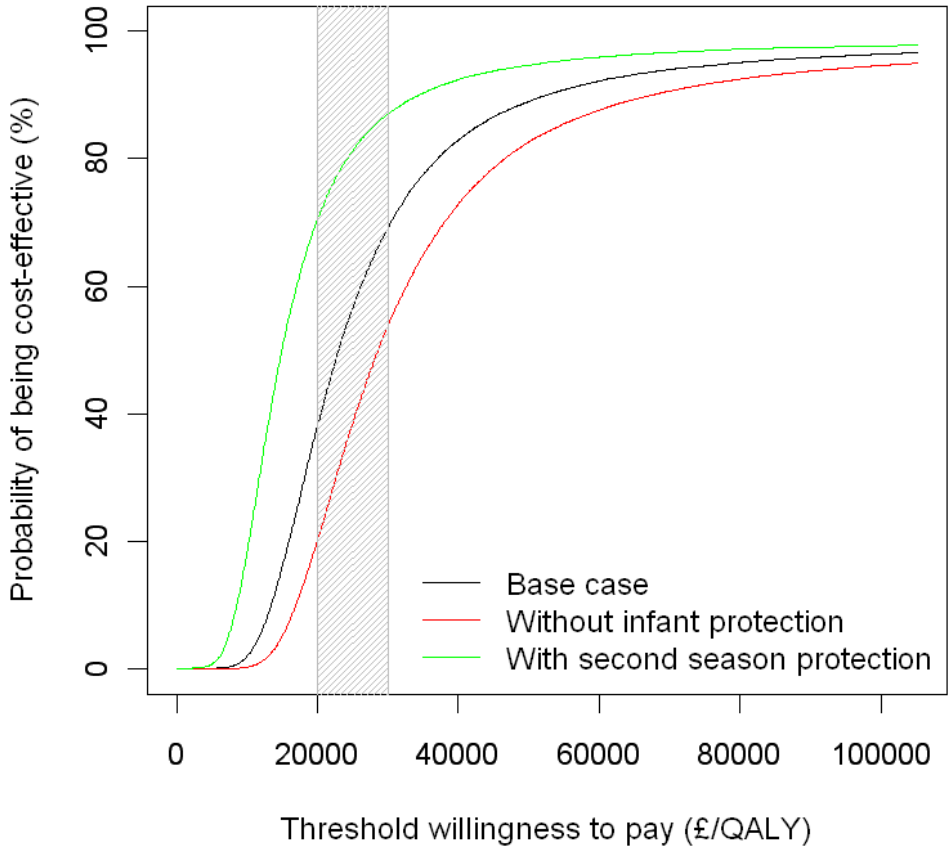
Figure 4. Univariable sensitivity analysis on QALY loss for clinically apparent influenza and administrative cost of vaccination. Shaded bars indicate the region £20,000-£30,000 per QALY gained.

Figure 5. Incremental cost-effectiveness of extending a vaccination programme starting in September, to different months of the year, when the vaccine (a) protects for a single season and (b) protects partially up to a second season. Infant protection is assumed.

