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Influenza vaccination reduced myocardial infarctions in UK older adults: a prior event rate ratio study

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Sensitivity analyses

Effectiveness of influenza vaccination on MI

Weighted results and PERR adjustment

From the IPTW analysis, adjusting for measured confounders, the results were variously distributed around unity (Table 1). No results for any cohort's study (blue circles in fig 1) were significantly different from the null, but the largest protective effect was estimated for 2003 with an HR of 0.78 (95% CI: 0.59, 1.01), respectively. The HRs from 2004 onwards were above one, indicating harmful effects with HRs as high as 1.28 (95% CI: 0.95, 1.74) in 2009. Once the PERR method had been applied to the weighted estimates, the HRs (blue triangles in fig 1) fell below one and were in closer agreement with those from the PERR-adjusted unweighted-Cox models (grew triangles in fig 1), indicating a protective effect from vaccination against MIs, although those for 1997 and 2001 were not statistically significant. The diagnostic plots (Supplementary figures 1-5) of the standardised and unstandardised mean differences of potential confounders in the study periods revealed better balance was generally achieved for the earlier cohorts, noting that not all the variables contributed to the propensity score. It was also apparent that after 2001, age became the leading variable with the greatest imbalance between vaccination groups. This seemed to coincide with the shift from risk-based vaccination prior to the policy introduction to the age-based eligibility criterion for vaccination.

Cohort	Weighted HR for each period		PERR applied to weighted HR
	Prior	Study	
1997	1.63 (1.17, 2.28)	1.00 (0.65, 1.55)	0.61 (0.36, 1.03)
1998	1.86 (1.41, 2.44)	0.88 (0.62, 1.25)	0.48 (0.31, 0.73)
1999	2.25 (1.80, 2.81)	0.99 (0.79, 1.24)	0.44 (0.32, 0.58)
2000	1.22 (1.02, 1.47)	0.86 (0.72, 1.01)	0.70 (0.55, 0.91)
2001	1.36 (1.10, 1.67)	1.09 (0.88, 1.34)	0.80 (0.60, 1.07)
2002	1.61 (1.25, 2.08)	1.04 (0.81, 1.33)	0.64 (0.47, 0.88)
2003	1.79 (1.42, 2.27)	0.78 (0.59, 1.04)	0.44 (0.29, 0.61)
2004	1.77 (1.42, 2.22)	1.22 (0.94, 1.59)	0.69 (0.48, 0.93)
2005	1.66 (1.34, 2.04)	1.08 (0.86, 1.35)	0.65 (0.48, 0.90)
2006	2.07 (1.62, 2.64)	1.17 (0.85, 1.61)	0.57 (0.39, 0.79)
2007	2.55 (1.92, 3.38)	1.11 (0.81, 1.52)	0.44 (0.29, 0.66)
2008	1.61 (1.24, 2.09)	1.07 (0.77, 1.50)	0.67 (0.44, 0.99)
2009	2.05 (1.61, 2.59)	1.28 (0.95, 1.74)	0.63 (0.42, 0.89)
2010	2.76 (2.14, 3.55)	1.24 (0.88, 1.75)	0.45 (0.29, 0.65)
2011	2.09 (1.70, 2.58)	1.00 (0.78, 1.28)	0.48 (0.34, 0.64)

Table 1: Inverse probability treatment weighted hazard ratios (95% confidence intervals) for the study and prior periods of each cohort from 1997 to 2011 with the PERR method applied.

