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

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

4 Short title: Influenza vaccine in reducing myocardial infarctions

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## 20 **Abstract**

### 21 **Objective**

22 We aimed to estimate the real-world effectiveness of the influenza vaccine against  
23 myocardial infarction (MI) and influenza in the decade since adults aged  $\geq 65$ y were  
24 first recommended the vaccine.

### 25 **Study design and setting**

26 We identified annual cohorts, 1997 to 2011, of adults aged  $\geq 65$ y, without previous  
27 influenza vaccination, from UK general practices, registered with the Clinical Practice  
28 Research Datalink. Using a quasi-experimental study design to control for  
29 confounding bias, we estimated influenza vaccine effectiveness on hospitalisation for  
30 MI, influenza and antibiotic prescriptions for lower respiratory tract infections.

### 31 **Results**

32 Vaccination was moderately effective against influenza, the prior event rate ratio  
33 (PERR)-adjusted hazard ratios [HR] ranging from 0.70 in 1999 to 0.99 in 2001.  
34 PERR-adjusted HRs demonstrated a protective effect against MIs, varying between  
35 0.40 in 2010 to 0.89 in 2001. Aggregated across the cohorts, influenza vaccination  
36 reduced the risk of MIs by 39% (95%confidence interval: 34%, 44%).

### 37 **Conclusions**

38 Effectiveness of the flu vaccine in preventing MIs in older UK adults is consistent  
39 with the limited evidence from clinical trials. Similar trends in effectiveness against  
40 influenza and against MIs suggest the risk of influenza mediates the effectiveness

41 against MIs, although divergence in some years implies the mechanism may be  
42 complex.

43 **Word count: 200**

44 **Keywords**

45 Real-world evidence; vaccine effectiveness; influenza; myocardial infarction; prior  
46 event rate ratio; unmeasured confounders

47 **Running title: Influenza vaccination and myocardial**  
48 **infarctions: PERR study**

49

50 **1. Introduction**

51 Influenza vaccination is currently recommended for adults aged  $\geq 65$ y, a group which  
52 has a high risk of influenza mortality [1]. While vaccination is primarily intended to  
53 protect against influenza [2], there are potential benefits against its complications [3–  
54 5]. Increased cardiovascular conditions coincide with influenza epidemics, [6] with an  
55 elevated risk of acute myocardial infarction (MI) within seven days of laboratory-  
56 confirmed influenza infection in adults aged  $\geq 65$ y [7,8] and within one year of acute  
57 respiratory infection [9]. The influenza virus may increase the risk of MI directly via a  
58 cardiac inflammatory response, and indirectly by activation of inflammatory pathways  
59 and atherosclerosis [10,11]. The most recent Cochrane review [12] on influenza  
60 vaccines for preventing cardiovascular disease included three large randomised

61 clinical trials (RCT) with MI outcomes that detected no significant effect of influenza  
62 vaccination [13–15]. However, the findings were based on a range of ages, and were  
63 not restricted to the older population. Encouraging uptake of the influenza  
64 vaccination remains a key component of public health, but evidence for potential  
65 secondary benefits from the vaccine with respect to prevention of myocardial  
66 infarction still awaits support from RCTs [16].

67 Population studies using electronic health records (EHRs) have demonstrated a  
68 protective effect of influenza vaccination, reducing the risk of MI in the year following  
69 vaccination by 7% to 20% in older patients [17–19]. However, EHRs are not primarily  
70 purposed for research, and are prone to bias from unmeasured confounding [20,21].

71 An alternative to EHRs is claims data, which are records of claims for services from  
72 health insurance companies. Claims data may overstate the effectiveness of  
73 vaccination, reflecting the health-seeking behaviours of relatively healthy vaccine  
74 recipients ("healthy user bias") [22]. Universal healthcare systems are more likely to  
75 represent World Health Organisation guidelines in offering the influenza vaccine to  
76 high-risk groups, and so data from these systems, like that supplied by the Clinical  
77 Practice Research Datalink for this study, may be affected by bias that understates  
78 effectiveness (confounding by indication). However, both confounding by indication  
79 and healthy user bias may operate simultaneously in observational studies of  
80 influenza vaccine effectiveness, and it is recommended that this is addressed  
81 through avoidance of unspecific outcomes (such as all-cause mortality) alongside  
82 use of appropriate methods for confounding control [22].

