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Impact of influenza, herpes zoster, and pneumococcal vaccinations on the incidence of a cardiovascular events in subjects aged over 65 years: a systematic review

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1 **Impact of influenza, herpes zoster, and pneumococcal**
2 **vaccinations on the incidence of a cardiovascular events in**
3 **subjects aged over 65 years: a systematic review**

4 **ABSTRACT:**

5 This systematic review aims to summarise the impact of vaccination against influenza,
6 shingles and pneumococcus on the incidence on the risk of cardiovascular events (CVE)
7 within the elderly.

8 This protocol was developed in accordance with PRISMA guidelines. We conducted a
9 literature search and identified all relevant articles published regarding the matter up to
10 September 2022.

11 We retrieved 38 studies (influenza vaccine = 33, pneumococcal vaccine = 5, Zoster vaccine =
12 2). 28/2 studies have shown that influenza and pneumococcal vaccines lower significantly the
13 risk of cardiovascular disease in the elderly. Also, repeated influenza vaccination shows a
14 consistent and dose-dependent protective effect against acute coronary syndromes and stroke.
15 Moreover, dual influenza and pneumococcal vaccination was associated with lower risks of
16 some cardiovascular events (stroke, congestive heart failure, ischemic heart disease,
17 myocardial infarction). However, the impact of PCV13 on cardiovascular events has not been
18 studied, nor the currently recommended vaccination schedule (PCV13+PPV23). As for herpes
19 zoster vaccination, only the protective effect against stroke has been studied with the live
20 attenuated herpes zoster vaccine, but no studies have been conducted with the recombinant
21 subunit herpes zoster vaccine.

22 This review outlines the benefits of the vaccines mentioned above, beyond their preventive
23 action on infectious diseases. It is intended for health professionals who wish to inform and
24 advise their elderly patients.

25 **KEYWORDS: (6 words)**

26 Influenza, herpes zoster, pneumococci, vaccine, cardiovascular event, elderly person

27

28 **1. INTRODUCTION:**

29 Elderly people are particularly at risk of developing certain infections due to immune
30 senescence, age-related specific organ physiological changes and other factors (dementia,
31 institutionalization etc...) frequently met in this population. [1]–[3]. Among these infections,
32 influenza, pneumococcal and zoster infections are an important cause of high morbidity and
33 mortality in the elderly [4]–[6].

34 These infections are vaccine-preventable diseases (VPD), and the effectiveness of vaccines to
35 reduce them has been largely demonstrated in the elderly [7]. Large cohort studies have
36 shown that influenza vaccination reduces influenza-like diseases, pneumonia and the risk of
37 death among elderly persons [8]. As for invasive pneumococcal disease (IPD) prevention,
38 many studies and six meta-analyses found significant effectiveness of the PPV-23 [9]. More
39 recently, the PCV13 vaccine has also demonstrated efficacy against community-acquired
40 pneumonia and IPD episodes in patients over 65 years of age [10]. Regarding the live
41 attenuated varicella zoster virus vaccine (ZVL), it was shown to be 62% effective in
42 preventing herpes zoster and 81% effective in preventing post-herpetic neuralgia [11].

43 Beyond the burden of infectious diseases, these infections are also responsible for some non-
44 infectious illnesses like cardiovascular events. As a matter of fact, an increased risk of
45 cardiovascular disease during influenza infection has been established by Warren-Gash [12],
46 [13]. Risk of acute cardiovascular events and risk of stroke were shown to increase
47 respectively fivefold and threefold in the first three days after respiratory tract infection [14].
48 Moreover, Chow *et al.* highlighted that 11.7% of adults with laboratory-confirmed influenza
49 had an acute cardiovascular event during the first years. The most common events (non-
50 mutually exclusive) were acute heart failure (6.2%) and acute ischemic heart disease (5.7%)
51 [15]. In recent years some studies have found that acute infections especially pneumonia, are
52 associated with a transient increasing risk of acute vascular events [14], [16], [17]. In fact,
53 acute cardiac events are frequent in pneumococcal pneumonia and are associated with
54 increased mortality [18]. Regarding zona, Seo *et al.* revealed that severe herpes zoster (HZ)
55 requiring hospitalization significantly increased the risk of myocardial infarction (MI) (HR,
56 1.831; 95% CI, 1.354–2.476), ischemic stroke (HR, 1.523; 95% CI, 1.212–1.915) and heart
57 failure (HR, 2.034; 95% CI, 1.615–2.562) [19]. Recent studies suggested that the risk of
58 stroke may be increased in the year following an acute episode of HZ, possibly also mediated
59 by Varicella-Zonas Virus (VZV) replication in arterial walls, resulting in cerebral
60 vasculopathy [20].

