Estimates of influenza vaccine effectiveness in primary care in Scotland vary with clinical or laboratory endpoint and method – experience across the 2010/11 season

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Abstract

Aim

This study examines estimation of seasonal influenza vaccine effectiveness (VE) for a cohort of patients attending general practice in Scotland in 2010/11. The study focuses on the variation in estimation of VE for both virological and clinical consultation outcomes and understanding the dependency on date of analysis during the season, methodological approach and the effect of use of a propensity score model.

Methods

For the clinical outcomes, three methodological approaches were considered; adjusted Poisson multi-level modelling splitting consultations in vaccinated individuals into those before and after vaccination, adjusted cox proportional hazards modelling and finally the screening method. For the virological outcome, the test-negative case-control study design was employed.

Results

VE was highest for the most specific outcomes of ILI (Poisson end-of-season VE=47% (95% CI: -69%, 83%); Cox VE=34% (95% CI: -64%, 73.2%); Screening VE=52.8% (95% CI: 3.8%, 76.8%)) and a virological diagnosis (VE=54% (95% CI: -37%, 85%)). Using the Cox approach, adjusted for propensity score score only gave VE=46.5% (95% CI: -30.4%, 78.0%).

Conclusion

Our approach illustrated the ability to achieve relatively consistent estimates of seasonal influenza VE using both specific and less specific outcomes. Construction of a propensity score and use for bias adjustment increased the estimate of ILI VE estimated from the Cox model and made estimates more similar to the Poisson approach, which models differences in consultation behaviour of vaccinated individuals more inherently in its structure. VE estimation for the same data was found to vary by methodology which should be noted when comparing results from different studies and countries.

Introduction

Estimates of influenza vaccine effectiveness (VE) vary by season, population examined, study methodology, outcome measured, time of estimation and statistical methodology hindering comparability between studies [1,2]. In season 2010/11 mid-season estimates of influenza VE from both laboratory confirmed cases [3-5] and consultation data [6] and end-of-season estimates [7,8] have indicated seasonal influenza VE ranging from 31% to 72% with effectiveness greater in individuals who had exposure to pandemic strain-specific vaccination (PIV) in 2009/10 and trivalent seasonal influenza vaccination (TIV) in 2010/11.

Laboratory-confirmed endpoints generate the highest estimates of VE with the test negative design [9] commonly used, such as in Pebody *et al*. [7], however using a convenience sample may lead to bias in the control group. Cohort designs such as defined in Castilla *et al*. [10] allow for monitoring of clinical endpoints such as influenza-like illness (ILI) but their observational nature leads to confounding by indication - whether this be presented as the 'healthy vaccine effect' where healthy individuals are less likely to have an outcome inflating VE (often observed with death or hospitalisation outcomes), or conversely the 'health seeking behaviour effect' where vaccinated individuals are more likely to consult their general practitioner decreasing VE. The monitoring of clinical endpoints which occur more commonly than ILI, such as acute respiratory illness (ARI) may lead to less reliable estimates due to reduced specificity especially if the incidence of influenza is low compared to other circulating respiratory pathogens. Consistency of the case definition used for such consultation groupings between countries is also required for comparability [2].

The statistical methodology adopted for the study depends on the data format, whether it be individual or aggregate, and the study design used. For aggregated cohort data, the screening method [11] can be used but has limited ability to capture time dependency - an essential component for influenza vaccine effectiveness as the baseline hazard of ILI changes during the season and individuals move from an unvaccinated state to a vaccinated one at the same time as influenza is circulating. Individual-level analysis can capture this, either using a Poisson approach offsetting by person-time in the vaccinated and unvaccinated groups [12] or Cox proportional hazards [13] These differ in how changes in the levels of the hazard over time is modelled - for Poisson time is added as a covariate and the hazard assumed to be constant within each time period whereas the Cox model accounts for time implicitly and no assumption is made regarding the shape of the hazard rate over time. Estimates from the Poisson and Cox approaches will be similar [1] if the time period is chosen appropriately and all else is equal. The Cox approach may be inappropriate

if the proportionality assumption of the hazard between the unvaccinated and vaccinated groups over time is violated.

Using a cohort of Scottish primary care patients for season 2010/11, we examine these issues using one dataset. For all individuals in our data, we consider three consultation outcomes and laboratory confirmed infection for a nested sample of the cohort. For the consultation outcomes, VE estimated by individual-level Poisson and Cox approaches and aggregate-level screening method are compared. The use of propensity scores is explored to reduce confounding by indication in our models. In addition, we consider weekly estimates of VE and highlight estimation issues during the season. In this way, we aim to understand the variation in influenza VE by the outcome chosen and statistical methodology used and outline the advantages and disadvantages of each.

Methods

Cohort

The study population is composed of individuals of the PIPeR Cohort, as described elsewhere [1]. Individual level data on influenza-related primary care consultations, vaccination records and deaths for all permanent patients from each of the 17 primary care practices is recorded. Patients who die are censored at date of death. The cohort is assembled on 1st October 2010 and followed up until 31st March 2011. Qualifying at risk individuals in Scotland (those aged 65 and over and individuals with chronic health condition) were offered vaccination with trivalent seasonal influenza vaccination (TIV) (see supplementary materials for details), which includes H1N1v, and had potentially received pandemic strain-specific vaccination (PIV) in season 2009/10. Vaccinations with TIV post 1st September 2010 are included.

The consultation outcomes considered are: the total number of primary care influenza-like illness consultations (ILI), all acute respiratory infection consultations (which includes influenza-like illness) (ARI), and all ARI excluding those which are Asthma-related (ILIARI). Consultations occurring within 14 days of the date of TIV are not recorded as a vaccine failure.