83 The absence of routine testing in the UK for influenza in suspected cases precludes  
84 the possibility of using a test-negative case-control design usually favoured in many  
85 vaccine effectiveness studies [23]. The absence of a standard alternative treatment to

86 vaccination rules out the active comparator new user design popular in  
87 pharmacoepidemiology studies [24]. Many investigations of influenza vaccine  
88 effectiveness adjust for possible confounding bias with a pre flu season estimate, but  
89 these estimates can be seen to suffer from imprecision for specific outcomes, such  
90 as influenza-like illness, that occur infrequently outside of the flu season [22]. For  
91 assessing vaccine safety, the self-controlled case series (SCCS) design was  
92 developed [25] and has previously been used to estimate the risk of myocardial  
93 infarctions after acute respiratory tract infections [8]. This compares a defined  
94 exposure risk period to a baseline risk period within the same individual, relying on  
95 the assumption of time-invariant confounding. The SCCS is well-suited to  
96 investigation of transient exposures and acute outcomes, but the need for clearly  
97 defined exposure and baseline periods makes studies of late onset effects of  
98 vaccination more difficult. Generalisability may also be limited as only exposed  
99 patients with events are included and the method cannot estimate absolute  
100 incidence.

101 An alternative cohort-based strategy is to adopt a new user design, selecting  
102 patients not vaccinated in the previous flu season, and use effect estimates from this  
103 previous season as a representative measure of the confounding bias during the flu  
104 season under study (prior event rate ratio (PERR) adjustment) [26].

105 Using the PERR study design and comparing the results to those adjusted for  
106 measured confounders through weighting, we took a robust approach to the problem  
107 of confounding bias in our investigation of the real-world effectiveness of influenza  
108 vaccination against the risk of MI. This was a study of UK adults aged  $\geq 65$ y for a  
109 period beginning in 1997 when the policy to vaccinate older adults was introduced.  
110 Annual estimates of vaccine effects were calculated from 1997 to 2011 to explore

111 the variation in effectiveness due to antigenic drift and any impact from the  
112 emergence of new viral pathogens during that period [27–29]. We estimated vaccine  
113 effectiveness against influenza infection as a secondary outcome.

## 114 **2. Methods**

### 115 **2.1. Study population**

116 Annual cohorts were identified using data from the UK Clinical Practice Research  
117 Datalink's (CPRD) Gold database [30] for patients registered with up-to-research-  
118 standard general practices linked to hospital episode statistics (HES) and mortality  
119 data from the Office of National Statistics (ONS). Recruitment began on the 1<sup>st</sup>  
120 September, the index date for each year, from 1997 to 2011. Inclusion criteria were  
121 applied to ensure that patients were alive and at least 65 years of age at the start of  
122 recruitment; had been registered at the practice for at least 5 years and consulted at  
123 least once in that time. Not all records can be linked to HES data, and so these were  
124 excluded from this study [31].

### 125 **2.2. Study design and follow-up**

126 The study comprised annual cohorts of eligible patients, with no record of a previous  
127 influenza vaccination. In each cohort, patients entered the exposed group if they had  
128 had receipt of an influenza vaccine recorded between the index date and 31<sup>st</sup>  
129 January inclusive, using the immunisation file and therapy files of the CPRD  
130 (Supplementary material: appendix). Unvaccinated patients were designated as  
131 controls. The start of follow-up began 14 days after vaccination to allow time for full  
132 immunogenicity. To achieve a similar distribution of start dates between the

133 exposure groups and avoid imbalance in survival times, the start dates were mapped  
134 from vaccine recipients onto the unvaccinated controls according to their age, sex  
135 and GP practice. Each cohort was followed for a year, censoring on subsequent  
136 vaccination, death or departure from the practice.

### 137 **2.3. Outcomes**

138 The primary outcome was admission to hospital for myocardial infarction, coded  
139 according to ICD-10 (Supplementary material: appendix), serving as the endpoint in  
140 the primary survival analysis. No distinction was made between first and subsequent  
141 MI events, so the outcome is a mix of both. To ensure follow-up did not begin while  
142 already under observation in hospital for MI, follow-up did not start until discharge for  
143 those patients admitted to hospital with MI before recruitment. Subsequent MI events  
144 recorded during a hospital spell after admission were not counted.

145 The secondary outcome was a composite of either hospitalisation or treatment for  
146 probable or definite influenza. Treatment for probable influenza included  
147 prescriptions for antiviral drugs used to treat influenza, or antibiotics accompanied  
148 by a clinical code for lower respiratory tract infections, as a possible secondary  
149 infection to influenza (Supplementary: appendix). Hospitalisations for influenza were  
150 identified from the HES data by their corresponding ICD10 admission codes.