61 Despite the well-known benefits of vaccines [7], and although vaccination coverage varies by
62 country, the coverage of vaccines recommended for the elderly is not optimal. Influenza
63 vaccination coverage almost always falls short of the World Health Organization's (WHO's)
64 target of 75% of older adults [21] with 59,9 % in France [22]. Pneumococcal vaccination
65 uptake is around 4,8% in older adults [23], and shingles uptake rates is lower than 10% in
66 France [24]. This low vaccine coverage in elderly seems to be the results of multiple factors
67 such as vaccine hesitancy [25], lack of health literacy [26] and lack of healthcare providers
68 advise [27]. Several updated reviews on infectious diseases among the elderly [3] and
69 associated vaccinations [7] were published and are helping physicians to discuss about the
70 benefits of vaccines in reducing infectious diseases. However, perceived risks of vaccine-
71 preventable diseases may be low in elderly and complacency may lead to the absence of
72 vaccination [28]. On the other hand, in a study using data from the 2019 Health Barometer of
73 Santé Publique France, 53% of the people aged from 18 to 85 years old feared stroke and 45%
74 of them feared myocardial infarction [29].

75 The aim of this systematic review is to identify and measure the impact of influenza, herpes
76 zoster and pneumococcal vaccinations on the incidence of cardiovascular events in people
77 aged 65 years and older. Providing data highlighting the protective effect of these vaccines
78 against some cardiovascular events can provide new arguments to promote vaccination in this
79 vulnerable population.

80 **2. MATERIALS AND METHODS**

81 This protocol has been developed following the Preferred Reporting Items for Systematic
82 Review and Meta-Analysis (PRISMA) guidelines, as shown in the PRISMA checklist – [30].
83 The systematic review was prospectively registered with Prospective Register of Systematic
84 Reviews (PROSPERO; registration number: CRD42021261176). No significant changes were
85 made to the protocol

86 ***Literature search strategy.*** We determined the selection criteria for the data collection and
87 identified all the relevant articles published on the subject up to September 2022. We
88 consulted the Medline database (Pubmed), Embase and Cochrane Library with our search
89 criteria to retrieve articles published in French and English, related to the subject in adults
90 aged over 65 years and individual medical subject heading (MeSH) terms.

91 The keywords of the searches were for **vaccine [1]** ("vaccines" [MH] OR "vaccines" [TW]
92 OR "vaccine" [TW] OR "Vaccination" [TW] OR "immunization" [TW] OR "adult
93 immunization" [TW]) ; for **Herpes zoster [2]** ("herpes zoster" [MH] OR "Zona" [TW] OR
94 "shingles" [TW] OR "post-herpetic neuralgia" [TW]); for **Pneumococcal [3]** ("pneumococcal
95 infections" [MH] OR "Pneumococcal Disease" [TW] OR "streptococcus pneumoniae
96 infection" [TW] OR "pneumococcal" OR "Streptococcus pneumoniae") ; for **Influenza [4]**
97 ("influenza, human" [MH] OR "influenza" [TW] OR "flu" [TW] OR "influenza virus" [TW])
98 ; for **cardiovascular diseases [5]** ("cardiovascular diseases" [MH] OR "cardiovascular
99 accident" [TW] "cardiovascular mortality" OR "cardiovascular morbidity"OR "cardiovascular
100 events"). The search equations in Pubmed, Embase and Cochrane Library were combinations
101 of the previous equations with a filter setting the age to 65 years and older.

102 The reference lists of relevant studies and meta-analyses already carried out were examined to
103 identify additional studies. The method used was consistent with the recommendations
104 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [30].

105 **Data management** We downloaded references identified in the searches (electronic database
106 and additional searches) into Zotero® reference management software. Once duplicates are
107 removed, the remaining references were exported into Abstrackr
108 (<http://abstrackr.cebm.brown.edu/account/login>).

