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

S1. Hospitalisations

Hospital admissions were extracted from the Hospital Episode Statistics (HES), a database containing records of all patients admitted to National Health Service (NHS) hospitals in England. Records extracted were those from week 40, 2000 to week 12, 2009 who (i) had a code for influenza-like respiratory illness (J0-J4) and (ii) either had a pregnancy code (O00-O99, Z33, Z34, Z35), or were infants below 6 months of age. Admissions with a code for a clinical risk group for influenza vaccination [1] were excluded (B18, D73, E1-E4 chronic renal disease, I05 – I09, I11 – I15, I20 – I22, I25- I28, I34 – I39 chronic heart disease, J4 chronic respiratory disease, K70 – K77 chronic liver disease, N01 – N08, N11 – N19 chronic renal disease).

In addition, weekly counts of respiratory pathogens in the 15-44 year old age group from week 40, 2000 to week 12, 2009 were extracted from LabBase2, a surveillance database that records the number of laboratory confirmed samples of various pathogens reported to the Health Protection Agency [2]. Data for the following pathogens were extracted: adenovirus, coronavirus, *Haemophilus influenzae*, influenza A, influenza B, *Mycoplasma pneumoniae*, parainfluenza, respiratory syncytial virus (RSV), rhinovirus and *Streptococcus pneumoniae*.

Multiple linear regression was used to estimate the proportion of hospitalisations that are due to various pathogens, using weekly counts of laboratory reports as explanatory variables. The most parsimonious model was chosen using using backward stepwise selection, with

variables excluded if they had a value of $p<0.05$ or a negative coefficient. Goodness of fit was evaluated using the adjusted R^2 value defined as:

$$\text{adjusted } R^2 = 1 - \left(\frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - \bar{y})^2} \right) \left(\frac{n-1}{n-p-1} \right)$$

where y_i are the data points (with average $\bar{y}$) and $\hat{y}_i$ are the model estimates. The total number of predicted hospitalisations due to influenza as well as their distribution by trimester of pregnancy was then extracted. The analysis was conducted for both pregnant women and for infants aged 1-6 months old.

In pregnant women, the most parsimonious model consists of variables for influenza A, influenza B, RSV, *H. influenzae* and rhinovirus (adjusted R^2 = 0.6182; see Figure A1). The contribution of each pathogen to the hospitalisation data is shown in Figure A2. The model predicts that there are 815 (95% CI 650 – 980) hospitalisations due to influenza a year, so the predicted annual incidence of hospital admission in pregnant women of 0.13% (95 CI 0.11 - 0.16). This is much greater than the average number of 83 hospitalisations per year recorded with admission codes for influenza (J10 and J11), suggesting that a substantial proportion of hospitalisations for influenza are not coded as influenza.

The model suggests that *H. influenzae* and rhinovirus make an increasing contribution to hospitalisations for respiratory conditions after 2002. This is consistent with laboratory reports showing a steady increase in the number of *H. influenzae* isolates after 2002 and with observations that non-capsulated *H. influenzae* is more common among women of

childbearing age [3]. However, the increase in laboratory reports may also have been due to better reporting of non-invasive cases of *H. influenzae* in recent years.