### 151 **2.4. Statistical analysis**

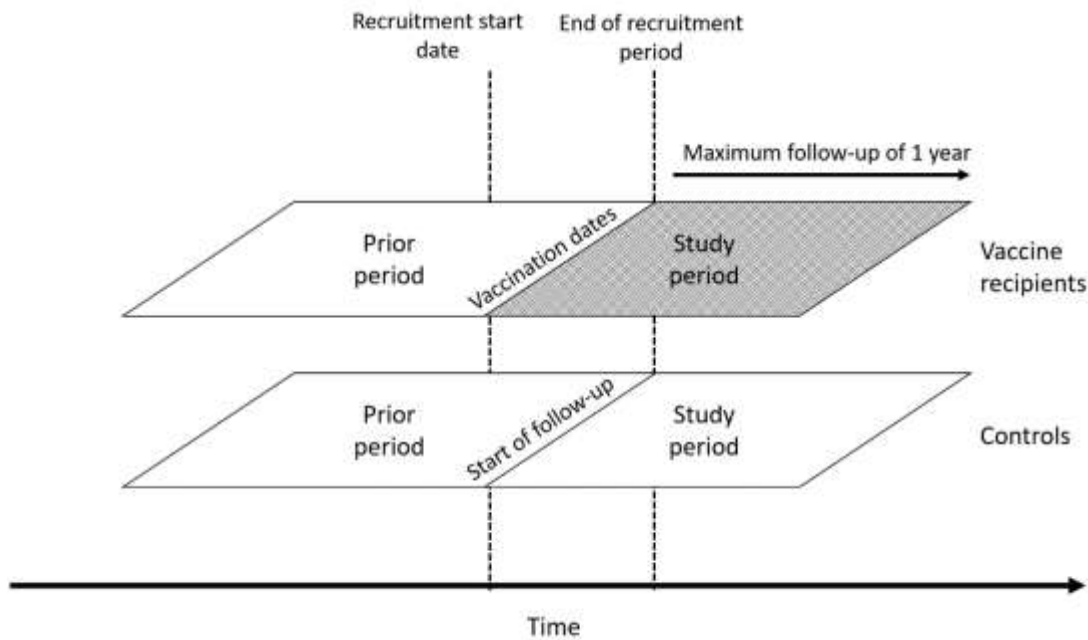
152 The effect of influenza vaccination on survival times until MI was analysed using Cox  
153 regression adjusting for age (centred on 65 years) and sex, censoring on death,  
154 leaving their practice or subsequent vaccination.



155 *2.4.1. Adjustment for confounding bias*

156 The prior event rate ratio (PERR) method was applied to mitigate for confounding  
157 bias (also considered to be selection bias), from both observed and unobserved  
158 sources [26,32]. The PERR method, a before-and-after, quasi-experimental study  
159 design can be applied to survival and rate data, and uses a period before the study  
160 period as a measure of the pre-existing confounding bias with which to adjust biased  
161 estimates from the study period (Fig 1). This relies on meeting assumptions [33,34],  
162 notably time-invariant confounding bias across the periods, although this is mitigated  
163 against by restricting follow-up to one year with adjacent prior and study periods. The  
164 method has recently been used to estimate the effectiveness of aspirin in reducing  
165 cardiovascular events in patients with pneumonia [35]. It has also been applied to  
166 estimate the effectiveness of the influenza vaccine in reducing antibiotic  
167 prescriptions, in which the estimates were shown to be robust when checked against  
168 simulated data [36].

169



171

172 **Fig 1: Schematic of the PERR study design.**

173 Vaccinated patients are selected from 1<sup>st</sup> September to 31<sup>st</sup> January. Start of follow-  
 174 up dates for the controls are mapped from the vaccination dates of vaccinees. Event  
 175 times are compared for vaccinated and control patients during a 1 year study period  
 176 and a 1 year prior period, preceding the study period by exactly 1 year.

177

178 For an estimate of overall effectiveness, all cohorts were aggregated and analysed  
 179 using PERR-adjusted Cox models adjusting for age and sex. As the same patients  
 180 could be represented across several cohorts, resulting in a lack of independence  
 181 between observations, these were analysed using robust standard errors, clustered  
 182 on an individual patient level.

183 **2.4.2. Sub-group analysis**

184 Further analysis tested for any moderating effect of age, by modelling the interaction  
 185 between age and vaccination status and their main effects, to which the PERR  
 186 adjustment was applied.

### 187 2.4.3. *Sensitivity analysis*

188 Results from the PERR method were compared to those from Cox models adjusted  
189 for measured confounders made through an inverse probability treatment weighted  
190 (IPTW) analysis of each cohort (Supplementary material: sensitivity analyses). The  
191 propensity scores, summarising the probability of vaccination and used as the  
192 weights, were derived as the predicted probabilities from a logistic regression model  
193 for vaccination fitted to potential confounders found to be associated with the  
194 outcome, according to the significance of their coefficients at the 5% level. The  
195 variables included in the propensity score model were selected following this data-  
196 driven approach from candidate confounders: sex, age, conditions based on the  
197 Quality Outcomes Framework rules [37,38] and deficits in the electronic Frailty Index  
198 (eFI) [39], as well as the eFI itself. The PERR method was also subsequently  
199 applied to the weighted results of the study and prior periods.

