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Original Article

Effectiveness of seasonal influenza vaccine in preventing medically attended influenza infection in England and Wales during the 2010/2011 season: a primary care-based cohort study

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Background Estimates of seasonal influenza vaccine effectiveness (VE) are affected by factors such as the strain of the current circulating influenza virus and characteristics of the host.

Objective The objective of this study was to provide VE estimates for the 2010/2011 seasonal trivalent influenza vaccine (TIV) in preventing medically attended influenza in England and Wales for the season 2010/2011.

Methods A cohort study design was employed using electronic health records extracted from 104 GP practices in the Royal College of General Practitioners (RCGP) primary care sentinel network. Endpoints included influenza-like illness (ILI), lower respiratory tract infection (LTRI) as well as PCR-confirmed influenza from patients swabbed from practices participating in a swabbing scheme. Adjustment was made for age, month, underlying chronic condition, region and number of consultations in the 12 months prior to the study period. In addition to the cohort analysis, a nested test-negative case–control analysis (TNCC) was carried out using the swab-negative results as controls.

Results In the cohort analysis, VE against LRTI was −0·5% [95% CI: (−7·0%, 7·5%)], against ILI was 37·8% [95% CI: (32·3%, 43·0%)] and against PCR-confirmed influenza was 50·0% [95% CI:(25·9%, 65·6%)] for type A and 44·4% [95% CI: (10·1%, 65·6%)] for type B. Using the TNCC design, the type A VE was 56·5% [95% CI: (30·4%, 72·7%)] and for type B was 54·0% [95% CI: (21·0%, 73·3%)].

Conclusions This study shows that the 2010/2011 TIV provided moderate protection against the circulating influenza strains for the 2010/2011 season. It also suggests that VE against the less specific diagnosis of ILI can be found, but less specific endpoints such as LRTI are not useful.

Keywords Cohort, influenza, trivalent influenza vaccine, vaccine effectiveness.

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Introduction

A new seasonal trivalent influenza vaccine (TIV) is formulated each year due to antigenic and genetic changes in the circulating influenza strain viruses and waning population immunity.[1]

Recently TIV vaccine effectiveness (VE) has started to be taken into account for the World Health Organization's (WHO) yearly recommendation of the influenza vaccine composition. Timely VE estimation is also important to ensure optimal in-season identification of any reduction in VE to enable the adaptation of public health intervention measures, such as alternative use of antivirals.

Following the rapid development and licensure of several pandemic vaccines in 2009 with the emergence of the pandemic A(H1N1) 2009 virus, the UK introduced a pandemic influenza vaccination programme in autumn 2009 in addition to the seasonal 2009/10 TIV programme. For the 2009/2010 season, a general practitioner (GP) cohort study was undertaken in England and Wales to estimate the monovalent pandemic VE. This demonstrated a VE of 21% [95% CI: (5%, 34%)] against GP consultation with influenza-like illness (ILI) and an effectiveness of 64% [95% CI: (−6%, 88%)] for laboratory-confirmed H1N1 infection.[2]

In the first post-pandemic season in 2010/2011, the UK experienced widespread influenza transmission with A (H1N1)2009 being the dominant circulating strain, but with influenza B transmission occurring both simultaneously and later in the season.[3] The 2010/2011 seasonal TIV included

influenza antigens against the strains A/California/7/2009 (H1N1), A/Perth/16/2009(H3N2) and B/Brisbane/60/2008.[4]

The English and Welsh Chief Medical Officers' (CMO) advice to GPs in England and Wales, respectively, is to offer the annual influenza vaccination to those aged 65 or more and those between 6 months and 65 years who belong to one or more of the following risk groups: those with underlying chronic respiratory disease, chronic heart disease, chronic renal disease, chronic liver disease, chronic neurological disease, diabetes, immunosuppression or pregnant. In addition, vaccination is recommended for those living in long-stay residential homes, carers and healthcare workers in direct contact with patients.[5] Vaccine coverage for 2010/2011 TIV in England by the end of the campaign was reported as 73% for all those aged 65 years and more and as 50% for those in a clinical at-risk group between 6 months and 64 years.[6]

Different study designs have been used previously to estimate TIV VE including case–control, cohort and screening study designs.[7] The test-negative case–control (TNCC) design has been extensively utilised recently, although some concerns have been expressed about the method.[8] In this article, a cohort design was used to provide estimates of the effectiveness of the 2010/2011 TIV in preventing influenza infection in England and Wales for the season 2010/2011 both overall and by age group for a range of clinical and laboratory-confirmed endpoints. In addition, we took the opportunity to perform a nested TNCC with the results compared with those from the cohort study.