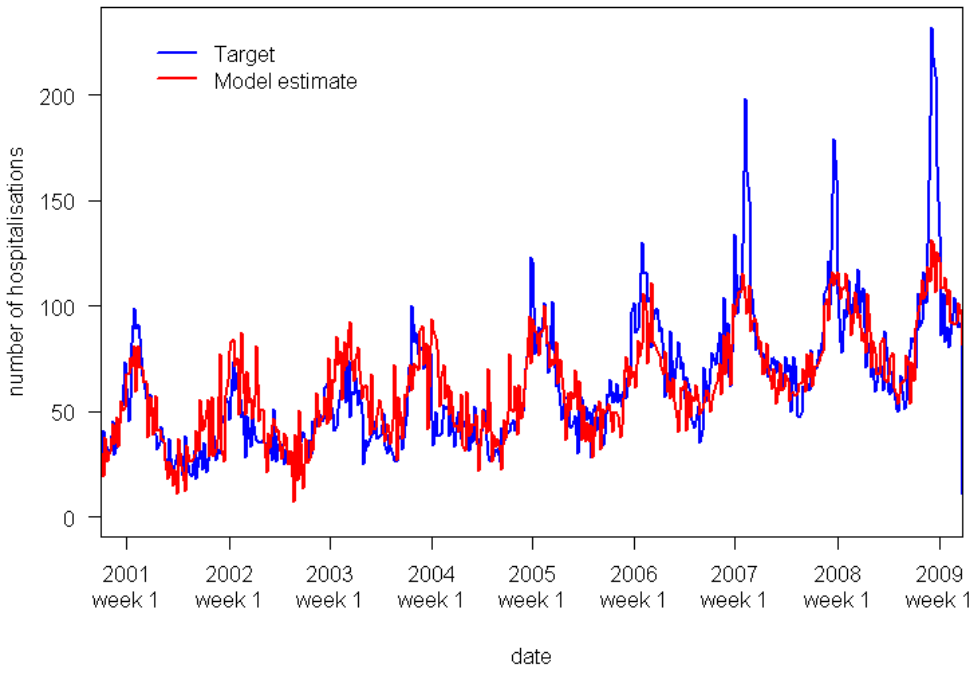

Figure A1. Hospitalisation for influenza-related respiratory conditions in pregnant women according to HES data (blue line) and most parsimonious model predictions (red line).

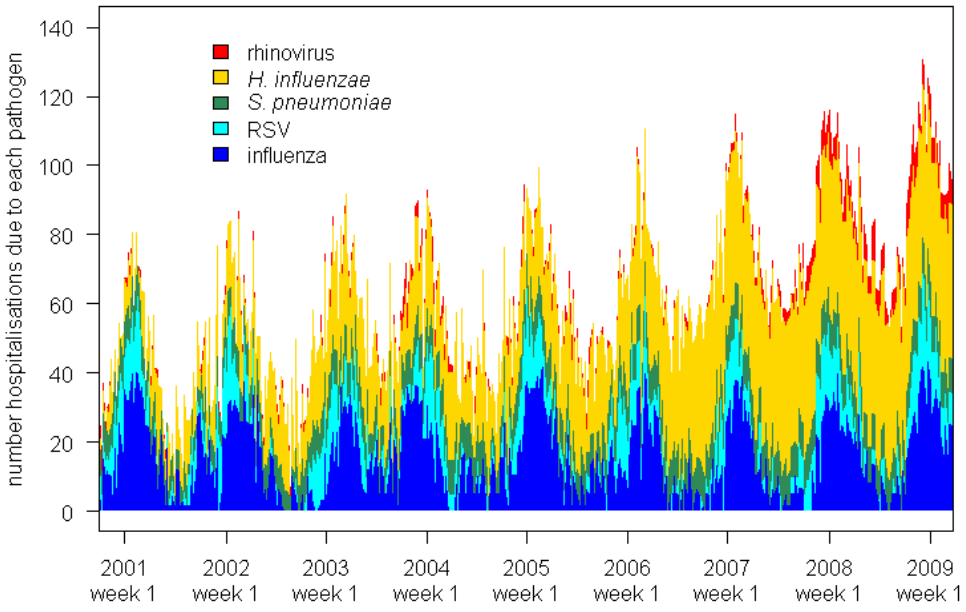

Figure A2. Most parsimonious model predictions about the contribution of pathogens to hospitalisations for influenza-related respiratory conditions in pregnant women.

If year of admission is included as a categorical explanatory variable in the model, then the most parsimonious model provides a slightly better fit (adjusted R^2=0.7069 instead of 0.6182). Both *H. influenzae* and rhinovirus drop out of the final model, with their contribution replaced by a constant value that increases for the later years. This model predicts that the number of hospitalisations due to influenza is 866 (95% CI 720 – 1010) per year, giving a predicted annual incidence of hospital admission in pregnant women of 0.14% (95 CI 0.11 - 0.16), almost the same as the previous model. The model with year of admission as a categorical variable was not used in further analysis, since the increase in accuracy was not great enough to justify the introduction of a variable with uncertain biological interpretation.