200 In a further comparison (Supplementary material), confounding was also adjusted for  
201 using the Pairwise formulation of the PERR method [33,40]. This makes the  
202 adjustment within each exposure group before estimating the adjusted effect of  
203 exposure: this method is less sensitive to censoring and unmeasured, but otherwise  
204 balanced, covariates when the assumptions of the PERR method are satisfied.

205

## 206 **3. Results**

### 207 **3.1. Cohort characteristics**

208 There was an increase in cohort size from 62 644 in 1997 to 130 460 in 2011. The  
209 annual percentage rate of influenza vaccinations among the  $\geq 65$  year old patients of  
210 the cohorts varied between 8.5% and 12.3% from 1997 to 1999 (Table 1), increasing  
211 to 39.5% in 2000 with the introduction of the policy to increase vaccine coverage.  
212 Thereafter, the annual vaccination rate fluctuated between 12.9% in 2007 and 24.5%  
213 in 2005.

214 There was an overall decrease in the mean age of vaccine recipients from 76y in  
215 1998 to 70y in 2011, at which point vaccinated patients were on average 3.5y  
216 younger than the controls (Table 1). Patients with at least one QOF-registered  
217 disease comprised 68.2% of the vaccine recipients compared to 54.1% of the  
218 controls in the 1997 cohort, but by 2011 this disparity, largely influenced by the  
219 prevalence of hypertension (Supplementary Table), had steadily reduced to 60.5%  
220 and 58.1%, respectively. The difference between vaccination groups in the  
221 prevalence of the next most frequent morbidity, coronary heart disease, also  
222 narrowed and similar declining trends were seen in atrial fibrillation, asthma, chronic  
223 obstructive pulmonary disease, depression and strokes (Supplementary Table).

Year	N	N vaccinated	% vaccinated	Vaccine status	Admitted with MI (% patients)	Mean age (y)	% male	% patients with $\geq 1$ QOF disease
1997	62644	7687	12.3	Controls	0.68	74.1	41.9	54.1
				Vaccinated	0.91	74.3	41.9	68.2
1998	68421	5801	8.5	Controls	0.69	74.0	42.3	54.4
				Vaccinated	0.95	76.2	42.3	71.6
1999	72288	8686	12.0	Controls	0.70	73.9	42.7	54.3
				Vaccinated	1.19	75.4	42.7	70.4
2000	73527	29058	39.5	Controls	0.82	74.5	42.8	53.5
				Vaccinated	0.86	72.9	42.8	61.7
2001	58998	13753	23.3	Controls	0.76	74.6	41.6	53.1
				Vaccinated	1.05	73.2	41.6	62.6
2002	56370	9875	17.5	Controls	0.79	74.4	41.7	52.6
				Vaccinated	0.96	71.9	41.7	63.1
2003	59851	10943	18.3	Controls	0.83	74.4	42.0	53.5
				Vaccinated	0.67	71.5	42.0	62.3
2004	69285	11896	17.2	Controls	0.66	74.2	42.6	53.6
				Vaccinated	0.74	71.3	42.6	65.0
2005	81591	20027	24.5	Controls	0.67	74.4	42.7	53.8
				Vaccinated	0.67	70.9	42.7	60.0
2006	77136	10635	13.8	Controls	0.62	74.1	43.0	54.9
				Vaccinated	0.64	70.6	43.0	61.1
2007	87388	11286	12.9	Controls	0.60	73.8	44.0	55.1
				Vaccinated	0.59	69.9	44.0	61.6
2008	97355	16225	16.7	Controls	0.69	73.6	44.3	55.8
				Vaccinated	0.53	69.6	44.3	60.7
2009	103538	14839	14.3	Controls	0.60	73.3	44.7	56.0
				Vaccinated	0.65	69.6	44.7	61.3
2010	113666	15197	13.4	Controls	0.61	73.4	44.9	57.2
				Vaccinated	0.43	69.6	44.9	60.8
2011	130460	20302	15.6	Controls	0.64	73.4	45.2	58.1
				Vaccinated	0.51	69.9	45.2	60.5

224 *Table 1: Each annual cohort's characteristics describing vaccination status, hospital*  
225 *admissions for myocardial infarctions, age, sex and proportions of patients with*  
226 *diseases monitored under the Quality Outcomes Framework (QOF)*

227  
228

## 229 3.2. Effectiveness of vaccination on influenza hospitalisations

230 Without adjustment for confounding bias, Influenza vaccination was associated with  
 231 an elevated risk of influenza, although the HRs in the prior vaccine-free periods were  
 232 also in excess of 1.0 indicating possible bias between the two groups (Table 2).  
 233 However, after adjusting for confounding with the PERR method, influenza  
 234 vaccination was effective in reducing influenza, with HRs ranging from 0.70 (95% CI:  
 235 0.62, 0.79) in 1999 to a maximum of 0.99 (95% CI: 0.87, 1.12) in 2001. While the  
 236 incidence of influenza outcomes remained relatively stable at around 3 to 4% in each  
 237 cohort, there was an overall increase in the proportion that was due to hospital  
 238 admissions from 15% in 1997 to 49% in 2011 (Table 2). There was no discernible  
 239 relationship between the rise in hospital admissions and the effect of vaccination.