109 **Study selection.** Two levels of screening for eligibility were performed. The first level was
110 performed by two independent reviewers (AA, EBN) using titles and abstracts from assess
111 and excluding papers that do not meet eligibility criteria. The screening process was
112 performed using Abstrackr. The second level was carried out using the full-text article and
113 two authors (AA, EBN) assessed the papers against the inclusion criteria for the review to
114 determine their eligibility for inclusion. In case of disagreement, we called upon a third
115 reviewer (GG). We prioritized randomized controlled trials, case-control study, prospective
116 and retrospective cohorts and systematic reviews. We retained studies with subgroup analyses
117 in the over-65 age group.

118 **Types of participants and study.** Any study which measures the impact of influenza, herpes
119 zoster or pneumococcal vaccination on the risk of cardiovascular events compared to non-
120 vaccinated people, conducted in a clinical or real-life population. We excluded studies with
121 participants aged < 65 years of age and who had no unvaccinated control group or self-control
122 group. Studies that included participants without age criteria, were retained if subgroup

123 analyses for age were performed including people 65 and over. Studies were excluded if the
124 different age groups were not well-defined, or if there was a comparison of different doses or
125 vaccine protocol without an unvaccinated group. The review authors resolved disagreements
126 through a consensus-based decision, or if necessary, discussion with a third reviewer.

127 Risk of bias for included studies were assessed in duplicate by investigators. The Cochrane
128 risk of bias tool was used to examine the quality of randomized clinical trials [31] and the
129 Newcastle-Ottawa Scale for observational studies [32]. Differences were discussed, and
130 settled by the entire study team if unresolved.

131 **3. RESULTS:**

132 ***Search Results***

133 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study
134 flow diagram of the search for the updated and extended review is shown in Figure 1.
135 Electronic searches identified 1062 records. On the basis of titles and abstracts, we excluded
136 752 records and assessed 141 full-text records for eligibility. Of 141 records examined in full,
137 we considered 38 to be eligible for inclusion, and we found 30 additional studies by searching
138 the reference sections of relevant reviews and by updating our search of ongoing trials on the
139 databases (Figure 1).

140 ***Included studies***

141 For details on the characteristics of individual studies retained, see Table 1, 2 and 3.

142 ***Design of studies included***

143 The designs of the studies were 1 randomised clinical trial, 13 retrospective cohort studies, 10
144 prospective cohort studies, 13 case-control studies and 1 meta-analysis. Follow-up was
145 provided from 64 weeks to 13 years after vaccination.

146 ***Outcome measures***

147 We included thirty articles dealing with influenza vaccination compared with a placebo or no
148 vaccination, as reported in Figure 1. Five articles reported the effect of pneumococcal
149 vaccination on cardiovascular events in vaccinated people compared to a placebo or no
150 vaccination and two articles discussed the effect of zona vaccination (see Figure 1). Among
151 these articles, n= 7 reported the vaccination impact on cardio-vascular diseases (CVD), n= 2

152 reported its impact on Major Adverse Cardiovascular Events (MACE), n= 11 reported its
153 impact on Myocardial Infarction (MI), n= 3 reported its impact on Ischemic Heart Disease
154 (IHD), n=2 reported its impact on Acute Coronary Syndrome (ACS), n= 1 reported its impact
155 on Atrial Fibrillation (AF), n=12 reported its impact on Congestive-Heart Failure (CHF),
156 n=14 reported its impact on Stroke.

157 ***Risk of bias in included studies***

158 Based on the Newcastle Ottawa evaluative scale, the overall quality assessments of the
159 included case-control and cohort studies ranged from fair to good, see Table 4 and Table 5.

160 Risk of bias for the clinical trial is shown in Table 6, based on the Cochrane scale.

161 **3.1. Impact of vaccines on the occurrence of cardio-vascular diseases** 162 **(CVD)**

163 Some studies have gathered the cardio vascular diseases without going through details on the
164 type of these diseases.

165 **3.1.1. Impact of influenza vaccine**

166 The impact of influenza vaccine on the occurrence of cardio-vascular diseases (CVD) was
167 assessed in 1 study, 3 other studies reported its impact on hospitalisation for CVD. Song *et al.*
168 [33] evaluated the effectiveness of influenza and pneumococcal vaccines against pneumonia
169 and acute exacerbation of cardiopulmonary diseases among the elderly aged ≥ 65 years with
170 influenza-like illness (ILI). Overall, seasonal influenza vaccination lowered the risk of acute
171 exacerbation of cardiovascular disease (51%), in the elderly aged ≥ 65 years.