Methods

Study design

The cohort study design as used with similar data in previous years has been described in detail by Hardelid *et al.*[2] In brief, routine electronic primary care data from 104 GP practices in England and Wales that had been entered into GP health information systems between 1 September 2005 and 31 March 2011 as part of the Royal College of General Practitioners (RCGP) primary care sentinel network were extracted. Eighty of these practices participated in an influenza sentinel swabbing scheme.[2] The collection, testing and entry of the results into the patient records have been described in detail elsewhere.[2] The cohort study period was set between 1 September 2010 and 31 March 2011. Individuals were included in the study if they had been registered with a practice by 1 September 2010. The outcome variables of interest were as follows: (i) influenza-like illness (ILI) defined as combination of acute onset, cough and systemic symptoms (such as fever, headache myalgia); (ii) lower respiratory tract illness (LRTI) defined as acute bronchitis or bronchiolitis, including bronchitis unspecified and pneumonia; (iii) acute respiratory tract illness (ARTI) defined as all other respiratory tract infections (excluding the above), including upper respiratory tract infections and excluding otitis media; (iv) nasopharyngeal swab positive for influenza A strains [A/California/7/2009(H1N1) or A/Perth/16/2009 (H3N2)], and (v) swab positive for strain B/Brisbane/60/2008.

The explanatory variables at the individual level were the date of the seasonal 2010/11 TIV vaccination, age at the beginning of the study period (grouped into 1–4, 5–14, 15–44, 45–64, 65–74, 75 + years of age), month of consultation, gender and history of underlying chronic conditions in the 5 years prior to the beginning of the study (chronic conditions include heart disease, lung disease, diabetes mellitus, chronic renal disease, dementia, stroke, immunosuppression). For the vaccination variables, immunity was assumed to start 14 days or more following the date of vaccination with 2010/2011 TIV. Vaccination with the previous season TIV was not included in the analysis due to colinearity (of those vaccinated with the 2009/2010 TIV, 84% had received the 2010/2011 TIV). Propensity to consult was defined as the number of GP consultations between 1 September 2009 and 31 August 2010 grouped into no consultations and then quartiles. At the practice level, the explanatory variables were Index of Multiple Deprivation deciles (IMD) based on the practice postcode and the region/Strategic Health Authority (SHA).

As an alternative study design to the cohort, a nested test-negative case–control analysis (TNCC) was carried out using the PCR-confirmed type A results as cases and the swab-negative results as controls. The analysis was repeated using the type B positives as cases.

Statistical analysis

Poisson regression models were used for VE estimation separately for each outcome. A backward stepwise procedure was carried out by excluding variables that altered the risk ratio by <5%. The final model included, apart from the 2010/2011 seasonal TIV, the remaining variables following the stepwise process and any other variables that remained in the models of the other outcomes. The models were also run after stratifying by age group, month and risk group. The season 2010/2011 TIV VE was defined as follows:

$$\mathrm{VE} = 1 - \mathrm{RR}_{\mathrm{TIV}},$$

where $\mathrm{RR}_{\mathrm{TIV}}$ denotes the relative risk for the 2010/2011 seasonal TIV.[2]

A logistic regression model was used for the nested case–control study design using the same exposures included in the final cohort model. The season 2010/2011 TIV VE was defined as follows:

$$\mathrm{VE} = 1 - \mathrm{OR}_{\mathrm{TIV}},$$

where OR_{TIV} denotes the odds ratio for the 2010/2011 seasonal TIV.[3]

Stata MP was used for the statistical analysis.[9]

Results

The initial data set comprised of 1 005 132 registered individuals in the participant 104 RCGP practices. After exclusions due to deaths and de-registrations, 940 343 individuals were included in the analysis. Of these, 185 542 (19·73%) received the 2010/2011 seasonal trivalent influenza vaccine. The overall vaccine coverage for ages 1–64 was 8·8%, whereas for 65 years or older was 72·8%. The vaccine coverage for those under 65 years who belonged to a clinical risk group was 50·7%. The numbers of vaccinated individuals and the number of ILI, LRTI and PCR-confirmed events are shown in Table 1.