Potential confounders considered are age, gender, the presence of chronic disease (coronary heart disease, chronic liver disease, chronic respiratory disease, chronic liver disease, neurological disorders and immunosuppression), previous vaccination with seasonal or pandemic vaccination in 2009/10, the number of ILIARI consultations in the previous season (0, 1, 2+) - used as a measure of health seeking behaviour - and Carstair's deprivation score for the area of residence [14]. For those aged under 65, chronic risk group status is assigned at the beginning of the cohort and individuals are assumed to remain in that status.

Vaccine effectiveness

For the consultation outcomes VE is estimated by comparing adjusted hazard rates in the vaccinated and unvaccinated using both Cox proportional hazards clustered on practice. The proportional hazards assumption is tested by visual inspection of the Schoenfeld residuals which should no trend over time if proportionality holds. This Cox estimates are compared to VE estimated from a time adjusted Poisson regression multi-level model, nested on practice. In the Poisson model vaccination status is assigned retrospectively and further stratified – those who are not vaccinated with TIV by end of the season are classed as "never vaccinated". Those who have a TIV by the end of the season begin in the "before vaccination" class. Their vaccination status is then a time dependent covariate which changes to "after vaccination" when the vaccine has been received. Vaccine effect is then

calculated as a comparison of adjusted rates in the after vaccination and before vaccination group, taking into account the time, in weeks, throughout the season, and aims to make comparison between two groups which are more similar in terms of their health-care seeking behaviour (for more details see Kavanagh *et al*. [1])). Both models are adjusted by all confounding factors mentioned previously.

For comparison, VE estimation using the screening method [11] with aggregated GP practice level data stratified by gender, age group (0-64, 65+) and for the under 65s only risk group membership (yes/no), is illustrated for the three consultation groupings ILI, ARI and ILIARI. The screening method is run for three time periods defined by cut off periods for vaccination and consultation; vaccination by end of December/January/February and consultations in January/February/March. For each time period, VE is estimated from the intercept term of a multi-level logistic regression model adjusted for age, sex and risk group with practice included as a random effect.

Allocation bias in receiving the TIV is a problem with observational studies [15] which we attempt to eliminate using covariate adjustment. For a sensitivity analysis, we consider the use of propensity scores [16] and examine the effect this has on the end-of-season estimates using the Cox proportional hazards model. The propensity of an individual to receive the seasonal vaccine in 2010/11 is predicted using a non-parsimonious logistic regression model based on the covariates described previously. This model is estimated on two-thirds of the data and validated on the remaining data via using the Receiver-Operating Characteristic (ROC) curve and the associated area under the curve (AUC). This score is then estimated for each individual in the cohort and used to reduce bias by two alternative methods; (i) using the deciles of the score as the only adjusting factor and (ii) one-to-one matching of vaccinated to non-vaccinated individuals based on the score (randomly within a defined caliper of 0.25 times the standard deviation of the logit of the score [17]).

Virological swab tests for influenza are collected in Scotland as part of routine influenza surveillance. These data can be linked to the PIPeR cohort, details are in [1], and a nested case control analysis is used to estimate VE using a generalised additive logistic regression model, adjusted for age, risk group status and the temporal trends in swab positivity - modelled by a cubic spline based upon week of sample collection [18]. This is regarded as a gold standard as a hard laboratory endpoint is available and adjustment for confounders possible.

All analysis was conducted using R version 2.14.1 [19].

Results

Demographics

The 2010/11 cohort is composed of 93,380 eligible individuals, 49.8% male, mean age 40.7 years, with 16.8% over 65 and 4.3% under 5 years old (Table 1) and is well matched to the population of Scotland (48.5% male, 5.6% under 5, 16.8% over 65 [20]). Of those under 65, 16.3% are in at least one clinical risk group. A total of 877 patients, 0.94% of the cohort, had at least one virology test with 642 patients tested in the period 1st October 2010 to 31st March 2011. Whilst 50% of the cohort is female they account for 59% of those who consulted for an ILIARI and 57% of those tested. The major selection bias for virological testing is age where there is over representation, compared to consultations, among those swabbed in the 15-44 age group and under representation among children aged under 5. There is also a deprivation bias with patients in a more deprived neighbourhood more likely to be swabbed, but little bias associated with risk group membership and seasonal vaccination in the previous year.

Vaccine uptake

Vaccine uptake is highest in those 65 and over (66.5% for men and 65.6% for women) and for those under 65 at risk uptake is 46.8%; these figures are lower than the national figures of 75.4% in those over 65 and 56.1% in those under 65 at risk [21] possibly reflecting the more disadvantaged nature of the cohort (Table 1). Vaccination was primarily delivered in late October and November (93% of over 65s who are eventually vaccinated have been so by the end of November 2010). Overall, 19.1% of the cohort received the seasonal influenza vaccination in 2010/11. Uptake varies between the GP practices ranging from 58.4% to 77.6% for the over 65s and 35.7% to 66.6% for the under 65s at risk.

Consultations

Consultation rates per 1000 person days, between 1st October 2010 and 31st March 2011, split by vaccination status at the time of consultation illustrate that substantially lower ILI rate in both the unvaccinated and vaccinated compared to the less specific ILIARI and ARI consultation groupings (Table 2). Overall crude rate ratios (RR) for ILIARI and ARI show an increased risk of consultation in those vaccinated (ILIARI RR=1.2; ARI RR=1.4) but a decreased risk for ILI in the vaccinated (ILI RR=0.6). The incidence of ILI declines linearly with age – 0.019 per 1000py in those aged 0-4 declining to 0.003 per 1000py in those aged 75+. Age modifies the reduction in risk of ILI observed with vaccination – young vaccinated individuals (aged less than 15 years) have no ILI consultations recorded indicating RR=0 but for those aged 75+ there is an increased risk of consultation with vaccination RR=1.34. There is however limited power to test this due to the small number of ILI consultations (n=18) in those vaccinated. The majority of the consultations occur in the non-vaccinated group partly reflecting that the majority of individuals in the cohort (80.9%) do not receive vaccination.