Cohort	Prior			Study			PERR
	Outcomes	Hospital admissions	HR	Outcomes	Hospital admissions	HR	HR
1997	2747	5.8%	2.01 (1.84, 2.20)	2548	15.0%	1.53 (1.38, 1.69)	0.76 (0.67, 0.86)
1998	2692	13.2%	2.07 (1.87, 2.29)	2627	23.9%	1.46 (1.30, 1.64)	0.71 (0.61, 0.82)
1999	2748	17.0%	2.12 (1.94, 2.32)	2780	27.4%	1.48 (1.34, 1.63)	0.70 (0.62, 0.79)
2000	2741	17.7%	1.65 (1.53, 1.78)	2621	22.8%	1.37 (1.27, 1.48)	0.83 (0.74, 0.93)
2001	1831	16.5%	1.48 (1.34, 1.63)	2000	29.2%	1.46 (1.33, 1.61)	0.99 (0.87, 1.12)
2002	1722	17.8%	1.87 (1.68, 2.08)	1759	33.1%	1.44 (1.28, 1.61)	0.77 (0.67, 0.90)
2003	1856	19.7%	2.00 (1.81, 2.22)	1911	32.9%	1.46 (1.31, 1.63)	0.73 (0.64, 0.84)
2004	2187	20.8%	1.97 (1.79, 2.16)	2420	32.0%	1.53 (1.39, 1.69)	0.78 (0.70, 0.89)
2005	2735	18.5%	1.70 (1.57, 1.84)	2697	32.3%	1.31 (1.20, 1.43)	0.77 (0.69, 0.86)
2006	2553	20.6%	2.13 (1.94, 2.34)	2597	31.6%	1.58 (1.42, 1.74)	0.74 (0.66, 0.83)
2007	2867	18.5%	1.76 (1.60, 1.93)	2793	32.3%	1.47 (1.33, 1.64)	0.84 (0.73, 0.96)
2008	3280	18.8%	1.80 (1.66, 1.96)	3291	35.7%	1.35 (1.23, 1.47)	0.75 (0.66, 0.83)
2009	3586	21.5%	1.92 (1.77, 2.08)	3144	34.8%	1.47 (1.34, 1.62)	0.77 (0.69, 0.86)
2010	3561	23.9%	1.92 (1.77, 2.09)	3490	37.5%	1.80 (1.66, 1.97)	0.94 (0.85, 1.05)
2011	4025	24.3%	2.24 (2.09, 2.41)	4127	48.6%	1.82 (1.69, 1.96)	0.81 (0.73, 0.89)

240 *Table 2: Results for the number of (composite influenza) outcomes; percentage of*  
 241 *outcomes that were hospital admissions for suspected influenza; and the prior, study*  
 242 *period and PERR-adjusted hazard ratios (95% confidence intervals) of influenza*  
 243 *vaccination group for each annual cohort, adjusted for age and sex.*