From the GP practices that participated in the swabbing scheme, a total of 3072 swab results were recorded. Of these, 731 (23·8%) were confirmed as influenza type A and 509 (16·6%) as type B, the remainder were influenza negative. Of the 731 type A samples, 6 were H3N2, whereas the remainder were H1N1. From the practices that participated in the swabbing, there were 7153 individuals who reported ILI symptoms and 1699 (23·8%) of them had swab results. Examining individuals with ILI, those who were swabbed had a mean age of 33 years (SD = 20), whereas those who were not swabbed had a mean age of 37 years (SD = 20) ($P < 0·001$). For the same group of individuals, there was no significant difference in the influenza vaccination status, gender, month of vaccination or belonging to a risk group between those swabbed and those not swabbed. For individuals with LRTI and ARTI events, swab results were available for 2·6% (136 of 5196) and 2·5% (1210 of 49 017) of them, respectively.

The final models were adjusted for age group, month, underlying chronic condition, number of consultations in the 12 months prior to the study period and region. The crude and adjusted VE estimates for 2010/2011 seasonal TIV are given separately for each outcome (Table 2). Of the adjusted variables, age had the highest impact on the VE estimate. The adjusted VE for the ILI endpoint was estimated as 37·8% [95% CI: (32·3%, 43·0%)]. The effect of propensity to consult was examined by excluding it from the model resulting in a reduced adjusted VE estimate of 24·6% [95% CI: (17·7%, 30·8%)]. For the PCR-confirmed endpoint (for any type of influenza), the adjusted VE was 47·4% [95% CI: (29·0%, 61·0%)]. For influenza type A infection, the VE was 50·0% [95% CI: (25·9%, 65·6%)], whereas it was 44·4% [95% CI: (10·1%, 65·6%)] for influenza type B. There was no significant evidence of effectiveness using the LRTI [−0·5%; 95% CI: (−7·0%, 7·5%)] or the ARTI [−8·0%; 95% CI: (−11·4%, −4·7%)] endpoints. After including in the adjusted variables those who received the pandemic A (H1N1)2009 vaccine, the VE estimate for ILI was reduced to 33·3% [95% CI: (27·1%, 39·0%)] and the VE for

Table 1. Numbers vaccinated, influenza-like illness (ILI), LRTI, acute respiratory tract illness (ARTI) and PCR-confirmed events by month, age group and whether belonging to a risk group

Variable	Level	Total number of participants	Numbers vaccinated (%)	Number of events (%)			
				ILI	LRTI	ARTI	PCR-confirmed
Month	September	940 343	236 (0·03)	235 (0·02)	738 (0·08)	7472 (0·79)	1 (0·00)
	October	932 630	78 142 (8·38)	414 (0·04)	971 (0·10)	9188 (0·99)	7 (0·00)
	November	924 453	142 771 (15·44)	539 (0·06)	947 (0·10)	10 090 (1·09)	42 (0·01)
	December	917 078	164 706 (17·96)	4058 (0·44)	1607 (0·18)	16 402 (1·79)	767 (0·11)
	January	911 360	179 324 (19·68)	3119 (0·34)	1130 (0·12)	10 324 (1·13)	358 (0·05)
	February	904 959	182 859 (20·21)	718 (0·08)	765 (0·08)	8403 (0·93)	54 (0·01)
	March	899 254	182 699 (20·32)	355 (0·04)	849 (0·09)	9137 (1·02)	11 (0·00)
Age group	1–4	45 659	1428 (3·13)	550 (1·20)	408 (0·89)	11 614 (25·44)	118 (0·35)
	5–14	109 594	4722 (4·31)	1047 (0·96)	230 (0·21)	11 133 (10·16)	251 (0·31)
	15–44	372 139	20 086 (5·40)	4535 (1·22)	1601 (0·43)	24 763 (6·65)	607 (0·22)
	45–64	252 093	42 159 (16·72)	2493 (0·99)	1994 (0·79)	12 232 (4·85)	238 (0·13)
	65–74	83 392	58 038 (69·60)	451 (0·54)	1007 (1·21)	3648 (4·37)	22 (0·03)
	75+	77 466	59 109 (76·30)	311 (0·40)	1320 (1·70)	2874 (3·71)	4 (0·01)
Belonging in	No	784 544	96 460 (12·30)	7799 (0·99)	4307 (0·55)	54 492 (6·95)	1061 (0·18)
A risk group	Yes	155 799	89 082 (57·18)	1588 (1·02)	2253 (1·45)	11 772 (7·56)	179 (0·15)
Total		940 343	185 542 (19·73)	9387 (1·00)	6560 (0·70)	66 264 (7·05)	1240 (0·18)*