There is a steep increase in the number of consultations around the start of December with the majority of ILI consultations occurring in this month. ILIARI consultations peaked in late December 2010 and early January 2011.

Vaccine effectiveness

VE estimates vary dependent on the consultation grouping, the time of measurement and the statistical method (Table 3). Generally the Poisson and screening methods generate the most similar point estimates for VE, with the Cox estimates lower. Estimates earlier in the season have wider associated confidence intervals in particular for the rarer outcome of ILI (Figure 1). End of season VE estimates are positive for all three approaches with estimates highest for ILI and lowest for ILIARI. For ILI, both the Cox and Poisson models estimated positive protective effect however the small number of ILI events (*n*=190) affected the precision of the estimate and the confidence interval spanned zero (Cox ILI VE=33.7% (95% CI: -64.0, 73.2%); Poisson ILI VE=46.5% (95% CI:-69.3, 83.1)%). For ILIARI and ARI the Poisson model gave positive significant VE and whilst point estimates from the Cox model were positive, the confidence interval spanned VE=0. For ILI, the Cox model estimated that individuals with at least 1 ILIARI consultation in the previous year were 2.3 times (95% CI: 1.5, 3.5) more likely to consult with an ILI this season than those with none, and those with two or more previous consultations were 3.1 times (95% CI: 1.6, 6.2) more likely to consult with an ILI. In the Poisson model structure the level is similar at 2.2 times (95% CI: 1.3, 3.9) and 2.7 times (95% CI 1.1, 6.8) respectively.

End of season unadjusted estimates using the Cox method show negative VE for ILIARI and ARI indicating that negative confounding leading to lowered VE is present for these outcomes. For ILI this is not the case as adjusted estimates are lower which is due to the effect modification of age.

Weekly estimates illustrate that ILI VE estimation was not possible until well into the season with stable estimates obtained by mid-January (Figure 1). For ILIARI and ARI the large numbers of events lead to more stable estimation from the beginning of November. From November to the beginning to January the VE estimates from the Poisson model give consistently higher estimates than using Cox proportional hazards (Figure 1). After the beginning of January, coinciding with a decrease in influenza circulating in the community [21], the estimates from these two models diverge with the estimates from the Poisson model reaching an asymptote and the Cox estimate decreasing. Visual inspection of the schoenfeld residuals for each of ILI, ILIARI and ARI showed no trend over time and hence no violation of the proportional hazards assumption.

The propensity model had good predictive power in assigning vaccination status (AUC=0.948). Comparison of the adjustment due to the propensity score can be made by comparing to the unadjusted estimates. The score does little to adjust for confounding in the ILI estimate where age is the main factor. For ILIARI and ARI the score provides increases the estimates markedly and to a level greater than the individual covariate adjustment can achieve. The matched cohort reduced the sample size substantially to 13742 from a potential maximum of 32562 if each vaccinated individual could have been matched. Estimates of VE from the matched cohort were the lowest of all methods and for ILIARI showed a negative effect (Table 3).

A total of 208 individuals tested positive for influenza, yielding positivity rate of 32.3%. The majority of the swabbed patients were unvaccinated at the time of swabbing (*n*=561); and only 81 were swabbed post vaccination. Among those not vaccinated, swab positivity is similar among those in a risk group (34 positive, 75 negative; 31.2%) compared to those not in a risk group (160 positive, 294 negative; 35.2%). Relatively few vaccinated patients were tested - 81 patients and only 8 were positive for H1N1v and 6 positive for Influenza B (Table 4).

Adjusting for the other factors in the model there was no evidence of any effect on swab positivity of age group, risk group, deprivation and gender (Table 5). Relative to those who were unvaccinated at the time of swabbing the odds ratio of testing positive with TIV seasonal only is 0.46 (95% CI: 0.15, 1.37), corresponding to a VE of 54% (95% CI: -37, 85%). With PIV only VE=60% (95% CI: 16, 81%) and with the combination VE=72% (95% CI: 34, 88%). There is no evidence that the addition of TIV to PIV conveys additional protection (Interaction test *p*=0.57). There is more imprecision when looking at H1N1v and Flu B separately and while the estimated odds ratios are less than 1 the confidence intervals are wide. The general pattern is that the TIV has better protection against Flu B, while PIV and the combination having the better VE against H1N1v.

Restricting the analysis to those targeted for vaccination reveals highest estimates for those who received both PIV and TIV; against all influenza VE=68% (95%CI: 22, 87%), against H1N1v VE=81% (95% CI 36, 94%) and against Influenza B VE=35% (-127, 81%)

Discussion

Outcome

For ILIARI and ARI consultations all end of season estimates of VE were statistically significant however the small number of consultations observed for ILI leads to a larger variability in the estimate and hence insignificance of the positive VE result (Cox VE=33.7% (95% CI: -64.0, 73.2%)). The point estimate is however very similar to those calculated by Castilla *et al.* [6] using the same method (VE=31% (95% CI 20, 40%) for medically attended ILI). The low numbers of ILI consultations observed over the season, which with the exception of the pandemic season in 2009/10 is not unusual in this cohort, do however impair the strength of the conclusions which can be reached and highlights the need to monitor various consultation groupings. These findings of a positive VE estimate for ILIARI and ARI are of public health importance since even a low VE in these groups may have a large public health benefit. This is because the number of people affected by these clinical conditions dwarves the size of the population recorded as having ILI and thus may have a large impact on the overall programme effectiveness of the annual seasonal influenza programme.