244

245 **3.3. Effectiveness of influenza vaccination on MI**

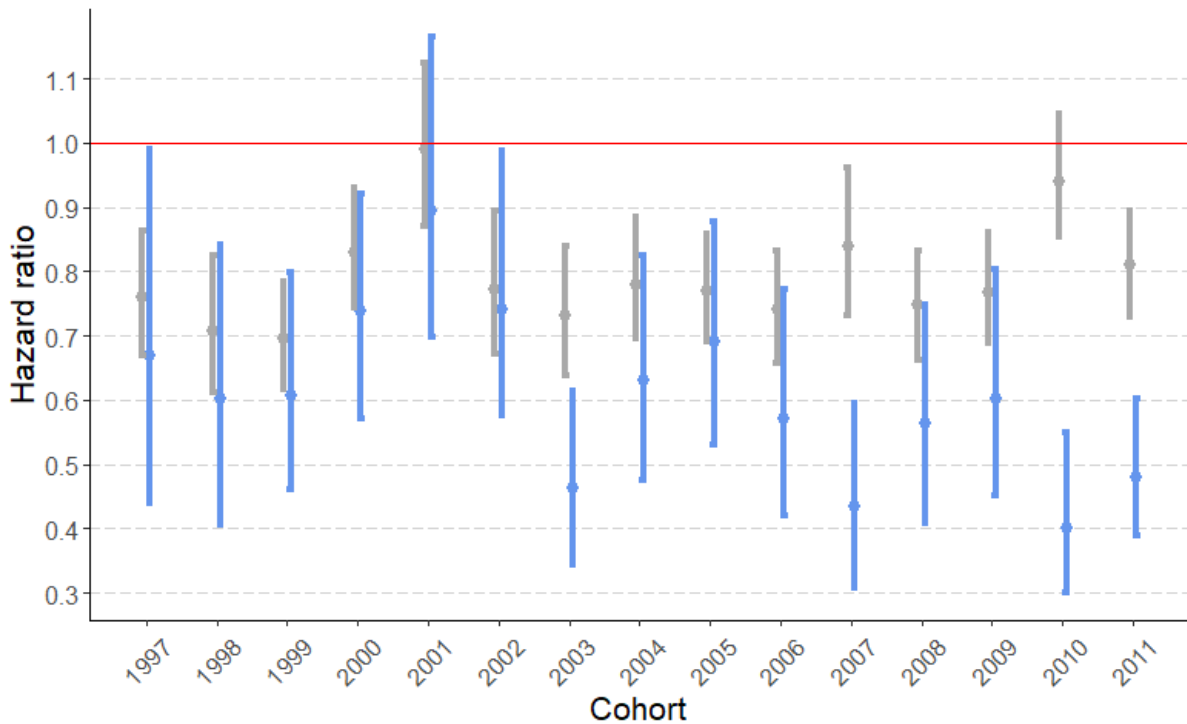
246 Influenza vaccination was associated with an elevated risk of MI according to the  
 247 HRs of the naive model (adjusted only for age and sex) (Table 1). However, the  
 248 HRs in the prior period were also in excess of 1.0 (Table 3**Error! Reference source**  
 249 **not found.**), indicating the possible presence of a pre-existing bias between the  
 250 groups. Adjusting for this confounding bias through the PERR method, the PERR-  
 251 adjusted HRs ranged from 0.40 (95% CI: 0.30, 0.55) in 2010 to 0.89 (95% CI: 0.70,  
 252 1.17) in 2001, indicating reduced rates of MI following influenza vaccination (Table 3;  
 253 blue markers in Fig 2).

Cohort	Prior HR	Study HR	PERR HR
1997	1.96 (1.42, 2.70)	1.31 (1.02, 1.68)	0.67 (0.44, 0.99)
1998	2.05 (1.58, 2.66)	1.23 (0.94, 1.63)	0.60 (0.41, 0.84)
1999	2.59 (2.09, 3.20)	1.57 (1.27, 1.94)	0.61 (0.46, 0.80)
2000	1.43 (1.19, 1.72)	1.06 (0.90, 1.24)	0.74 (0.57, 0.92)
2001	1.55 (1.26, 1.90)	1.38 (1.14, 1.67)	0.89 (0.70, 1.17)
2002	1.90 (1.49, 2.41)	1.31 (1.04, 1.64)	0.74 (0.58, 0.99)
2003	2.02 (1.62, 2.52)	0.93 (0.73, 1.19)	0.46 (0.34, 0.61)
2004	2.09 (1.71, 2.56)	1.32 (1.06, 1.64)	0.63 (0.48, 0.83)
2005	1.67 (1.37, 2.03)	1.15 (0.95, 1.40)	0.69 (0.53, 0.88)
2006	2.21 (1.78, 2.74)	1.26 (0.98, 1.62)	0.57 (0.42, 0.77)
2007	2.67 (2.15, 3.32)	1.16 (0.90, 1.50)	0.44 (0.31, 0.59)
2008	1.74 (1.41, 2.16)	0.98 (0.79, 1.23)	0.56 (0.41, 0.75)
2009	2.06 (1.69, 2.50)	1.24 (1.00, 1.54)	0.60 (0.45, 0.80)
2010	2.34 (1.93, 2.83)	0.94 (0.74, 1.19)	0.40 (0.30, 0.55)
2011	2.09 (1.76, 2.48)	1.00 (0.82, 1.22)	0.48 (0.39, 0.60)

255 *Table 3: Results for the prior, study period and PERR-adjusted hazard ratios (95%*  
256 *confidence intervals) of influenza vaccination on myocardial infarction for each*  
257 *annual cohort, adjusted for age and sex*

258

259



260

261 **Fig 2: The PERR-adjusted hazard ratios for the estimated effect of influenza**  
262 **vaccination on influenza and myocardial infarctions from 1997 to 2011.**

263 Grey markers: composite outcome for influenza. Blue markers: hospital admissions  
264 for myocardial infarction. Errors bars: bootstrapped 95% confidence intervals.

265

266 The influenza vaccine demonstrated a greater effectiveness against MIs than against

267 influenza, itself, across all years, and for most years, this rise and fall in

268 effectiveness against MI seemed to follow the effectiveness against influenza (Fig 2).

269 However, there were exceptions. The estimates for 2003, 2007 and 2010-11

270 demonstrated the greatest effectiveness against MIs and suggested the vaccine

271 afforded significantly more protection against MIs than influenza, itself.

