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

Short title: Influenza vaccine in reducing myocardial infarctions

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Abstract

Objective

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

Study design and setting

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

Results

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

Conclusions

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

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

Word count: 200

Keywords

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

Running title: Influenza vaccination and myocardial infarctions: PERR study

1. Introduction

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

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

Population studies using electronic health records (EHRs) have demonstrated a protective effect of influenza vaccination, reducing the risk of MI in the year following vaccination by 7% to 20% in older patients [17–19]. However, EHRs are not primarily purposed for research, and are prone to bias from unmeasured confounding [20,21]. An alternative to EHRs is claims data, which are records of claims for services from health insurance companies. Claims data may overstate the effectiveness of vaccination, reflecting the health-seeking behaviours of relatively healthy vaccine recipients (“healthy user bias") [22]. Universal healthcare systems are more likely to represent World Health Organisation guidelines in offering the influenza vaccine to high-risk groups, and so data from these systems, like that supplied by the Clinical Practice Research Datalink for this study, may be affected by bias that understates effectiveness (confounding by indication). However, both confounding by indication and healthy user bias may operate simultaneously in observational studies of influenza vaccine effectiveness, and it is recommended that this is addressed through avoidance of unspecific outcomes (such as all-cause mortality) alongside use of appropriate methods for confounding control [22].

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

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

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

Using the PERR study design and comparing the results to those adjusted for measured confounders through weighting, we took a robust approach to the problem of confounding bias in our investigation of the real-world effectiveness of influenza vaccination against the risk of MI. This was a study of UK adults aged ≥65y for a period beginning in 1997 when the policy to vaccinate older adults was introduced. 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 1st
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 31st
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

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

2.3. Outcomes

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

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

2.4. Statistical analysis

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

2.4.1. Adjustment for confounding bias

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

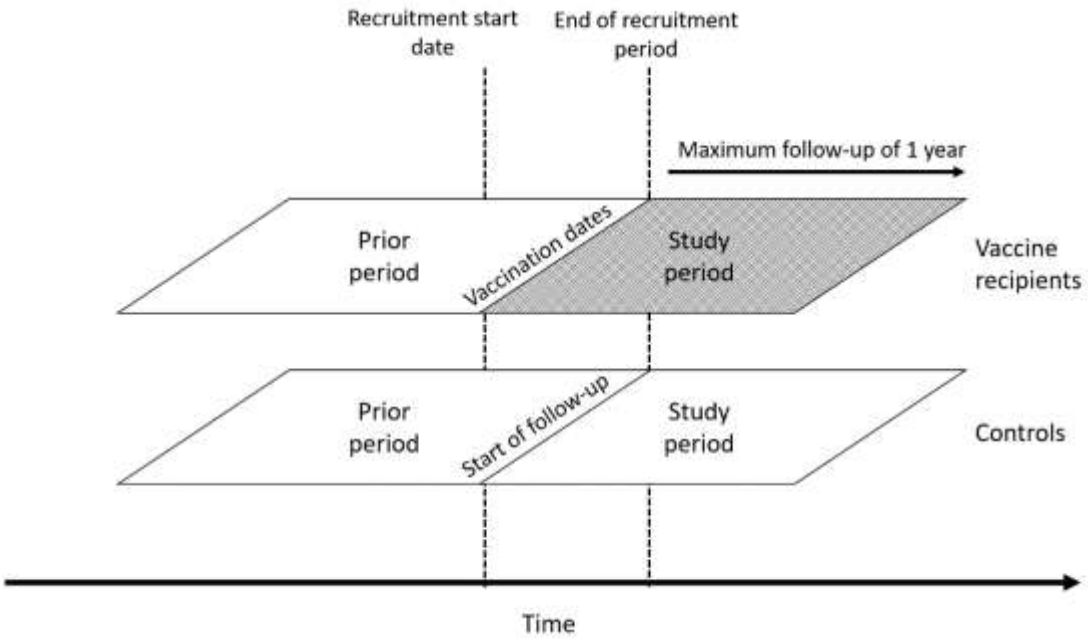

***Fig 1:* Schematic of the PERR study design.**
Vaccinated patients are selected from 1st September to 31st January. Start of follow-up dates for the controls are mapped from the vaccination dates of vaccinees. Event times are compared for vaccinated and control patients during a 1 year study period and a 1 year prior period, preceding the study period by exactly 1 year.