*From 697,596 individuals covered by 80 practices.

Table 2. Crude and adjusted 2010/2011 influenza VE estimates by outcome

Outcome	*n* events/person-years Amongst unvaccinated (%)	*n* events/person-years Amongst vaccinated (%)	Crude VE, % (95% CI)	Adjusted VE, %* (95% CI)
ILI	8453/462 927 (1·83)	934/68 378 (1·37)	25·2 (20·0, 30·1)	37·8 (32·3, 43·0)
LRTI	4843/462 927 (1·05)	1717/68 378 (2·51)	−140·0 (−153·6, −127·2)	−0·5 (−7·0, 7·5)
ARTI	58 752/462 927 (12·69)	7512/68 378 (10·99)	13·4 (11·3, 15·5)	−8·0 (−11·4. −4·7)
PCR-confirmed (any type)	1172/342 556 (0·34)	68/51 438 (0·13)	61·4 (50·7, 69·7)	47·4 (29·0. 61·0)
PCR-confirmed influenza A	691/342 556 (0·19)	40/51 438 (0·08)	61·4 (47·0, 72·0)	50·0 (25·9, 65·6)
PCR-confirmed influenza B	481/342 556 (0·14)	28/51 438 (0·05)	61·2 (43·3, 73·5)	44·4 (10·1, 65·6)

*Adjusted for underlying chronic condition, number of consultations in the 12 months prior to the study period and region.

PCR-confirmed any type of influenza was reduced to 42·5% [95% CI: (21·5%, 57·8%)].

The adjusted VE estimates for the ILI endpoint stratified by age group, month and risk group are given in Table 3. The ILI VE estimate was highest in December declining to no VE in February and March. The VE against ILI was protective in the under 5-year-olds, whereas there was no evidence of protection for those over 75 years. Individuals belonging to a risk group had only slightly lower VE point estimates compared with those who did not.

Table 3. Adjusted 2010/2011 seasonal influenza VE estimates for influenza-like illness (ILI) events stratified by month, age group and whether belonging to a risk group

Variable	Adjusted ILI VE, % (95% CI)**
September	99·9 (−inf, 100·0)*
October	23·6 (−50·3, 61·2)
November	22·4 (−12·6, 46·5)
December	51·8 (44·0, 58·4)
January	34·0 (24·3, 42·4)
February	2·6 (−28·2, 25·9)
March	−67·0 (−134·7, −18·8)
<5 years	72·2 (11·5, 91·2)
5–14 years	35·9 (4·1, 57·2)
15–44 years	45·5 (34·6, 54·6)
45–64 years	32·2 (22·4, 40·8)
65–74 years	43·2 (29·7, 54·0)
75 + years	−4·5 (−42·2, 23·2)
Not in risk group	35·0 (26·6, 42·5)
Any risk group	38·7 (30·6, 45·8)

*There were no ILI patients who received the seasonal influenza vaccine.
**Adjusted for underlying chronic condition, number of consultations in the 12 months prior to the study period and region.