272



### 273 **3.4. PERR adjustment of aggregated results**

274 Having aggregated the data, the HR of the effect of influenza vaccination on MIs,  
275 adjusted for age and sex, was 1.18 (95% CI: 1.12, 1.25), indicating an elevated risk  
276 among vaccine recipients, but in the prior period this was even larger at 1.93 (95%  
277 CI: 1.83, 2.04). After adjustment with PERR, the HR of for the vaccine effect was  
278 0.61 (95% CI: 0.56, 0.66) meaning that the average reduction in hazard ratio of MIs,  
279 as a measure of vaccine effectiveness, from 1997 to 2011 was 39% (95% CI: 34%,  
280 44%).

### 281 **3.5. Sub-group analyses**

282 No significant effect on the influenza outcome was detected from the interaction  
283 between age and vaccination status (not shown). For the MI outcome, there was a  
284 significant interaction effect between vaccination and age in years 2004, 2008, 2010  
285 and 2011 with HRs above unity (Table 4). All other interactions were not significant  
286 and either at or above one, apart from the 1997 and 2005 cohorts, for which the  
287 main effects of vaccination were also among the weakest of the cohorts. Given that  
288 all the point estimates for the vaccination main effect were below one, then the  
289 interpretation of the interactions for the 12 cohorts with interaction HRs above one is  
290 that for those years, the effectiveness of vaccination appeared to wane with age. For  
291 example, the hazard of an MI after vaccination in 2009 was estimated to be 0.55 at  
292 65y, but according to the interaction this had increased to 0.67 at 85y.

293

Cohort	HR vaccination	HR vaccine*age
1997	0.78 (0.23, 1.32)	0.98 (0.93, 1.04)
1998	0.59 (0.13, 1.05)	1.00 (0.95, 1.05)
1999	0.44 (0.21, 0.67)	1.03 (0.99, 1.07)
2000	0.62 (0.38, 0.86)	1.02 (0.99, 1.05)
2001	0.74 (0.43, 1.05)	1.02 (0.99, 1.05)
2002	0.55 (0.29, 0.81)	1.02 (0.99, 1.05)
2003	0.36 (0.20, 0.52)	1.02 (0.99, 1.05)
2004	0.44 (0.25, 0.63)	1.04 (1.01, 1.07)
2005	0.88 (0.50, 1.26)	0.98 (0.95, 1.01)
2006	0.48 (0.25, 0.72)	1.02 (0.99, 1.06)
2007	0.40 (0.22, 0.59)	1.02 (0.99, 1.05)
2008	0.38 (0.21, 0.54)	1.05 (1.01, 1.08)
2009	0.62 (0.38, 0.86)	1.01 (0.98, 1.04)
2010	0.29 (0.15, 0.44)	1.03 (1.00, 1.06)
2011	0.34 (0.22, 0.46)	1.04 (1.01, 1.06)

295 *Table 4: PERR-adjusted hazard ratios (95% CIs) of vaccination main effect and its*  
 296 *interaction with age on myocardial infarctions for annual cohorts, from the model*  
 297 *including age (centred on 65 years) and sex main effects and interaction.*

## 299 **4. Discussion**

300 The aggregated annual vaccine effectiveness against MIs from 1997 to 2011 was  
301 estimated to be 39% (95% CI: 34%, 44%), varying between 11% in 2001 and 57% in  
302 2010, and against influenza, itself, from 1% in 2001 to 30% in 1999. Interestingly, the  
303 annual variation in effectiveness against influenza was closely mirrored by its  
304 effectiveness against MI for most years, suggesting possible mediation of the  
305 prevention of MIs in those years via an effect on influenza. For four of the 15 years,  
306 the effect on MI deviated markedly from that on the influenza outcome with no  
307 overlap in CIs in 2003, 2007 and 2010-11. The point estimates for the effect on MI  
308 were consistently further from the null HR of 1 than the effect on influenza. This  
309 could be due to differences in recording the outcomes and the inclusion of primary  
310 care data in the influenza outcomes. Further investigation including replication of this  
311 study in a different healthcare system for the same time period may yield further  
312 insight into whether this might be due to annual variation in the virulence of the  
313 circulating strains, specificity of the outcomes (e.g. whether or not laboratory  
314 confirmed diagnoses are available) or residual unadjusted bias. It is also possible  
315 additional mechanisms mediate the vaccine effect on MI that are not directly related  
316 to the prevention of influenza. The divergence between the estimates for the MI and  
317 influenza outcomes in 2010 and 2011 follows the emergence of a novel strain of  
318 influenza A H1N1 in 2009 [41]. However, understanding the effect of vaccination on  
319 this particular zoonotic strain is complex and is further complicated by the use of  
320 data from the year prior to the study period to adjust for time-invariant confounding  
321 bias. Averaging over year-to-year variation, we noted our aggregated result of 39%

322 agreed closely with the estimate of 33% reported by one of the few randomised trials  
323 of influenza vaccination reporting MI as a secondary outcome [14].