172 For CVD hospitalisation, Wang *et al* [34], elucidated the cost-effectiveness of a community
173 vaccination program in all the elderly, and validated further the consistent effect of influenza
174 vaccination worldwide. The risk difference of hospitalization in cardiovascular diseases
175 among the vaccinated and unvaccinated subjects in the year after the immunization program
176 was risk difference (RD) -1.6% , (95% CI: $0 -3.0$; -0.1) and the RR was 0.50 , (95% CI: $0.27-$
177 0.91). The preventable fractions by vaccination was then 50% . Additionally, Nichol *et al.* [35]
178 assessed the influence of influenza vaccination on hospital presentations for heart disease.
179 When the odds of hospitalization for ischemic heart disease and congestive heart failure were
180 analysed separately, the reductions were also significant in every case except that of ischemic
181 heart disease during the 1999–2000 season (reduction, 10% ; $P=0.12$). In contrast, the study
182 by Chang *et al.* [36] did not show significant effect of vaccination on heart disease.

183 For older patients with heart failure, Liu *et al.* [37] evaluated the effects of influenza
184 vaccination on all-cause mortality and hospitalization for cardiovascular diseases and IHD
185 (ischemic heart disease) in elderly patients. In the Cox proportional-hazards analysis, after
186 adjustments for various factors, influenza vaccination was found to be associated with a
187 reduced risk of hospitalization due to CVD (HR, 0.84; 95% CI, 0.76–0.93) during the
188 influenza season. During the non-influenza season, influenza vaccination was not statistically
189 associated with a reduced risk (HR, 1.04; 95% CI, 0.91–1.18).

190 3.1.2. Impact of Pneumococcal vaccines

191 The impact of pneumococcal vaccine on CVD was evaluated in one meta-analysis and one
192 study.

193 Marra *et al.* [38] realized a meta-analysis summarizing available evidence on the impact of
194 PPV23 on CVD across all ages. A total of 15 unique studies looked at PPV23 and its effects
195 on any CVD event. When analysing individuals by age: PPV23 significantly decreased the
196 risk of CVD events (RR: 0.94; 95% CI: 0.89-0.99; I2 = 26.2%; p = 0.19) for individuals aged
197 ≥ 65 years.

198 In the study of Song *et al.*, [33] the PPV23 did not lower the risk of acute exacerbation of
199 CVD in the elderly aged ≥ 65 years. During the A/H3N2-dominant season with poor
200 influenza vaccine effectiveness (2014–2015 season), PPV23 showed significant effectiveness
201 against acute exacerbation of cardiopulmonary disease. During seasons with good influenza
202 vaccine effectiveness (2015–2016 and 2016–2017), the PPV23 was effective at preventing
203 acute exacerbation of chronic heart disease (71.0%) during the A/H1N1-dominant 2015–2016
204 season.

205 3.1.3. Impact of Herpes zoster vaccine

206 We did not retrieve studies about the HZ vaccine effect on the occurrence of CVD.

207 3.2. Impact of vaccines on occurrence of major adverse cardiovascular 208 events (MACE)

209 MACEs were defined as death, hospitalization for acute coronary syndrome, hospitalization
210 for heart failure and hospitalization for stroke [39].

211 3.2.1. Impact of Influenza vaccine

212 Two studies evaluated the impact of influenza vaccine on the occurrence of MACE. Both
213 found that influenza vaccine reduced the risk of MACE among elderly patients.
214 Phrommintikul *et al.* [40] evaluated the effects of influenza vaccine on cardiovascular

215 outcomes in patients with acute coronary syndrome. The effects of vaccination on MACE
216 were adjusted with age, sex, serum creatinine, ACE-I treatment, and coronary
217 revascularization. Patients in the vaccine group had significantly lower incidence of MACE
218 than patients in the control group after adjusting with the above parameters [adjusted RR 0.69
219 (0.54–0.90)] in the year following vaccination. Chiang *et al.* [39] conducted a population-
220 based case-control study to determine the protective effect of influenza vaccine against
221 primary MACEs in elderly patients. The adjusted ORs (aORs) for MACEs in those with
222 influenza vaccination and/or ILI after adjustment. Influenza vaccination was associated with
223 reduced odds of MACEs (aOR 0.80, 95% CI 0.78-0.82, $P < .001$).