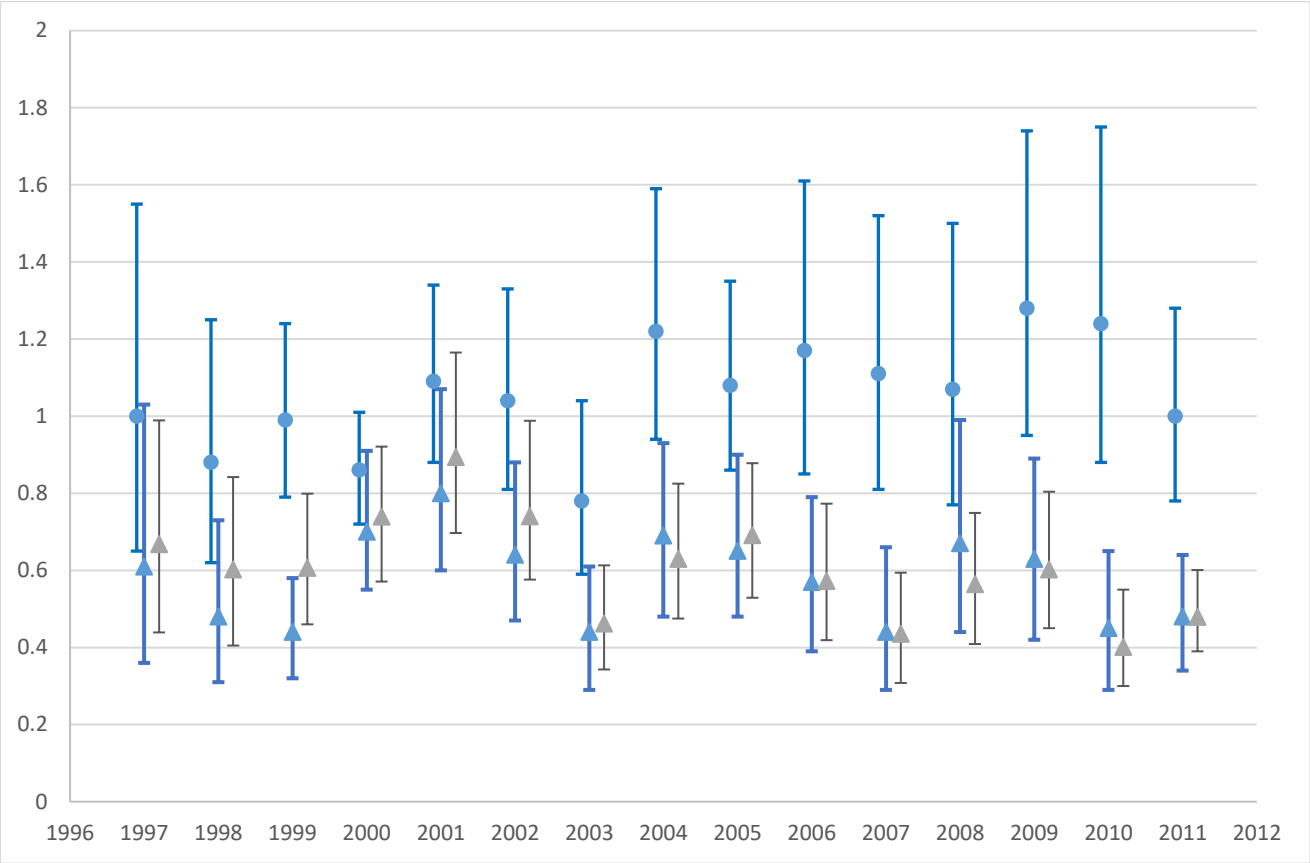

Fig 1*: I*nverse probability treatment weighted hazard ratios for the study periods (blue circles) and PERR-adjusted hazard ratios (grey triangles) from 1997 to 2001. Error bars represent 95% confidence intervals for the HRs.

Pairwise estimates

The HRs of vaccination effect from the pairwise model (Table 2), in which age, sex and period were adjusted for, were consistently further from unity than the PERR estimates with the lowest Pairwise HR (blue triangles in Fig 2) being 0.38 (95% CI: 0.27, 0.54) in 2003 and 0.38 (95% CI: 0.27, 0.52) in 2010 compared to 0.46 (95% CI: 0.34, 0.61) and 0.40 (95% CI: 0.30, 0.55) from the PERR method, for the same years, respectively (grey circles in Fig 2) in 2003. This would indicate a marginally greater overall protective effect of vaccination against MI than that estimated through the PERR method. There are notably fewer subjects in each cohort compared to

those for the PERR method. This is a characteristic of the Pairwise method, as only those individuals, whose shortest survival time from either period ending in an outcome, contribute information to the likelihood function.