The nested TNCC analysis was carried out using 1832 swab PCR-negative samples as controls. Of those tested positive against influenza type A and type B, 5·5% (40 of 731) and 5·5% (28 of 509) had been immunised, respectively, whereas of those tested negative against influenza type A and type B, 15·5% (283 of 1832) had had the seasonal influenza vaccine. The final models were adjusted for age group, month, underlying chronic condition, number of consultations in the 12 months prior to the study period and region. The adjusted VE estimate for any type of influenza for the season 2010/2011 TIV was 53·6% [95% CI: (32·0%, 68·3%)]. The adjusted VE for influenza type A was 56·5% [95% CI: (30·4%, 72·7%)] and for type B was 54·0% [95% CI: (21·0%, 73·3%)] (Table 4).

Discussion

A cohort study was carried out using data collected as part of the RCGP GP sentinel network. The results showed evidence of statistically significant protection of the 2010/2011 seasonal TIV in England and Wales for both ILI and PCR-confirmed influenza endpoints. Using a non-specific endpoint such as ILI as an alternative to PCR-confirmed influenza has merit, given the improved precision due to the large numbers of ILI cases especially when carrying out a mid-season analysis when the study sample size is smaller. Finally, the nested TNCC study design VE estimates were very similar to the cohort VE estimates that can be viewed as a validation of the TNCC approach.

Table 4. Crude and adjusted 2010/2011 influenza VE estimates by outcome for the nested TNCC study

Outcome	Vaccinated/total controls (%)	Vaccinated/total cases (%)	Crude VE, % (95% CI)	Adjusted VE, % (95% CI)*
PCR-confirmed (any type)	283/1832 (15·5)	68/1240 (5·5)	68·2 (58·2, 75·9)	53·6 (32·0, 68·3)
PCR-confirmed influenza A	283/1832 (15·5)	40/731 (5·5)	68·3 (55·4, 77·5)	56·5 (30·4, 72·7)
PCR-confirmed influenza B	283/1832 (15·5)	28/509 (5·5)	68·1 (52·4, 78·7)	54·0 (21·0, 73·3)

*Adjusted for age group, month, underlying chronic condition, number of consultations in the 12 months prior to the study period and region.

The cohort and nested TNCC TIV VE estimates in this article were close to the 2010/2011 estimates from a previous TNCC study based on individuals swabbed from RCGP practices participating in the same influenza sentinel swabbing scheme as in the study presented in the present article.[10] In the previous TNCC study, data on vaccination, age and risk group status were collected on a form submitted with the swab. The overall VE estimate for laboratory-confirmed GP consultation for the UK-wide study, adjusted for age and month in this study, was 56% [95% CI: (42%, 66%)], similar to the laboratory-confirmed findings in this article.[10] A similar finding was reported from a cohort study in Spain where the laboratory-confirmed VE was estimated as 58% [95% CI: (16%, 79%)].[11] A European study based on sentinel practitioner surveillance networks from eight European countries using a TNCC approach estimated the VE of any type of influenza as 52% [95% CI: (29%, 72%)].[12] The subtype-specific TIV VE estimates were similar for influenza A and B infection during the 2010/2011 season and indicate moderate TIV protection. The 2010/2011 season was dominated by A(H1N1)2009 activity with co-circulation of influenza B: antigenic analysis of A(H1N1)2009 viruses found that they were similar to the A/California/07/2009 vaccine strain, and the majority of the influenza B viruses belonged to the B/Victoria lineage similar also to the 2010/11 TIV strain.[13]

For the ILI endpoint, the overall adjusted VE estimates are similar to previous cohort studies,[2,11] suggesting that influenza vaccination can prevent a significant proportion of ILI consultations during the influenza season. However, interpretation of VE against ILI needs to be done in the context of the specificity of this endpoint. For example, our study showed evidence that protection was lower in the 75-year-olds compared with the younger age groups, a finding also reported in the 2008–2010 RCGP cohort analysis.[2] This may be either a true effect suggesting higher protection of the TIV for younger age groups or it may be partly due to the lower influenza positivity rate for true influenza in this age group. Further work will be needed to confirm this.[14] The analysis also showed higher influenza VE for December when there is high influenza circulation, a finding reported elsewhere.[2] In such circumstances, other researchers have suggested using non-influenza months to adjust for the observed protection against ILI during this period.[15]

There were several limitations to the study. There was evidence that those persons presenting in primary care with ILI and being swabbed were not systematically different (apart from age) compared with those who were not swabbed. However, only 55% (1699 of 3072) of those swabbed had an ILI symptom recorded and 82% (2511 of 3072) had any type of acute respiratory illness recorded. This raises questions whether there was under-recording of clinical respiratory symptoms by GPs in the patient record. We do not believe that this should bias the VE estimates against ILI as there is no reason that failure to record ILI should be related to vaccination status. Another limitation is that the date the swab was taken was used for the analysis as the onset date of illness was not available. If the period between symptom onset and swabbing is long, this could result in false-negative samples. Moreover, 396 samples were taken, but were never recorded in the data set, which is something that can be improved in future studies.