The sample size for the virology is limited and relatively few vaccinated patients were tested with only 8 positive for H1N1v therefore VE is estimated with low precision. This clearly identifies the need for more virological testing. However in these times of financial austerity a pragmatic line has to be walked between the amount of testing that can be planned versus the public health benefit that can be derived from any expansion to the testing undertaken. It is difficult to separately estimate the effects of TIV from the PIV and there is a suggestion that PIV has as much of a protective effect as TIV. This is in contrast with results from the end of season 2010/11 UK case negative study [7], which has a much larger number of samples and some of the patients in this report contribute to the UK study. This study showed that PIV and TIV both had positive VE estimates in 2010/11 (PIV only: VE=28% (95% CI: -6%, 51%); TIV: VE=55% (95% CI: 31, 71%). There was a significant improvement in VE for those that had TIV compared to PIV but no significant improvement for those vaccinated with both. This does raise an important issue for VE estimation public health – how do we account for the effect (either positive or negative) for receipt of a prior seasonal influenza vaccine and just how far back should we go in the vaccination history? The cohort approach adopted here offers the attraction of being able to make adjustment in any estimation of VE for such concerns.

Methodology

There is no consensus on which cohort method should routinely be employed to provide estimated VE or which clinical endpoint should be used. Exploratory studies such as this as

pivotal in examining the relative performance of each method when applied to one dataset. Estimates were found to vary dependent on the statistical methodology used but the conclusions reached regarding effectiveness were mainly consistent. A summary of the advantages and disadvantages of methodologies examined is summarised in Table 6. The important public health point is that the analysis has demonstrated positive end of season point estimates of VE across all methods and consultation groupings except when using a matched propensity score analysis. The matched analysis whilst balancing the confounding variables in the unvaccinated and vaccinated groups lost a large proportion of vaccinated individuals due to an inability to find a match. This substantially reduced the number of outcomes observed with ILI numbers falling from 190 in the full cohort to 33 in the matched cohort hence affecting the estimates found. The study demonstrates some of the challenges and pit-falls to be avoided when undertaking pooling or meta-analysis of cohort estimates of vaccine effectiveness in any season. Interestingly, the adjusted screening method, which is the simplest and cheapest method for estimation of VE, gave estimates of VE which were similar to those from the individual based method, though without the full adjustment for multiple confounding variables. Using the Cox approach with vaccination propensity score adjustment only, was found to give higher VE than the fully adjusted Cox model. This approach may capture more of the unmeasured behaviour of individuals who do not consult or are unlikely to appear for vaccination when they should.

The Poisson model with retrospective stratification of the vaccinated to permit a comparison of those vaccinated in the period before vaccination with those vaccinated in the period after vaccination allows additional adjustment for different health seeking behaviour (essentially propensity to consult) as the comparison is closer to a within person comparison. This approach gives consistently higher estimates of VE than the Cox model which is directly attributable to the stratification as this is essentially the only difference between the model. This implies that the never vaccinated individuals are less likely to consult at a magnitude greater than that captured by the propensity to consult covariate, which had a similar effect size in both models. The differential may therefore be due to either a lack of adjustment in the Cox model for this behaviour or an over adjustment in the Poisson model. There may also be indication bias in the Poisson approach with individuals consulting and then going on to obtain the seasonal flu vaccination giving a regression to the mean problem. The adjustment for the propensity to consult using the number of ILIARI consultations in the previous year does not capture differences in consultation likelihood given the person truly having influenza or not. Those who have influenza may be more likely to consult than someone with another respiratory illness which may affect VE. In the before/after/never vaccination model, the variation in levels of influenza circulation throughout the season is accounted for by adjusting the model for time in weeks. We make the assumption that the temporal trend in consultations is the same in all three vaccination

groups. Given the relatively low numbers of consultations on a weekly basis, particularly for ILI, an interaction test has low power to test this assumption. Although we find little reason to doubt the validity of this assumption it could be considered a limitation of this modelling approach.

Comparison of the two methods in 2009/10 [1] gave similar VE differences for ILIARI and ARI but not for ILI where the Cox VE was higher than the Poisson approach albeit with overlapping confidence intervals. In 2009/10, ILI consultations occurred at a higher rate (0.45 per 1000 person week compared to 0.08 in 2010/11) and many of the consultations occurred in pre/during vaccination roll out, limiting comparability between the two years. Given that 2010/11 was also atypical due to the influence of both PIV and TIV, this limits the generalizability of the conclusions to other years and the analysis should be repeated in other influenza seasons.

Time

For the ILIARI and ARI outcomes the Cox and Poisson approaches diverge over time with the Cox VE decreasing, possibly attributable to an increased consultation rate amongst the vaccinated individuals relative to the unvaccinated or conversely a lower consultation rate in the unvaccinated individuals later in the season. The constancy of the Poisson estimate implies that the change is not attributable to changes in the consultation rates in those vaccinated but to the consultation rates in the never vaccinated individuals. The results appear to suggest that as the season progresses those individuals who are never vaccinated become less likely to seek an ARI or ILIARI consultation.

The divergence in estimates observed for ILIARI and ARI between the methods is not observed for ILI as the majority of ILI consultations occur by the end of January [21] whereas the consultations for ILIARI and ARI continue to occur.

An alternative explanation for the Cox VE decreasing over time could be that either the immunity derived from vaccination waned over time or that antigenic drift resulted in the vaccine being less well matched to the circulating virus over time. Evidence of reducing VE for ILI over the season exists for the 2011/12 [22] and 2012/13 season (in preparation).