324 Interaction analyses found protection against MI waned with age in all but three of  
325 the cohorts. However, there was no indication of a consistent age effect on  
326 vaccination against influenza, which was in accordance with findings from a test-  
327 negative study conducted in the same age group [42].

328 Our study took a robust approach to confounding bias, applying multiple methods to  
329 adjust for observed and hidden confounding. Adjustment for observed confounders  
330 alone did not account for all sources of bias as our IPTW analysis showed (results in  
331 supplementary S1 file). However, the proximity of the IPTW results to those adjusting  
332 for age and sex alone suggested the degree of unadjusted confounding did not  
333 notably affect the PERR estimates. Furthermore, we tested the robustness of the  
334 results to the assumptions of the PERR method, by applying the alternative  
335 formulation of the Pairwise method to arrive at strikingly similar estimates, albeit  
336 indicating a possibly greater protective effect of vaccination via this method (results  
337 in supplementary S1 file). Both methods, however, assume the absence of time-  
338 dependent confounding. This may be a particular problem for this age group, which  
339 is likely to be subject to time-varying confounders as frailty increases over time.  
340 However, the restriction to one year of follow-up could reasonably be expected to limit  
341 this source of bias. On the independence of outcomes, our study did not distinguish  
342 between the order of MI outcomes, which could be important for the first and  
343 subsequent MI events. Alternatives to the Cox model can account for the  
344 dependence between events [43–45], but further methodological work will be needed  
345 for their implementation in the PERR study design. Supported by linkage between  
346 CPRD and HES data, MI is well-recorded in the data and therefore missingness not

347 a likely source of bias [46]. Suspected influenza cases are not routinely confirmed by  
348 laboratory assays in the UK. Our study relied on a composite outcome consisting of  
349 hospitalisation for influenza or antibiotic treatment for possible secondary lower  
350 respiratory tract infections. Reducing antibiotic prescribing for treating secondary  
351 infections from influenza has previously been shown to be a benefit of the vaccine  
352 [36].

353 While our study provided a view of possible year-to-year variation in influenza  
354 vaccine effectiveness and showed a protective effect of vaccination consistent with  
355 other studies, estimation of vaccine effectiveness did not model the complex  
356 interplay between serological history of the patients and annual mismatches between  
357 the influenza vaccine and ever-evolving viral strains [47,48]. The causal mechanism  
358 and the role of influenza in mediating the effects of the vaccine may be complex [16],  
359 as evidenced by the divergence during 2003, 2007 and 2010-11 from the otherwise  
360 close agreement between the vaccine effects on influenza and MIs in our study.

361 Understanding this causal mechanism requires further study of the multiple  
362 pathways that can lead from flu to an acute coronary syndrome combined with  
363 support from randomised clinical trials of influenza vaccine as a preventive measure  
364 for cardiovascular disease (with influenza illness as a secondary outcome). We note  
365 that the risk of MI may vary between the first and subsequent occurrence, and so the  
366 effectiveness of the influenza vaccine against MI may vary accordingly. Further work  
367 will be needed to differentiate between primary and secondary occurrences of MI.

368

369 Overall, the evidence for a protective effect of the influenza vaccine against MIs from  
370 our aggregated analysis of older adults was consistent with the estimated 33%

371 effectiveness reported by the FLUCAD study across a wider age range [14],  
372 although their precision was affected by having fewer patients and fewer outcomes.  
373 The results from our study are also broadly in line with the conclusion of a protective  
374 effect against major adverse cardiovascular events as estimated in a previous  
375 systematic review of RCTs [49], and studies conducted on observational data [4,17–  
376 19,49–52]. However, these employed different methods of analysis, in which  
377 confounding bias may not have been fully addressed. Our findings also fit with the  
378 wider literature linking serious respiratory disease to MIs, to the extent that  
379 prevention for MIs is being trialled for patients with pneumonia [53].

380

## 381 **5. Conclusions**

382 Our study provides robust real-world evidence in a large, nationally representative  
383 cohort that influenza vaccination can offer stable protection against MIs among  
384 adults age  $\geq 65$ y. There was some evidence that vaccine effectiveness against MIs  
385 may decrease with age in this group. Future randomised trials are needed to test  
386 and refine strategies for MI reduction that focus on reducing serious viral and  
387 respiratory disease through vaccination.

388

389

## 390 **6. Ethics**

391 This study gained approval from the Independent Scientific Advisory Committee  
392 (ISAC protocol 14-159).

393 The authors declare that they have no known competing financial interests or  
394 personal relationships that could have appeared to influence the work reported in  
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