224 3.2.2. Impact of Pneumococcal and Herpes zoster vaccines

225 Pneumococcal and Herpes zoster vaccines effect on the occurrence of MACEs wasn't
226 evaluated in the literature.

227 3.3. Impact of vaccines on the occurrence of myocardial infarction (MI)

228 3.3.1. Impact of influenza vaccine

229 Regarding myocardial infarction (MI), 7 case-control studies 2 prospective cohort studies and
230 one retrospective cohort study were included. Meyers *et al.* [41], Heffelfinger *et al.* [42] and
231 Lavallée *et al.* [43] didn't reveal a MI risk reduction due to prior influenza vaccination for
232 people over 65 years or 75 years old. But these studies have relatively small numbers (335
233 and 339). Hsu *et al.* [44] studied two groups of individuals: those exposed to mismatched
234 vaccine strains during the 2007 influenza period, and those exposed to matched strains during
235 the 2008 influenza period. The MI hazards ratios (HRs) in the men and women exposed to
236 mismatched strains in 2007 were 0.990 (95% confidence interval [CI], 0.745–1.316) and
237 1.102 (95% CI: 0.803–1.513), respectively. The MI HRs were significant in the men exposed
238 to the matched strains in 2008 (HR: 0.681; 95% CI: 0.509–0.912) and were barely significant
239 in their female counterparts (HR: 0.737; 95% CI: 0.527–1.029). But the diagnosis period of
240 MI was not consecutive to vaccination for all patients: it ran from January to September 2008
241 or 2009 of the year following the influenza vaccination campaign (October to December 2007
242 or 2008). On the hand, Siriwardena *et al.* [45] investigated in a case-control study design on a
243 possible association between influenza or pneumococcal vaccination and acute myocardial
244 infarction. Findings were that influenza vaccination was associated with a significantly
245 reduced rate of MI (aOR 0.79; 95% CI 0.75-0.83). de Abajo *et al.* [46]

246 assessed how influenza vaccination was related to a lower risk of a first acute myocardial
247 infarction (AMI) through different epidemic periods. The overall risk reduction of AMI

248 among vaccinated persons was aOR 0.84 (95% CI 0.81 to 0.88) and was observed in
249 subgroups of 65 years and more. Moreover, Hung *et al.* [47] conducted a prospective cohort
250 study by recruiting outpatients aged ≥ 65 years with chronic illness to participate in a
251 pneumococcal polysaccharide vaccine (PPV) and trivalent influenza vaccine (TIV)
252 vaccination program. The TIV-alone had not significant reduction in MI (HR 0,87; 95% CI,
253 0,59–1,33; P=0.51). However, dual-vaccines (PPV+TIV) had a 48% reduction in MI (HR
254 0.52; 95% CI, 0.38–0.71; P<0.001) compared to the unvaccinated group. Recently
255 Christiansen *et al.* [48] examined the impact of influenza vaccination on the risk of
256 hospitalization for MI among patients aged 65 years or older surviving an ICU admission.
257 The 1-year risk of hospitalization for MI was 1.9% For vaccinated patients and 1.8% for
258 unvaccinated patients, with a corresponding adjusted HR of 0.93 (95% CI 0.83–1.03). Chiang
259 *et al.* [39] also determined the protective effect of influenza vaccine against MI in elderly
260 patients, especially those with ILI. Vaccination had significant protective effects in the MI
261 subgroups (aOR 0.80 ; 95% CI 0.76-0.84 ; P < 0.001). ILI significantly increased the risks of
262 MI (aOR 1.46; 95% CI 1.34-1.59; P <0.001). Vaccination neutralized the increased risk of MI
263 due to ILI (aOR 1.05 ; 95% CI 0.92-1.21; P = 0.440).

264 3.3.2. Impact of Pneumococcal vaccines

265 Pneumococcal vaccine effect on the occurrence of MI was evaluated in one meta-analysis.

266 Marra *et al.* [38] showed a modest risk reduction in MI following pneumococcal vaccination
267 in people aged 65 years and older (RR: 0.93; 95% CI: 0.88- 0.99; I2 = 31.0%; P = 0.20).

268 3.3.3. Impact of Herpes zoster vaccine

269 Zona vaccine effect on the occurrence of Myocardial Infarction (MI) wasn't reported in the
270 literature.

271 **3.4. Impact of vaccines on the occurrence of ischemic heart disease**

272 3.4.1. Impact of influenza vaccine

273 Influenza vaccine effect on the occurrence of Ischemic Heart Disease (IHD) was evaluated in
274 3 prospective cohorts.