For 1-6 month old infants, the most parsimonious model (adjusted R^2 = 0.3622; Figure A3) predicts that the majority of admissions are due to RSV with the remainder due to influenza A and rhinovirus. The number of hospitalisations due to influenza in this age group predicted by the model is 3401 (95% CI 2248 - 4554) per year, giving a predicted annual incidence of hospital admission of 1.25% (95 CI 0.8 – 1.67). This agrees with previous reports which have estimated the hospitalisation rate of infants under 6 months of age as being over 1% [4;5].

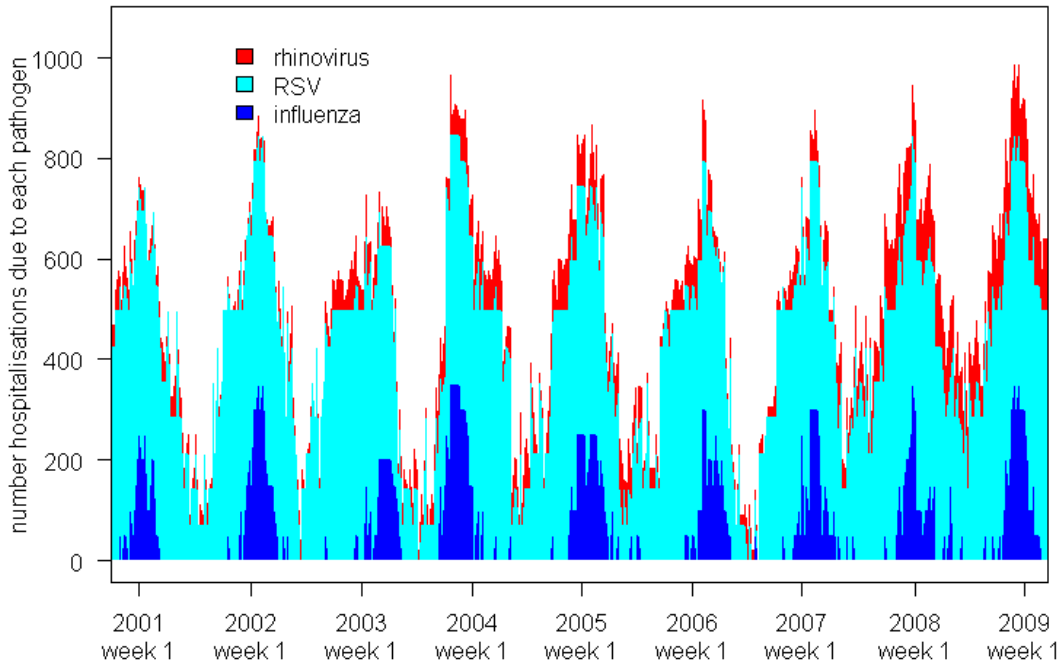

Figure A3. Most parsimonious model prediction about the contribution of pathogens to hospitalisations for influenza-related respiratory conditions in infants aged 1 to 6 months.

A recent review suggests that influenza hospitalisations during pregnancy are more likely to occur in the second or third trimester [5]. The odds ratio of such a hospitalisation in the

second or third trimester compared to the first, as presented in the review, was applied to the total number of influenza hospitalisations in pregnancy predicted by our model to give the risks of hospitalisation by trimester in Table A1:

	Trimester 1	**Trimester 2**	**Trimester 3**
Mean risk of hospitalisation	0.089%	0.112%	0.203%
Standard error of risk of hospitalisation	0.012%	0.016%	0.028%

Table A1. Mean and standard error of the risk of hospitalization for influenza by trimester.

The length of a hospital stay for influenza was determined using the seasonality of hospital episodes for pregnant women hospitalised with respiratory conditions reported in the HES database. First, the length of all such episodes in the database that began in a given week was summed. The proportion of these bed-days attributable to different respiratory pathogens was then determined using the proportion of hospital episodes in each week attributable to different pathogens (as determined earlier by fitting to seasonality in laboratory data). This assumed that each pathogen has a consistent average length of hospital stay. Influenza A and B were combined into a single group for the purposes of this analysis.

S2. Intensive care admissions

The table below gives the risk of intensive care admissions in patients hospitalised with influenza, as reported from published and unpublished sources.