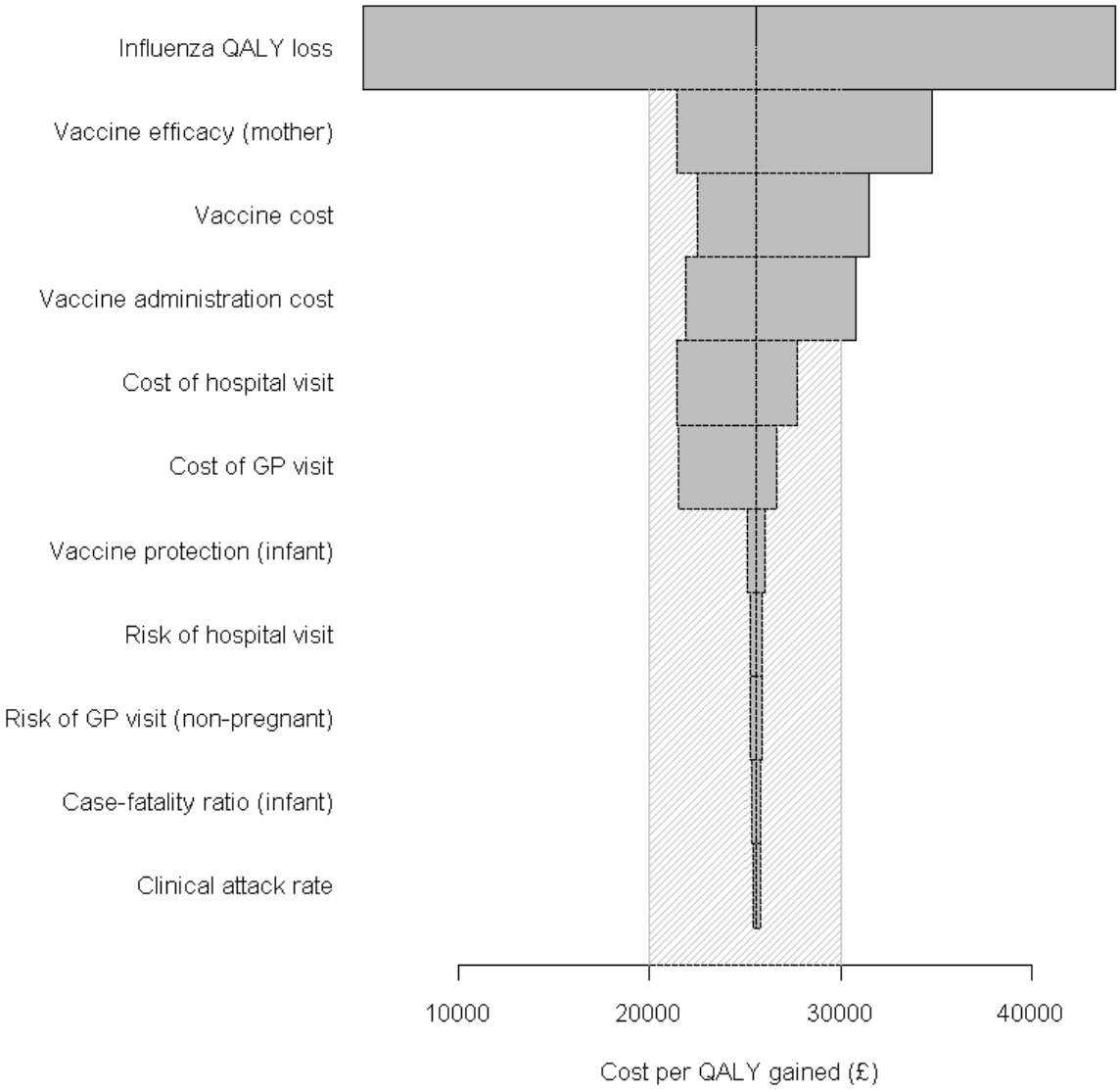
Vaccine – Jit – Figure 1



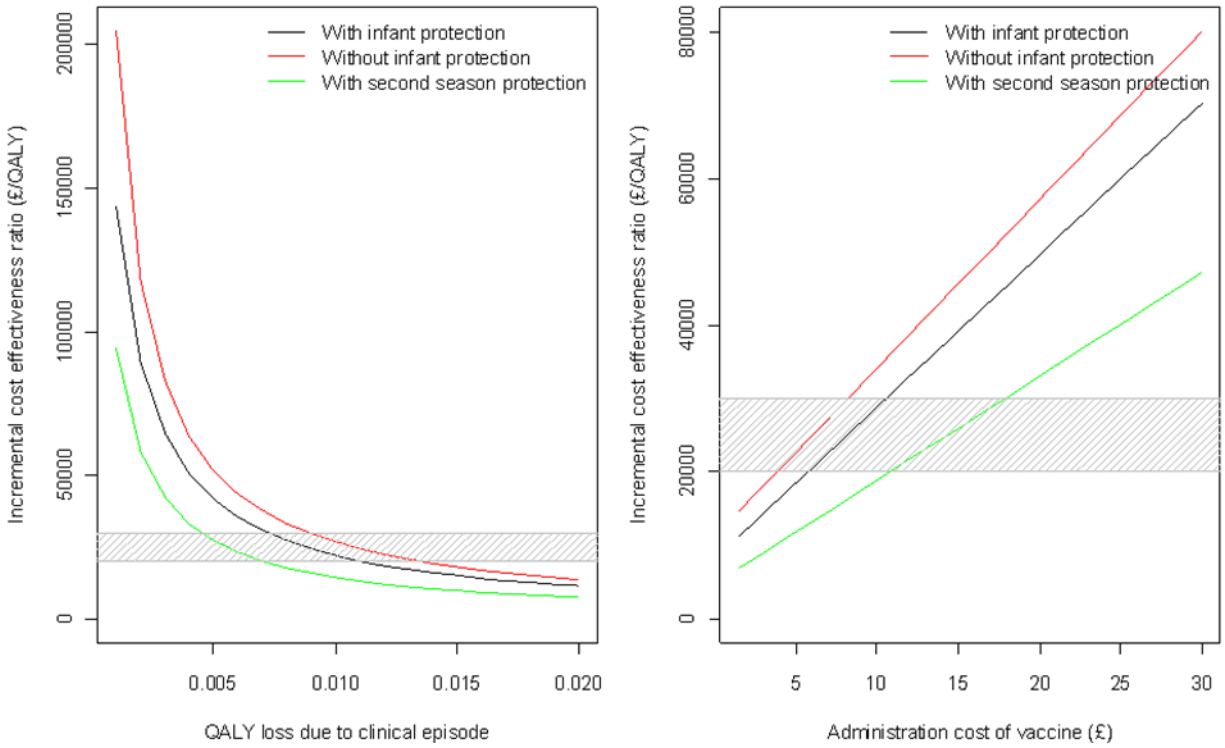
Vaccine – Jit – Figure 2



Vaccine – Jit – Figure 3



Vaccine – Jit – Figure 4



Vaccine – Jit – Figure 5