275 Huang *et al.* [49] investigated the influenza vaccine effect for IHD occurrence secondary to
276 Chronic obstructive pulmonary disease (COPD). In the Chi-square test analysis, influenza
277 vaccination was associated with a reduced risk of IHD (OR, 0.746; 95% CI: 0.595–0.937) in
278 elderly COPD patients in the age group of 71–80 years old. For the age group of 61-70 and
279 81-90 years old, the reduction was not statistically significant (OR, 0.86; 95% CI: 0.71–1.05

280 and OR 0.71; 95% CI: 0.41–1.21). When the odds of hospitalisation for ischemic heart
281 disease were analysed by Nichol *et al.*, the reduction was significant during the 1998-1999
282 season (OR=0.80; CI= [0.70–0.91]) and not significant during the 1999–2000 season (OR =
283 0.90 ; CI= [0.78–1.03]) . [35].Hung *et al.* [47] showed that the dual-vaccines effect
284 (PPV+TIV) was a 35% reduction in IHD (HR, 0.65; 95% CI: 0.54–0.78; P< 0.001, compared
285 with the unvaccinated group. In contrast, the TIV-alone had no significant reduction in IHD
286 (HR 0.87; 95% CI: 0.66–1.13; P=0.29).

287 3.4.2. Impact of Pneumococcal vaccines

288 Pneumococcal vaccine effect on the occurrence of IHD was evaluated in one prospective
289 study. Subjects who received PPV alone had no significant reduction of IHD (0.92 95% CI:
290 0.69-1.22) compared with the unvaccinated group. [47].

291 3.4.3. Impact of Herpes zoster vaccines

292 Zona vaccine effect on the occurrence of IHD wasn't reported in the literature.

293 3.5. Impact of vaccines on the occurrence of acute coronary syndrome

294 3.5.1. Impact of influenza vaccine

295 The impact of influenza vaccination on the occurrence of Acute Coronary Syndrome (ACS)
296 was reported in two studies.

297 Sung *et al.* [50] elucidated the potential protective benefit of influenza vaccination on
298 hospitalisation for ACS in a group of elderly Taiwanese patients with COPD. They conducted
299 a population-based cohort study using reimbursement claims from Taiwan's National Health
300 Insurance Research Database (NHIRD). The rate of hospitalisations for ACS after adjusted
301 for potential confounders was significantly lower, during all season, in both sexes and all
302 elderly-age groups (65–74 years adjusted HR 0.48, 95% CI 0.37–0.61, and 75 years and older
303 adjusted HR 0.41, 95%CI 0.29–0.57) in the influenza vaccination group than in the
304 unvaccinated group. For patients who did not experience pneumonic episodes, the vaccine
305 exerted a protective effect, thus preventing from ACS hospitalisations in both groups.
306 Influenza vaccination significantly reduced the number of hospitalisations for ACS regardless
307 of influenza seasonality. When the patients were stratified according to the total number of
308 vaccinations, the adjusted HRs for ACS hospitalisations were 0.48 (95% CI: 0.38–0.62) and
309 0.20 (95% CI: 0.14–0.28) for patients who received 2–3 and ≥ 4 vaccinations during the
310 follow-up period (all P < 0.001), respectively. More specifically, Ishigami *et al.* [51] assessed
311 the effectiveness of influenza vaccination among older adults with and without reduced
312 kidney function. Overall, influenza vaccination was associated with lower odds of coronary

313 heart disease (OR, 0.93; 95% CI: 0.88-0.97). When assessing by eGFR categories, the
314 association was consistent in eGFR \geq 30, but not significant in $<$ 30 mL/min/ 1.73 m² (ORs
315 of 1.03, 95% CI: 0.87-1.23 for coronary heart disease)

316 3.5.2. Impact of Pneumococcal and Herpes zoster vaccines

317 Pneumococcal and Herpes zoster vaccine effect on the occurrence of IHD wasn't retrieved in
318 the literature.

319 3.6. Impact of vaccines on the occurrence of atrial fibrillation

320 3.6.1. Impact of influenza vaccine

321 The role of influenza vaccination on Atrial fibrillation (AF) was reported in one study. Chang
322 *et al.* [52] investigated whether influenza infection was a risk factor of AF and studied
323 whether influenza vaccination could decrease the risk of AF. The subgroup analysis for the
324 patients over 65 years old showed that influenza vaccination (patients receiving vaccination
325 with (OR 0.881 95% CI: 0.836-0.928] P=0.0001) or without (OR 1.136 95% CI: 0.929 -
326 1.389] P=0.214) influenza infection) was consistently associated with a lower risk of AF
327 compared to patients without influenza infection and without vaccination (OR 1.182, 95% CI:
328 1.014- 1.378] P=0.032).