Cohort	Pairwise cohort	Pairwise HR
1997	656	0.51 (0.33, 0.79)
1998	888	0.56 (0.38, 0.83)
1999	960	0.55 (0.40, 0.76)
2000	1053	0.64 (0.49, 0.83)
2001	894	0.80 (0.59, 1.08)
2002	797	0.70 (0.49, 1.01)
2003	874	0.38 (0.27, 0.54)
2004	933	0.53 (0.38, 0.72)
2005	1020	0.53 (0.40, 0.71)
2006	938	0.49 (0.34, 0.70)
2007	995	0.39 (0.27, 0.56)
2008	1137	0.46 (0.33, 0.64)
2009	1241	0.53 (0.39, 0.72)
2010	1278	0.38 (0.27, 0.52)
2011	1566	0.44 (0.33, 0.58)

Table 2: Pairwise-adjusted hazard ratios (95% confidence intervals) for each annual cohort for the effect of influenza vaccination on MI hospital admissions.

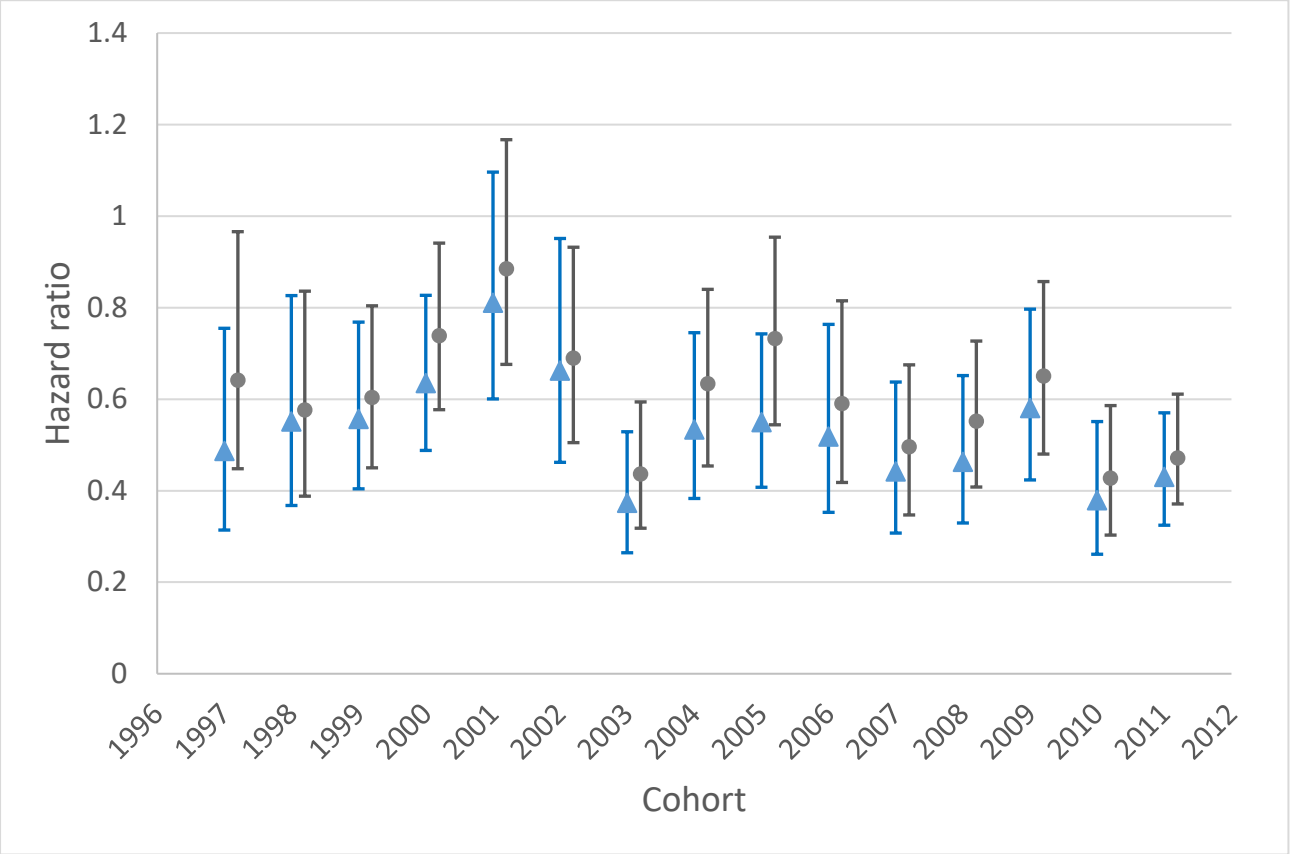

Fig 2: Hazard ratios of the estimated effect of influenza vaccination on MI hospital admissions from the PERR-adjusted model (grey dots) and the pairwise model (blue triangles) with errors bars representing 95% confidence intervals.

Effectiveness of vaccination on influenza

Pairwise estimates