As it has been shown in the past, the endpoints used in the analysis had different sensitivities and specificities that influence the VE estimates.[7] No significant protection of the 2010/2011 TIV was shown based on the LRTI and ARTI endpoints, which may be an indication of very low specificity. In particular, the VE estimate against ARTI endpoint was negative, which is likely to indicate residual confounding. These findings question the appropriateness of LRTI and ARTI endpoints for estimating seasonal influenza VE.

In conclusion, this study provides evidence that the 2010/2011 TIV provided moderate protection against influenza for the season 2010/2011. A retrospective cohort design was successfully used to estimate influenza VE adjusting for potential confounders, in particular propensity to consult,

with similar estimates obtained through a nested TNCC study.

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Conflict of interest

We declare that Douglas Fleming has served on advisory boards relating to influenza vaccine development and the burden of illness attributable to influenza (includes GSK, Medimmune, Sanofi Pasteur, Novartis). In addition, he has received support to attend international meetings. The other authors have no financial or other relationships that might lead to conflict of interest.

References

1 Chowell G, Miller MA, Viboud C. Seasonal influenza in the United States, France and Australia: transmission and prospects of control. Epidemiol Infect 2008; 136(6):852–864.

2 Hardelid P, Fleming DM, Andrews N *et al.* Effectiveness of trivalent and pandemic influenza vaccines in England and Wales 2008-2010: results from a cohort study in general practice. Vaccine 2012; 30 (7):1371–1378.

3 Pebody R, Hardelid P, Fleming DM *et al.* Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11. Euro Surveill 2011; 16(6):8–13.

4 HPA group. Influenza vaccine composition. Health Protection Agency 2012 February 28; Available at http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733812968#north1011 (Accessed 13 June 2012).

5 HPA group. Frequently asked questions on influenza. Health Protection Agency 2013 February 8; Available at http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733852084 (Accessed 4 April 2013).

6 Begum F, Pebody R. Seasonal influenza vaccine uptake amongst GP patient groups in England. Department of Health 2011 July 19; Available at http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_129856.pdf (Accessed 13 June 2012).

7 Kavanagh K, Robertson C, McMenamin J. Assessment of the variability in influenza A(H1N1) vaccine effectiveness estimates dependent on outcome and methodological approach. PLoS ONE 2011; 6(12):e28743.

8 Puig-Barbera J. 2010-2011 influenza seasonal vaccine, preliminary mid-season effectiveness estimates: reason for concern, confounding or are we following the right track? Euro Surveill 2011; 16(11):pii: 19821.

9 Stata [computer program]. Version 12.0. College Station, TX, 2011.

10 Pebody RG, Andrews N, Fleming DM *et al.* Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A (H1N1) 2009 vaccines in preventing influenza in the United Kingdom. Epidemiol Infect 2012; 1–11. [Epub ahead of print]

11 Castilla J, Martínez-Artola V, Salcedo E *et al.* Vaccine effectiveness in preventing influenza hospitalizations in Navarre, Spain, 2010-2011: cohort and case-control study. Vaccine 2012; 30(2):195–200.

12 Kissling E, Valenciano M, Cohen JM *et al.* I-MOVE multi-centre case control study 2010-11: overall and stratified estimates of influenza vaccine effectiveness in Europe. PLoS ONE 2011; 6(11): e27622.

13 HPA group. Surveillance of Influenza and other respiratory viruses in the UK. Health Protection Agency 2011; Available at http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1296687414154 (Accessed 12 December 2012).

14 Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12(1):36–44.

15 Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. J Infect Dis 2004; 190(1):1–10.