Conclusion

In conclusion, the results show that both individual based methodologies whilst not producing identical results produced broadly consistent conclusions regarding VE – namely that the seasonal influenza vaccine provided protection against influenza and its complications in the 2010/11 season. The Poisson model structure with further stratification of the unvaccinated group is more sensitive in accounting for healthcare

394 seeking behaviour over and above covariate adjustment however other methods trend in
395 the same direction giving consistent results i.e. whichever method is used the estimated VE
396 shows similar changes over time. Whilst virological data is known to produce gold
397 standard results, it is expensive. The small number of tests conducted in vaccinated
398 individuals consequentially limits interpretation. In Scotland this issue has been
399 acknowledged with current steps being taken to increase both the size of the cohort under
400 observation and allocation of increased resource to enable increased numbers of swabs to
401 be processed from patients with ILI and other ARI across all ages. In the absence of
402 increased testing clinical outcomes can be used as a surrogate. Ideally the most specific
403 clinical outcome would be used but ILI numbers may limit this, particularly for early season
404 estimation. In such cases ARI can be used whilst bearing in mind the reduced specificity and
405 likely lower estimates that will be produced. Given the variability of virus characteristics and
406 vaccine effectiveness it would be advisable that the application of these different methods
407 is validated in repeated seasons.
408
409 The differentials in VE due to outcome, time of analysis and method must be recognised
410 when comparing or pooling results across different studies/countries. Networks such as I-
411 MOVE (Influenza MOnitoring Vaccine Effectiveness) [23] facilitate discussion and planning
412 for how this might take place in the future.

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526 **TABLES**

Variable	Cohort Total=93380 Number (%)	At least 1 ILIARI consultation Total=3764 Number (%)	Influenza virology test Total=877 Number (%)
Gender			
Male	46,489 (49.8%)	1561 (41.5%)	378 (43.1%)
Female	46,891 (50.2%)	2203 (58.5%)	499 (56.9%)
Age group			
0-4	4052 (4.3%)	850 (22.5%)	122 (13.9%)
5-14	9581 (10.3%)	529 (14.1%)	101 (11.5%)
15-44	39290 (42.1%)	1079 (28.7%)	363 (41.4%)
45-64	24777 (26.5%)	772 (20.5%)	214 (24.4%)
65+	15,680 (16.8%)	534 (14.2%)	77 (8.8%)
Pandemic vaccination in 2009/10			
Yes	13,772 (14.7%)	872 (23.2%)	164 (18.7%)
No	79,608 (85.3%)	2892 (76.8%)	713 (81.3%)
Seasonal vaccination in 2009/10			
Yes	16,949 (18.2%)	841 (22.3%)	175 (20.0%)
No	76,431 (81.8%)	2923 (77.7%)	702 (80.0%)
In a chronic disease risk group			
Yes	14,146 (15.1%)	782(20.8%)	200 (22.8%)
No	79,234 (84.9%)	2982 (79.2%)	677 (77.2%)
Carstairs Quintile deprivation			
1 (Low)	8221 (8.8%)	281 (7.5%)	48 (5.5%)
2	15035 (16.1%)	656 (17.4%)	103 (11.7%)
3	19886 (21.3%)	693 (18.4%)	145 (16.5%)
4	20910 (22.4%)	868 (23.1%)	181 (20.6%)
5 (High)	28907 (31.0%)	1246 (33.1%)	400 (45.6%)
Unknown	421 (0.5%)	20 (0.5%)	0 (0.0%)

527 ***Table 1****: Comparison of the distributions of explanatory variables in the whole*
528 *cohort, among those in the cohort who consulted and among those in the cohort who*
529 *had a virological swab for symptoms commensurate with influenza.*

Age	In at least 1 chronic risk group	Gender	ILI in the unvaccinated	ILI in the vaccinated	ILIARI in the unvaccinated	ILIARI in the vaccinated	ARI in the unvaccinated	ARI in the vaccinated
Under65	No	Female	82/5584219 0.0147	0/106631 0.0000	2173/5584219 0.3891	40/106631 0.3751	2196/5584219 0.3933	53/106631 0.4970
Under65	Yes	Female	15/786411 0.0191	6/402708 0.0149	416/786411 0.5290	225/402708 0.5587	831/786411 1.0567	407/402708 1.0107
Under65	No	Male	58/6021612 0.0096	3/55025 0.0545	1659/6021612 0.2755	19/55025 0.3453	1701/6021612 0.2825	22/55025 0.3998
Under65	Yes	Male	11/741990 0.0148	2/356127 0.0056	263/741990 0.3545	163/356127 0.4577	566/741990 0.7628	257/356127 0.7217
65+		Female	5/767860 0.0065	3/818944 0.0037	231/767860 0.3008	310/818944 0.3785	267/767860 0.3477	371/818944 0.4530
65+		Male	1/579815 0.0017	4/639959 0.0063	155/579815 0.2673	215/639959 0.3360	179/579815 0.3087	248/639959 0.3875
Overall			**172/14481907 0.0119**	**18/2379394 0.0075**	**4897/14481907 0.3381**	**972/2379394 0.4085**	**5740/14481907 0.3963**	**1358/2379394 0.5707**

Table 2: Consultations (Number events/person days at risk and Rate per 1000 person days) between 1st October 2010 and 31st March 2011 stratified by vaccine status, gender, age and risk group (all individuals aged 65 or over are considered at risk).