The HRs from the pairwise method, while always further below the null, tracked very closely with the PERR-adjusted results, and ranged from 0.63 (95% CI: 0.54, 0.72) in 1999 to 0.90 (95% CI: 0.78, 1.05) in 2001 (Table 3; Fig 3).

Cohort	N	Pairwise HR vaccination
1997	4859	0.73 (0.63, 0.84)
1998	4869	0.65 (0.55, 0.77)
1999	5096	0.63 (0.54, 0.72)
2000	4920	0.76 (0.68, 0.86)
2001	3540	0.90 (0.78, 1.05)
2002	3200	0.71 (0.60, 0.84)
2003	3455	0.64 (0.55, 0.76)
2004	4227	0.72 (0.62, 0.84)
2005	5003	0.72 (0.63, 0.81)
2006	4732	0.70 (0.60, 0.81)
2007	5216	0.79 (0.68, 0.92)
2008	6023	0.69 (0.61, 0.79)
2009	6193	0.72 (0.63, 0.82)
2010	6486	0.86 (0.75, 0.98)
2011	7537	0.76 (0.68, 0.85)

Table 3: Hazard ratios (95% confidence intervals) from the pairwise analysis of the effect of influenza vaccination on the composite influenza outcome for each cohort. Note that each cohort is a reduced subset of patients with an outcome in either the prior or study period as demanded by the pairwise likelihood.