Study details	Risk	Sample size	Source
FLU-CIN Previously healthy pregnant women hospitalised for H1N1.	17.9%	28	A Hashim and J van Tam, personal communication
Chief Medical Officer Previously healthy pregnant women hospitalised for H1N1.	10.6%	94	C Campbell et al., personal communication
Regional Microbiology Network Previously healthy pregnant women hospitalised for H1N1.	6.25%	16	Data on file
Placebo arm of adults hospitalised with pneumonia in observational study of influenza vaccination in Canada.	2.8%	352	[6]
Placebo arm of adults hospitalised with influenza in observational study of antivirals in Canada.	16.4%	219	[7]
Study of children hospitalised with influenza from routine hospitalisation data in Canada.	7.6%	184	[8]

Study of children hospitalised with influenza from a review of laboratory reports and hospital charts in Canada.	12.0%	505	[9]

S3. GP consultations

The number of GP consultations for lower respiratory tract infections (LRTI) in 2000 – 2008 was extracted from the RCGP Weekly Returns Service database. Consultations for pleurisy, pneumonia, bronchitis, laryngitis and influenza-like illness were recorded as LRTIs. Upper respiratory tract infections (consisting mainly of colds and also of sinusitis, otitis media and tonsillitis cases) were not included as they appeared to be far less likely to be influenza-related. These data indicate that GP consultations for both LRTI have decreased in the period from 2000 to 2008. This is dominated by a decrease in consultations coded for bronchitis.

The proportion of these consultations due to LRTI was estimated using a regression model with LabBase2 reports as explanatory variables. Initially the data were fit without including an explanatory variable for the year in which the consultations occurred. The results of this fitting are shown in Figure A4, indicating that a good fit is not obtained because there is no isolate in the LabBase2 dataset that decreases in frequency from 2000-2008, and so the decrease in GP consultations over this period is not captured. The adjusted R^2 value for this fit is 0.4107.

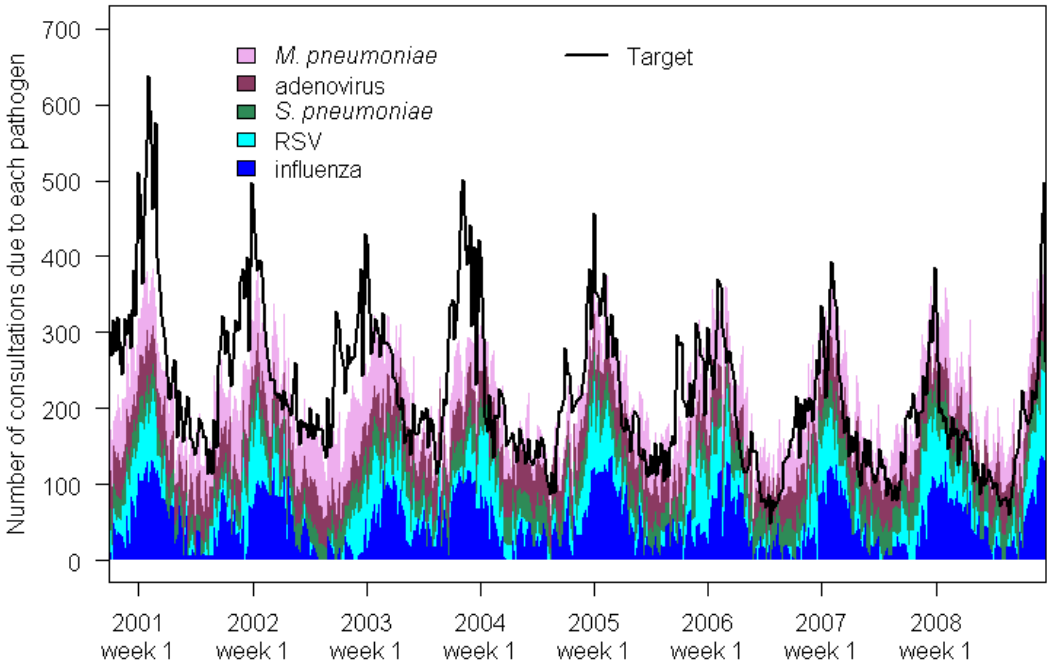

Figure A4. Contribution of each pathogen to the LRTI consultations when no explanatory variable is used to define the year of consultation.