		Consultation group					
Date	**Method**	**ILI**		**ILIARI**		**ARI**	
31/01/2011	Cox	37.9	(-33.0, 71.0)	20.8	(-0.8, 37.7)	30.3	(7.4, 47.5)
	Poisson Before/After	52.9	(-65.0, 86.5)	47.6	(39.8, 54.4)	61.0	(56.3, 65.1)
	Screening Adjusted	50.3	(-12.7, 78.1)	47.0	(31.4, 59.0)	52.9	(37.3, 64.6)
28/02/2011	Cox	30.3	(-83.8, 70.0)	18.8	(-0.9, 34.8)	27.1	(3.7, 44.9)
	Poisson Before/After	49.3	(-21.1, 78.7)	45.7	(38.2, 52.4)	59.9	(55.5, 63.9)
	Screening Adjusted	53.7	(0.2, 78.5)	46.7	(33.8, 57.1)	51.9	(37.2, 63.1)
End of season 31/03/2011	Cox	33.7	(-64.0, 73.2)	10.8	(-8.4, 26.6)	18.5	(-5.3, 36.9)
	Poisson Before/After	46.5	(-69.3, 83.1)	42.2	(34.5, 48.9)	57.5	(53.1, 61.5)
	Screening Adjusted	52.8	(3.8, 76.8)	37.9	(24.3, 49.0)	43.0	(27.2, 55.4)
	Cox unadjusted	46.9	(-10.0, 74.4)	-17.9	(-49.6, 7.1)	-45.4	(-15.4, -83.2)
	Cox Adjusted by propensity score deciles only	46.5	(-30.4, 78.0)	20.1	(3.0, 34.1)	30.2	(9.6, 46.2)
	Cox Matched cohort – no adjustment	24.1	(-77.4, 67.5)	-5.9	(-25.6, 10.7)	12.7	(-5.8, 27.9)

Table 3: Vaccine effectiveness estimates, split by consultation grouping examined, statistical method used and analysis date.

			Any Positivity					H1N1 Positive Only					Flu B Positive Only				
		No	Yes	OR	LCL	UCL	P	Yes	OR	LCL	UCL	P	Yes	OR	LCL	UCL	P
All Patients																	
Vaccinated	No	369	194	1.00				119	1.00				73	1.00			
at Swab	Yes	67	14	0.40	0.21	0.71	0.001	8	0.38	0.16	0.77	0.006	6	0.46	0.17	1.03	0.061
Under 65 and In a risk group for vaccination or 65+																	
Vaccinated	No	75	34	1.00				24	1.00				10	1.00			
at Swab	Yes	64	14	0.49	0.23	0.97	0.042	8	0.40	0.16	0.92	0.030	6	0.71	0.23	2.05	0.533
Under 65 and not in a risk group for vaccination																	
Vaccinated	No	294	160	1.00				95	1.00				63	1.00			
at Swab	Yes	3	0	0.00	0.00	4.49	0.274	0	0.00	0.00	7.59	0.434	0	0.00	0.00	11.49	0.561
All Patients																	
Vaccine Status	Unvaccinated	321	183	1.00				112	1.00				69	1.00			
at Swab	Pandemic Only	48	11	0.41	0.20	0.78	0.005	7	0.43	0.17	0.91	0.027	4	0.40	0.12	1.03	0.059
	Seasonal Only	18	5	0.50	0.16	1.28	0.157	4	0.66	0.18	1.82	0.443	1	0.29	0.01	1.46	0.159
	Both	49	9	0.33	0.15	0.65	0.001	4	0.24	0.07	0.61	0.001	5	0.49	0.16	1.17	0.113

Table 4: Numbers and crude Odds Ratios, 95% Confidence Intervals, and p value for testing an association between flu status and vaccine status at the time the swab was collected. Results are presented for Any Influenza Positivity, H1N1v positivity only and Influenza B positivity only. Vaccine status is presented in two ways. Vaccinated at swab refers only to the TIV seasonal vaccine in 2010-11 while Vaccine Status at swab refers to the combination of TIV seasonal vaccine in 2010-11 and monovalent pandemic vaccination in 2009-10.

		Overall Flu Positivity				H1N1 Positivity				Flu B Positivity			
All Patients		OR	LCL	UCL	P	OR	LCL	UCL	P	OR	LCL	UCL	P
	Intercept	0.41	0.23	0.72	0.002	0.23	0.11	0.46	0.000	0.12	0.05	0.29	0.000
Vaccine	Unvaccinated	1.00				1.00				1.00			
	Pandemic Only	0.40	0.19	0.84	0.016	0.46	0.19	1.15	0.096	0.36	0.12	1.12	0.077
	Seasonal Only	0.46	0.15	1.37	0.165	0.65	0.19	2.23	0.497	0.20	0.02	1.68	0.138
	Both	0.28	0.12	0.66	0.004	0.19	0.06	0.62	0.006	0.43	0.14	1.37	0.153
Age Group	0-4	1.00				1.00				1.00			
	5-14	1.60	0.76	3.35	0.217	0.58	0.20	1.69	0.321	3.48	1.30	9.31	0.013
	15-64	1.06	0.59	1.92	0.835	1.12	0.55	2.26	0.760	1.06	0.44	2.58	0.895
	65+	0.76	0.28	2.07	0.588	0.96	0.28	3.25	0.950	0.66	0.14	2.99	0.585
Risk Group	No	1.00				1.00				1.00			
	Yes	1.13	0.68	1.90	0.635	1.09	0.60	1.99	0.777	1.13	0.53	2.43	0.748
Under 65 and in risk group or Age 65+		OR	LCL	UCL	P	OR	LCL	UCL	P	OR	LCL	UCL	P
	Intercept	1.11	0.08	14.56	0.939	0.27	0.13	0.59	0.001	0.48	0.02	10.00	0.634
Vaccine	Unvaccinated	1.00				1.00				1.00			
	Pandemic Only	0.43	0.13	1.39	0.157	0.37	0.09	1.50	0.163	0.81	0.14	4.88	0.822
	Seasonal Only	0.60	0.19	1.94	0.396	0.77	0.21	2.84	0.690	0.40	0.04	3.80	0.426
	Both	0.32	0.13	0.78	0.012	0.19	0.06	0.64	0.007	0.65	0.19	2.27	0.499
Age Group	0-4	1.00				1.00				1.00			
	5-14	0.32	0.01	7.90	0.489	1.00				0.45	0.01	13.49	0.643
	15-64	0.41	0.03	6.03	0.512	1.00				0.15	0.01	3.00	0.214
	65+	0.26	0.02	4.30	0.349	0.81	0.27	2.42	0.703	0.09	0.00	2.27	0.146