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

2.4.2. Sub-group analysis

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

2.4.3. Sensitivity analysis

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

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

3. Results

3.1. Cohort characteristics

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

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

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

3.2. Effectiveness of vaccination on influenza hospitalisations

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

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

3.3. Effectiveness of influenza vaccination on MI

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

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

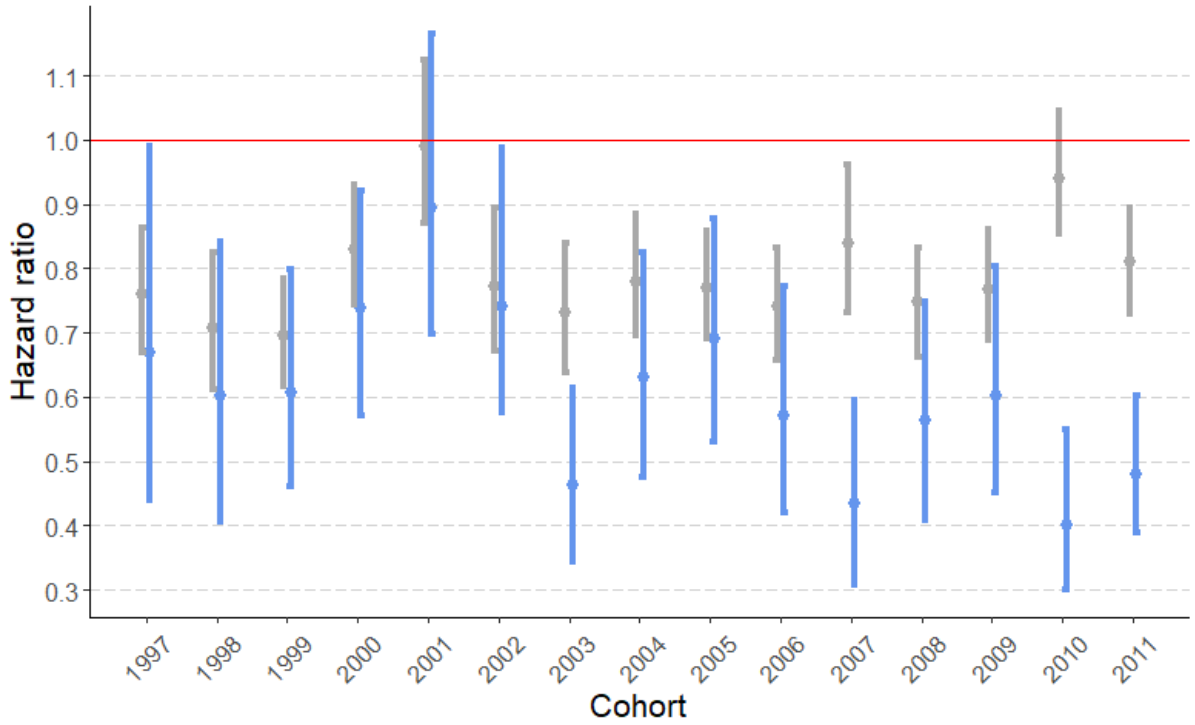

Fig 2: **The PERR-adjusted hazard ratios for the estimated effect of influenza vaccination on influenza and myocardial infarctions from 1997 to 2011.** Grey markers: composite outcome for influenza. Blue markers: hospital admissions for myocardial infarction. Errors bars: bootstrapped 95% confidence intervals.

The influenza vaccine demonstrated a greater effectiveness against MIs than against influenza, itself, across all years, and for most years, this rise and fall in effectiveness against MI seemed to follow the effectiveness against influenza (Fig 2). However, there were exceptions. The estimates for 2003, 2007 and 2010-11 demonstrated the greatest effectiveness against MIs and suggested the vaccine afforded significantly more protection against MIs than influenza, itself.

3.4. PERR adjustment of aggregated results

Having aggregated the data, the HR of the effect of influenza vaccination on MIs, adjusted for age and sex, was 1.18 (95% CI: 1.12, 1.25), indicating an elevated risk among vaccine recipients, but in the prior period this was even larger at 1.93 (95% CI: 1.83, 2.04). After adjustment with PERR, the HR of for the vaccine effect was 0.61 (95% CI: 0.56, 066) meaning that the average reduction in hazard ratio of MIs, as a measure of vaccine effectiveness, from 1997 to 2011 was 39% (95% CI: 34%, 44%).

3.5. Sub-group analyses

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

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)

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

4. Discussion

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

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

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

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

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

While our study provided a view of possible year-to-year variation in influenza vaccine effectiveness and showed a protective effect of vaccination consistent with other studies, estimation of vaccine effectiveness did not model the complex interplay between serological history of the patients and annual mismatches between the influenza vaccine and ever-evolving viral strains [47,48]. The causal mechanism and the role of influenza in mediating the effects of the vaccine may be complex [16], as evidenced by the divergence during 2003, 2007 and 2010-11 from the otherwise close agreement between the vaccine effects on influenza and MIs in our study. Understanding this causal mechanism requires further study of the multiple pathways that can lead from flu to an acute coronary syndrome combined with support from randomised clinical trials of influenza vaccine as a preventive measure for cardiovascular disease (with influenza illness as a secondary outcome). We note that the risk of MI may vary between the first and subsequent occurrence, and so the effectiveness of the influenza vaccine against MI may vary accordingly. Further work will be needed to differentiate between primary and secondary occurrences of MI.

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

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

5. Conclusions

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

6. Ethics

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

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

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