Since a poor fit was obtained, an explanatory variable for year of consultation was included . The results are shown in Figure A5A. Once a year variable was included it was possible to fit the data well (adj $R^2 = 0.6281$). However we observed that the factors estimated for the years 2006, 2007 and 2008 were negative (Figure A5B). These negative factors do not appear to have a biological interpretation. Hence the fitting procedure was repeated, this time forcing the explanatory variable for the year to be non-negative. The fit obtained was slightly better than when a factor for the year was not included (adj $R^2 = 0.4382$). However, as can be seen in Figure A6A, the fit does not appear to be particularly good. In addition, although the factors for the year of consultation are positive, the confidence intervals around the estimates of these factors are extremely large (Figure A6B)

A **B**

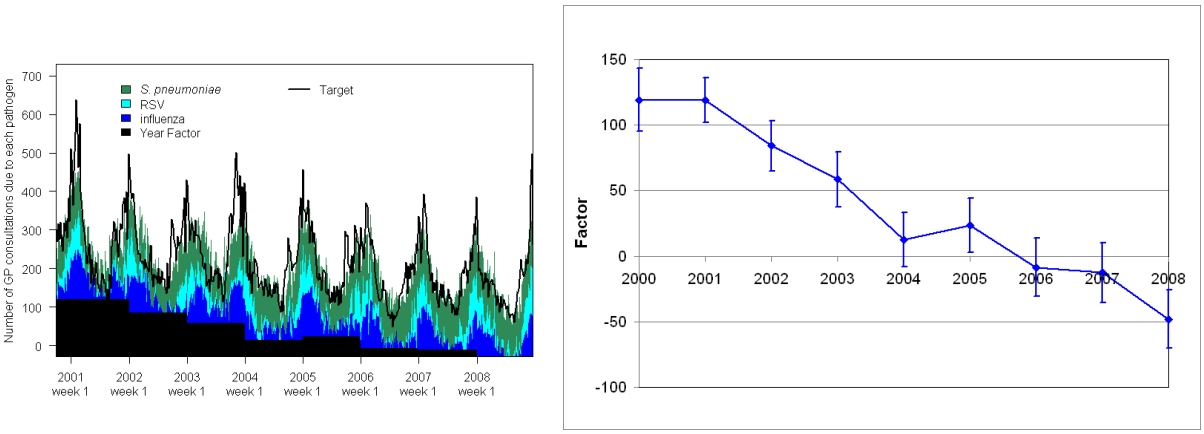

Figure A5. (A) Contribution of each pathogen to the model fit of LRTI consultations (B) Factors (±SE) estimated by the model for each year.

A **B**

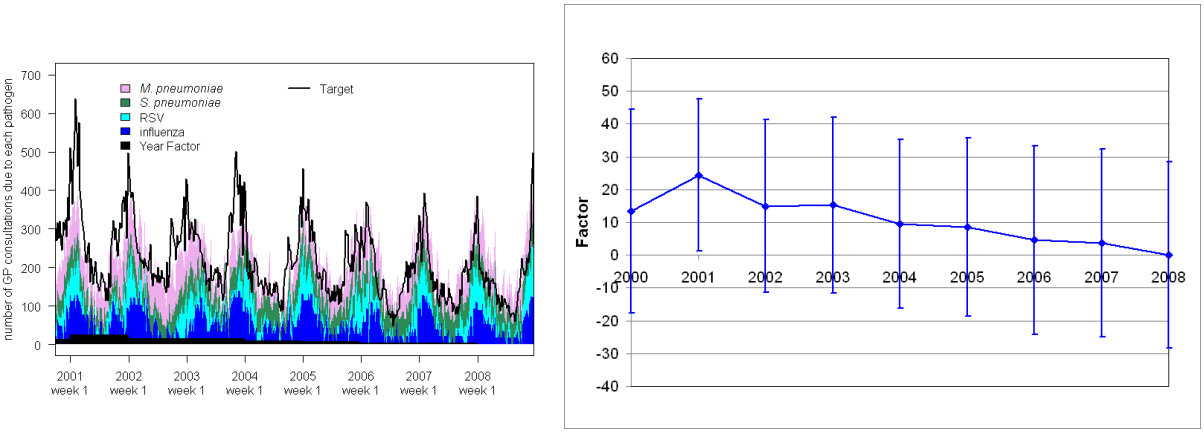

Figure A6. (A) Contribution of each pathogen to the model fit of LRTI consultations with a positive year factor(B) Factors (±SE) estimated by the model for each year.