Table 5: Parameter estimates (odds ratios and 95% confidence intervals) from the generalised additive model for swab positivity from models including the combination of TIV seasonal vaccine 2010-11 as well as last season's monovalent pandemic vaccine. Adjustment was made for Age group and risk group membership. Separate analyses were carried out for all patients and those targeted for vaccination (those over 65 or under 65 and in a risk group) and for overall flu positivity, H1N1v positivity only of Flu B positivity only.

Method	Advantages	Limitations	Possible indications/ recommendations
Cox cohort	• Prospective framework in assigning vaccination status • Individuals can have multiple consultation outcomes • Confounder adjustment	• Proportionality of the influenza rates between unvaccinated and vaccinated individuals over time assumed • VE may be underestimated if covariate adjustment for healthcare seeking behaviour is not sufficient	• Flexible method for analysis throughout the season
Poisson before/after/never cohort	• VE calculated by comparing consultation rates before and after vaccination reducing health seeking behaviour bias • Individuals can have multiple consultation outcomes • Confounder adjustment	• Assumes health care seeking behaviour is the same before and after vaccination • Retrospective framework in assigning vaccination status • Assumes the pattern of the trends over time to be similar in the three groups though the levels can be different	• Useful for end of season analysis if it is felt that unmeasured confounding due to differences in health seeking behaviour is present
Screening	• Can estimate VE when only aggregate level information is known	• Limited ability to adjust for temporal trends in influenza • Only records dichotomous consultation outcome (at least one yes/no) per individual • Vaccination status is static • Lack of adjustment for healthy vaccine effect • Limited confounder adjustment	• Useful when individual level data is not available
Test negative	• Highly specific outcome as uses virologically confirmed results • Excludes individuals with influenza who do not seek care, avoiding bias due to misclassifying non-consulting infected individuals as not infected • Avoids confounding by health care seeking behaviour by restricting population to those who seek care	• May be limited by small sample size especially in the vaccinated individuals resulting in wide confidence intervals. • Assumes incidence of non-influenza respiratory infections is similar between the vaccinated an unvaccinated • Assumes influenza VE does not vary across health-seeking strata	• Method of choice for “gold-standard” virological endpoint

Table 6: Summary of the advantages and disadvantages of the four methodologies considered in this paper

FIGURES

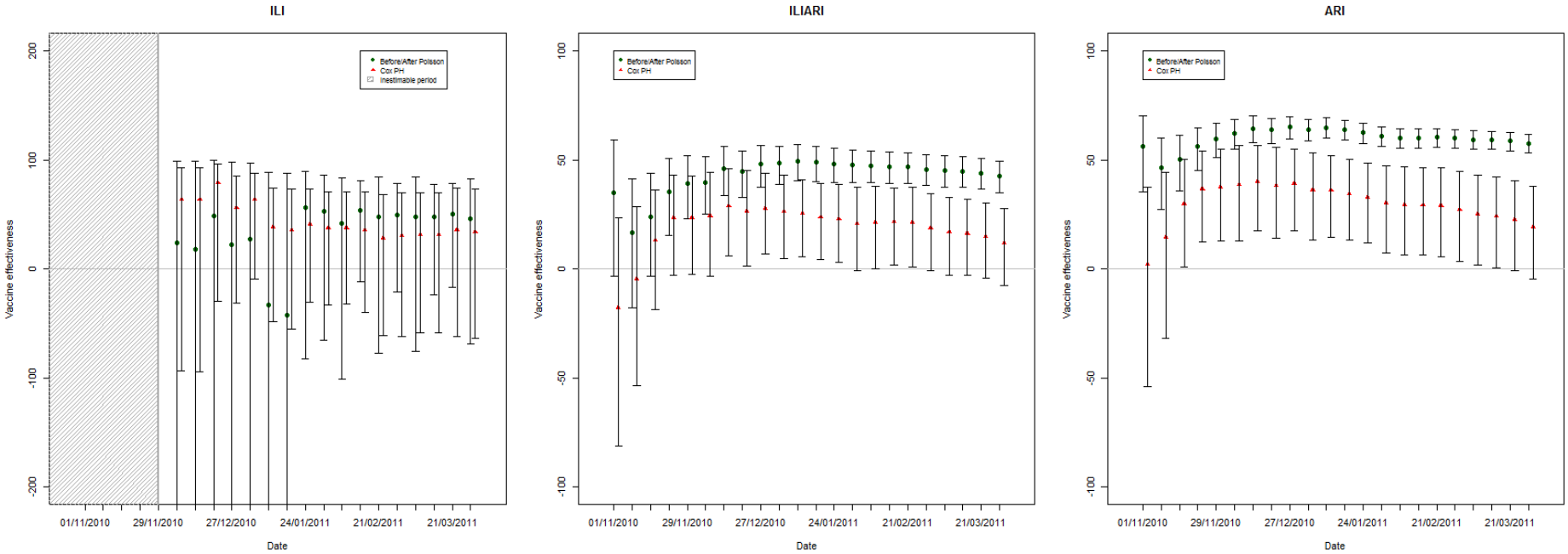

Figure 1: Vaccine effectiveness estimates over time split by statistical method and by consultation type

Supplemental Materials –

Vaccination

In 2010/11 no one particular seasonal influenza vaccine was delivered. Table A documents the vaccine supplier, name of product and vaccine type for each manufacturer. Vaccine lot numbers were incompletely recorded in the extract for vaccines used for each patient.