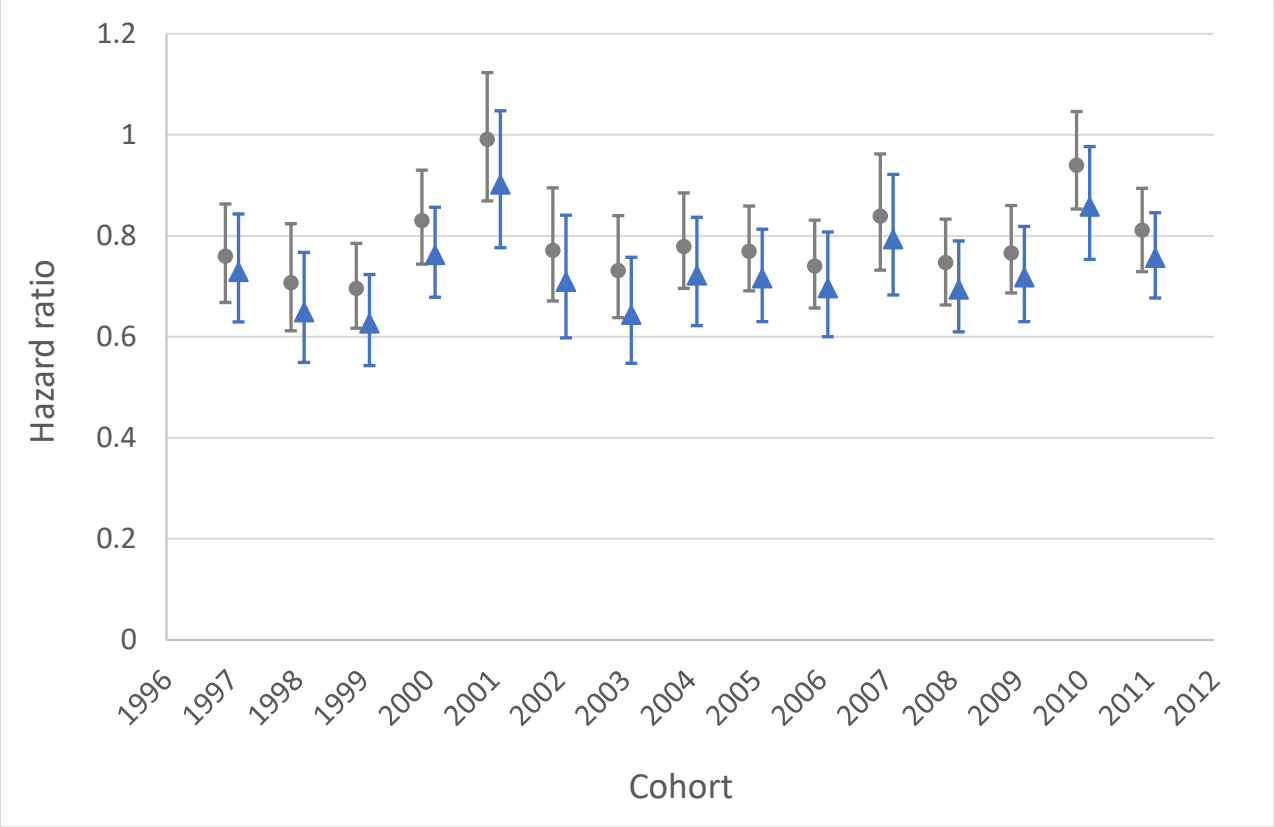

Fig 3: Hazard ratios for the effect of influenza vaccination on influenza outcomes from the PERR-adjusted model (grey dots) and Pairwise model (blue triangles) with errors bars representing 95% confidence intervals.

Appendix

Influenza vaccine codes in immunisation file:

6, 9039, 10821, 12104, 12336, 18330, 18684, 21123, 32942, 35655, 44555, 94301, 95092, 97941, 98047, 98183, 98184, 98217, 98234, 98302, 98303, 98306, 98449

Influenza vaccine codes in therapy file:

398, 639, 834, 922, 1329, 2139, 2552, 2601, 9710, 10030, 11824, 13595, 16585, 18612, 27407, 30156, 30198, 32391, 38421, 40760, 40876

ICD10 codes for myocardial infarction admissions to hospital in HES data:

I20.0, I21.0 - I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I21

Amoxicillin codes in therapy file:

9, 48, 62, 133, 427, 503, 585, 847, 870, 1637, 1722, 1812, 2153, 2281, 3669, 3742, 4154, 7737, 9243, 11613, 11634, 12378, 14371, 14386, 14396, 14407, 15148, 17711, 18786, 21799, 21827, 21829, 21844, 21845, 21963, 22015, 22016, 22017, 22415, 22438, 23238, 23740, 23967, 24150, 24200, 24203, 25484, 26157, 26262, 27714, 27725, 28870, 28872, 28875, 28882, 29337, 29463, 29697, 29858, 30498, 30528, 30743, 30745, 31014, 31286, 31423, 31535, 31661, 31801, 32622, 32640, 32872, 33109, 33110, 33112, 33165, 33222, 33343, 33570, 33689, 33690, 33692, 33696, 33699, 33706, 34001, 34042, 34232, 34384, 34435, 34638, 34679, 34714, 34760, 34775, 34852, 34855, 34857, 34885, 34912, 35570, 36054, 37755, 38684, 40238, 40243, 41090, 41818, 41835