The estimated number of GP consultations due to influenza using each of the fitting methods above (no year factor, year factor with no restrictions and positive year factor) was compared with the number of GP consultations that were recoded as influenza like illness (ILI) in the

RCGP dataset. The results are shown in Figure A7 and given in Table A2. Each fitting method estimates a similar number of influenza cases, both by week (panel A) and by year (panel B) and that these estimates are also very similar to the recorded ILI consultation rate.

We therefore decided to use a combination of the distributions of the RCGP recorded ILI consultation rate, and the distribution estimated from regression using a positive year factor for the number of GP consultations that were due to influenza. In reality the ILI consultations will contain some consultations that were not for influenza, but these will be offset by the fact that some consultations that *were* due to influenza will not appear as ILI. The combined distribution has a mean of 237,682 and a standard deviation of 39,191.

A **B**

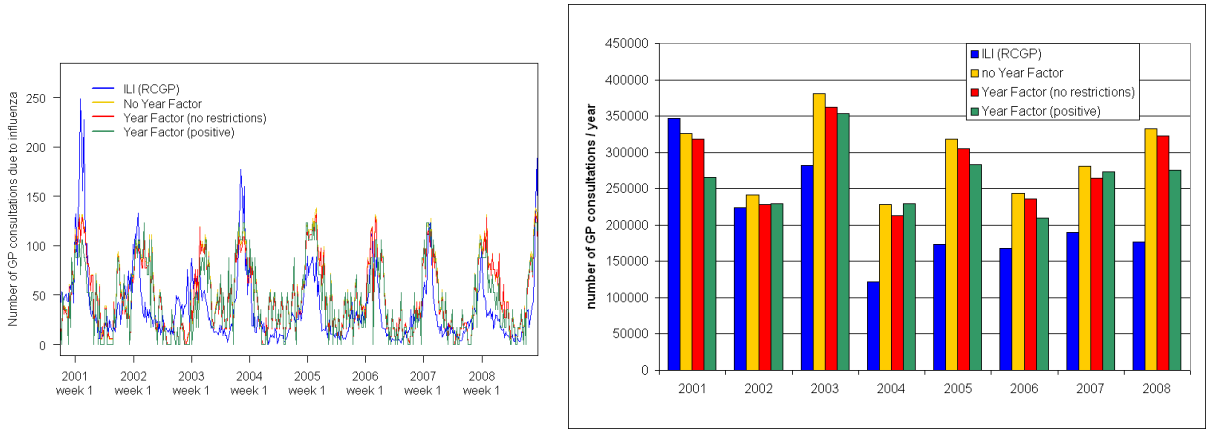

Figure A7. Comparison of model estimated consultation rates by week (A) and by year (B) with ILI consultation rate as extracted from the RCGP dataset.

	Mean number	Standard deviation number	Mean risk	Standard deviation risk
ILI (RCGP)	210,410	72,298	1.91%	0.66%
No year factor	294,070	35,508	2.67%	0.32%
Year factor (no restrictions)	281,299	29,297	2.55%	0.27%
Year factor (positive)	264,953	30,277	2.40%	0.27%
Combined distribution	237,682	39,191	2.16%	0.36%

Table A2. Estimated mean and standard deviation of the number and risk of GP consultations for influenza using each of the regression methods described above.

The standard deviation for ILI consultations was calculated using the inter-year standard deviation, while the standard deviation for the regression models are calculated using the regression uncertainty. Standard deviation for the combined model is calculated by averaging the variance from its two distributions.

Rates of GP consultation by trimester

Using the RCGP data and the regression performed using LabBase2 we were able to estimate the number of GP consultations for influenza in women aged 15-44 as 237,682(±39,191). We then estimated how many of these consultations occurred by pregnant women in each trimester of pregnancy.