All vaccines used were administered IM into deltoid muscle and in appropriate dose following manufacturer recommendations – vaccines administered were provided with needles already attached to barrel (see individual manufacturer for detail on gauge and needle length). All vaccine administration was in accordance with NHS Scotland recommendations for ensuring the maintenance of the cold chain. None of the influenza vaccines for the 2010/11 season contained thiomersal as an added preservative.

Concomitant vaccine administration into a different anatomical site (usually contralateral arm) for a small minority of individuals cannot be excluded for polysaccharide pneumococcal vaccination but this data was not collected (75% of those over the age of 65 60-70% of those under the age of 65 in an at risk group have previously received polysaccharide vaccine. Each year as each age cohort turns 65 individuals without prior vaccination are offered pneumococcal polysaccharide vaccination. Revaccination with pneumococcal polysaccharide vaccine is restricted to a small number of patients with chronic renal disease every five years. The overall number of patients in any season receiving concomitant pneumococcal polysaccharide vaccination is estimated to be around 1-2% of all influenza cases).

Table A: Seasonal influenza vaccine characteristics in Scotland in 2010/11

Supplier	Name of product	Vaccine Type
GlaxoSmithKline	Fluarix	Split virion, inactivated
MASTA	Imuvac	Surface antigen, inactivated, sub-unit
Novartis Vaccines	Agrippal	Surface antigen
	Begrivac	Split virion
	Fluvirin*	Surface antigen
Pfizer Vaccines (formerly Wyeth Vaccines)	Enzira	Split virion Inactivated
	Generic influenza vaccine	Split virion Inactivated
Sanofi Pasteur MSD	Inactivated influenza vaccine	Split virion
	Intanza**	Intradermal, split virion
Solvay Healthcare	Influvac	Surface antigen, inactivated, sub-unit
	Imuvac	Surface antigen, inactivated, sub-unit

Consultation Readcodes

The ILI, ARI (including influenza and asthma) and ILIARI (including influenza and excluding asthma) consultation groupings were created using the following case definitions shown in Tables B-D.

Table B: Asthma readcodes

Readcode	Readcode Description
H33..	Asthma
H330.	Extrinsic (atopic) asthma
H3300	Extrinsic asthma without status asthmaticus
H3301	Extrinsic asthma with status asthmaticus
H330z	Extrinsic asthma NOS
H331.	Intrinsic asthma
H3310	Intrinsic asthma without status asthmaticus
H3311	Intrinsic asthma with status asthmaticus
H331z	Intrinsic asthma NOS
H332.	Mixed asthma
H333.	Acute exacerbation of asthma
H334.	Brittle asthma
H33z.	Asthma unspecified
H33z0	Status asthmaticus NOS
H33z1	Asthma attack
H33z2	Late-onset asthma
H33zz	Asthma NOS

Table C: ARI readcodes

Readcode	Readcode Description
H0...	Acute respiratory infections
H05..	Other acute upper respiratory infections
H05z.	Upper respiratory infection NOS
H05z.	Upper respiratory tract infection NOS
H05z.	Viral upper respiratory tract infection NOS
H06..	Acute bronchitis and bronchiolitis
H06z.	Acute bronchitis or bronchiolitis NOS
H07..	Chest cold
H0y..	Other specified acute respiratory infections
H22..	Other bacterial pneumonia
H22..	Chest infection - other bacterial pneumonia
H22y.	Pneumonia due to other specified bacteria
H23..	Pneumonia due to other specified organisms
H23..	Chest infection - pneumonia organism OS
H260.	Lobar pneumonia due to unspecified organism
H3...	Chronic obstructive pulmonary disease
H3...	Chronic obstructive airways disease
H33..	Asthma
H33..	Bronchial asthma
H333.	Acute exacerbation of asthma
Hyu1.	[X]Other acute lower respiratory infections
Hyu10	[X]Acute bronchitis due to other specified organisms
H04..	Acute laryngitis and tracheitis
H05y.	Other upper respiratory infections of multiple sites
H0z..	Acute respiratory infection NOS
H22z.	Bacterial pneumonia NOS
H23z.	Pneumonia due to specified organism NOS
H25..	Bronchopneumonia due to unspecified organism
H25..	Chest infection - unspecified bronchopneumonia
H26..	Pneumonia due to unspecified organism
H26..	Chest infection - pneumonia due to unspecified organism
H33z0	Status asthmaticus NOS
H33z0	Severe asthma attack
Hyu0.	[X]Acute upper respiratory infections
Hyu11	[X]Acute bronchiolitis due to other specified organisms

Table D: ILI readcodes

Readcode	Readcode Description
G5203	Acute myocarditis - influenza
H2...	Pneumonia and influenza
H27..	Influenza
H270.	Influenza with pneumonia
H270.	Chest infection - influenza with pneumonia
H2700	Influenza with bronchopneumonia
H2701	Influenza with pneumonia, influenza virus identified
H270z	Influenza with pneumonia NOS
H271.	Influenza with other respiratory manifestation
H2710	Influenza with laryngitis
H2711	Influenza with pharyngitis
H271z	Influenza with respiratory manifestations NOS
H27y.	Influenza with other manifestations
H27y0	Influenza with encephalopathy
H27y1	Influenza with gastrointestinal tract involvement
H27yz	Influenza with other manifestations NOS
H2y..	Other specified pneumonia or influenza
H2z..	Pneumonia or influenza NOS
Hyu05	[X]Influenza and other manifestations, influenza virus identified
Hyu06	[X]Influenza and other respiratory manifestations, virus not identified
Hyu07	[X]Influenza and other manifestations, virus not identified