Doxycycline codes in therapy file:

264, 268, 970, 1046, 2202, 2884, 3152, 6396, 8724, 9267, 10454, 12987, 14904, 15071, 21038, 21828, 21860, 21878, 23405, 23432, 23819, 24126, 24149, 26392, 26747, 30739, 32066, 32419, 33671, 34175, 34300, 34423, 34594, 34765, 40391, 41560, 41605, 46807

Product codes in therapy file for antiviral drugs:

BNF code	CPRD prodcode	strength
Amantadine hydrochloride	5339	100mg
Amantadine hydrochloride	6035	50mg/5ml
Zanamivir	6610	5mg
Oseltamivir phosphate	10129	75mg
Oseltamivir phosphate	10131	75mg
Oseltamivir phosphate	10137	12mg/1ml
Oseltamivir phosphate	18863	60mg/5ml
Zanamivir	21169	5mg
Amantadine hydrochloride	21745	50mg/5ml
Amantadine hydrochloride	25890	100mg
Oseltamivir phosphate	38523	30mg
Oseltamivir phosphate	38955	30mg
Oseltamivir Phosphate	39252	45mg
Oseltamivir phosphate	39894	45mg
Oseltamivir phosphate	40710	15mg/1ml
Oseltamivir phosphate	42326	15mg/1ml
Oseltamivir phosphate	52526	15mg/1ml
Oseltamivir phosphate	53759	6mg/1ml
Oseltamivir phosphate	54814	30mg/5ml

Medcodes from clinical file for symptom descriptions used to qualify antibiotic codes:

Medcode	Description
293	Respiratory tract infection
4899	Recurrent chest infection
68	Chest infection
2581	Chest infection NOS
3358	Lower resp tract infection
5534	Pneumococcal infection
7074	Respiratory infection NOS
8025	Acute respiratory infections
14804	Sputum appears infected
16287	Chest infection - unspecified bronchopneumonia
17359	Chest infection - unspecified bronchitis
19400	Chest infection - pnemonia due to unspecified organism
21061	Chronic obstruct pulmonary dis with acute lower resp infectn
21113	Acute respiratory infection NOS
22795	Chest infection - other bacterial pneumonia
23640	Other specified acute respiratory infections
3382	Streptococcal infection
572	Pneumonia due to unspecified organism
886	Bronchopneumonia due to unspecified organism
1849	Lobar (pneumococcal) pneumonia
3683	Basal pneumonia due to unspecified organism

9639	Lobar pneumonia due to unspecified organism
10086	Pneumonia and influenza
11849	Other specified pneumonia or influenza
12423	Pneumonia due to streptococcus
13573	Influenza with bronchopneumonia
22009	Streptococ pneumon/cause/disease classified/oth chapters
23095	Bacterial pneumonia NOS
25694	Pneumonia due to other specified organisms
23333	Hypostatic pneumonia
24356	Hypostatic bronchopneumonia
1934	Laryngotracheobronchitis
1019	Acute bronchiolitis
17185	Acute bronchiolitis with bronchospasm
17917	Acute bronchiolitis NOS
29669	Acute bronchitis and bronchiolitis
41137	Acute bronchitis or bronchiolitis NOS
2195	Bronchiectasis
20364	Recurrent bronchiectasis
1234	Productive cough NOS
7708	Productive cough-yellow sputum
7773	Productive cough -green sputum
18907	Cough with fever
8760	[D]Positive culture findings in sputum
15430	[D]Sputum abnormal - colour

16026	Sputum examination: abnormal
24181	Sputum: mucopurulent
30754	Yellow sputum
36880	Green sputum