The RCGP data does not provide information on pregnancy status, so the incidence of GP consultations by trimester of pregnancy was estimated using data from the General Practice Research Database (GPRD). The GPRD contains medical records for about 2000 representative general practitioners in the United Kingdom [26]. All consultations for influenza-like illness (ILI) occurring between 1 January 1992 and 30 June 2007 for individuals aged 15-44 years and 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]. This was found to be 1.14 (1.05 – 1.22) during the first trimester, 1.25 (1.17 – 1.34) during the second trimester and 1.08 (1.00 – 1.15) during the third trimester.

We allow the distribution of GP consultations in the female adult population to be give by C so $C \sim N(237{,}682, 39{,}191^2)$. We label the trimesters with a subscript of i with i=0-5, where i=0 is 3 months pre pregnancy, and i=5 is 2-5 months post pregnancy. We consider three months pre pregnancy, and six months post pregnancy period as it was hypothesised that during these periods women may have different consulting tendencies. We allow r_i to be the relative incidence of GP consultations in trimester i compared to the non-pregnancy period. The log of r_i is normally distributed, and the parameters for the distribution are given in Table A3. We assume that p% of the female adult population are pregnant and that another p% of the female adult population make up the 3 month pre and 6 month post pregnancy groups. Using the average of data from 2002 – 2007 from the ONS, we obtain an estimate for the

female 15-44 population of England and Wales as 11,018,969 and the number of maternities each year as 637,585. Therefore we can estimate p as p= 5.79%. We use these values to estimate g_i, the number of GP consultations in trimester i, along with the risk of GP consultation in trimester i.

	Trimester 0	**Trimester 1**	**Trimester 2**	**Trimester 3**	**Trimester 4**	**Trimester 5**
Mean r_i	1.06	1.14	1.25	1.08	0.67	0.83
Mean log(r_i)	0.058	0.131	0.223	0.077	-0.400	-0.186
Standard deviation log(r_i)	0.041	0.038	0.035	0.036	0.045	0.043

Table A3. Relative incidence of GP consultation by trimester

We can write the expression for r_i as the product of (i) the ratio of the number of consultations to the number of women in trimester i, and (ii) the ratio of the number of women outside in pregnancy, pre-pregnancy or post-pregnancy period to the number of consultations outside this period. In other words,

$$r_i = \frac{g_i}{p/3} \frac{1-2p}{C - \sum_{i=0}^{5} g_i} \qquad (1)$$

We then let $R = \sum_{i=0}^{5} r_i$ and $G = \sum_{i=0}^{5} g_i$ and can sum equation 1 over I = 0-5 to give:

$$R = \frac{G3(1-2p)}{p(C-G)} \qquad (2)$$

and

$$G = \frac{pCR}{3(1-2p) + pR} \tag{3}$$

Combining equations 1-3 gives and expression for g_i as:

$$g_i = \frac{pr_i(C-G)}{3(1-2p)} = \frac{pCr_i}{3(1-2p) + pR} \tag{4}$$

Bootstrap sampling with a million samples is used on equation 4 to obtain the following distributions for g_i:

	Trimester 1	**Trimester 2**	**Trimester 3**
Mean of g_i	5228	5732	4953
Standard deviation of g_i	885	966	836

Table A4. Mean and standard deviations of the number of GP consultations by trimester

In order to work out the risk of attending a GP in each trimester we divide the numbers in Table A4 by the number of people in each trimester (637,585/3 = 212528) to give the results in Table A5.

	Trimester 1	**Trimester 2**	**Trimester 3**
Mean risk in trimester *i*	2.460%	2.697%	2.330%
Standard deviation of risk in trimester *i*	0.416%	0.454%	0.393%

Table A5. Mean and standard deviations of the risk of GP consultations by trimester

The total number of GP consultations for influenza during pregnancy is $\sum_{i=1}^{3} g_i$ and is 15,913(±2,686). The total risk of GP consultations during pregnancy is 2.496%(±0.421%).

The number GP consultations for influenza outside of pregnancy is given by $C - \sum_{i=1}^{3} g_i$. We also calculate this when bootstrapping equation 4, and find that there are 221,848(±36,595), and the risk of GP consultation for influenza outside of pregnancy is 2.137% (±0.353%). (Numbers in brackets are standard deviations).

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