329 3.6.2. Impact of Pneumococcal and Herpes zoster vaccines

330 Pneumococcal and Herpes zoster vaccine effect on the occurrence of AF wasn't reported in
331 the literature.

332 3.7. Impact of vaccines on the occurrence of Congestive Heart Failure (CHF)

333 3.7.1. Impact of influenza vaccine

334 Influenza vaccine effect on the occurrence of hospitalisations for CHF was evaluated in ten
335 studies.

336 First, Christiansen *et al.* didn't reveal that the risk of CHF was reduced by prior influenza
337 vaccination for people over 65 years old [48]. Seo *et al.* [53] estimated the effectiveness of
338 influenza vaccination on preventing hospitalisations in persons with cardiopulmonary disease
339 and established an evidence basis for recommendations on influenza vaccination in this
340 population. The vaccine effectiveness among patients on hospital presentations or IHD and
341 CHF was 56.0% in patients aged \geq 65 y (95% CI 32.1–71.4%, P < 0.001). In 1994, Nichol *et*
342 *al.* [54] have already wondered about the efficacy and cost effectiveness of influenza vaccine
343 administered to older persons living in the community. During the influenza season,
344 vaccination against influenza was associated with significantly fewer hospitalisations for
345 congestive heart failure (CHF) during the epidemic 1991-1992 season (a 37% reduction;

346 P=0.04). For the epidemic 1990-1991 and 1992-1993 season, odds ratios for CHF
347 hospitalisations were 0.73 and 1.05, not statistically significant. Besides, in 2019, Wu *et al.*
348 [55] assessed the association between influenza vaccination and the secondary prevention of
349 CVD among elderly persons. Compared with an unvaccinated cohort, the vaccinated cohort
350 had significantly lower rates of hospitalisations for cardiac failure (HR 0.83, 95% CI 0.74–
351 0.92). Kaplan–Meier curves of cumulative incidence showed that the curves of the two groups
352 separated gradually during the first 3 months of the follow-up period and differed
353 significantly at the end of follow-up. When, Nichol *et al.* [35] analysed the odds of
354 hospitalisations for CHF, the reductions were also significant (OR 0.81, 95% CI: 0.70–0.92).
355 Similar protective results have been reported in elderly patients with chronic kidney disease
356 [56], with reduced kidney function [51] and with chronic obstructive pulmonary disease [57].
357 More specifically, Fang *et al.* found a dose effect [56]. When patients were stratified by the
358 total number of vaccinations, hospitalisation-adjusted HRs were 0.60 (0.47-0.77), 0.30 (0.23-
359 0.41), and 0.10 (0.06-0.16) for patients receiving 1, 2 to 3, and 4 vaccinations during follow-
360 up, respectively (all p-values < 0.001). More for cardiovascular and cerebrovascular
361 diagnoses, Hung *et al.* [47] showed that dual-vaccines (PPV+TIV) resulted in a 19%
362 reduction in heart failure (HR, 0.81; 95% CI, 0.70–0.94; P=0.006), compared to the
363 unvaccinated group. In contrast, the TIV-alone had not significant reduction in heart failure
364 (HR 0.92; 95% CI, 0.73–1.16; P=0.50). Similarly with Chang *et al.* [58] the cumulative effect
365 of pneumococcal and influenza vaccines on the risk of death, hospitalisation, and
366 hospitalisation costs in Taiwanese people aged 75 years and older was also assessed.
367 Regarding the risk of hospitalisations, it was significantly lower (24%) in the group receiving
368 both of vaccines compared to the unvaccinated group. Getting both of vaccines resulted in a
369 significant 29% reduction in CHF risk compared to the flu vaccine alone.

370 3.7.2. Impact of Pneumococcal vaccines

371 The impact of pneumococcal vaccination in preventing from hospitalisation for CHF was
372 evaluated in 3 studies.

373 Chang *et al.* [58] assessed the additive effect of PPV and influenza vaccines on the risk of
374 mortality, hospitalisation, and hospitalisations expenses/costs in the elderly aged 75 years or
375 older in Taiwan. In terms of hospitalization risks for CHF, compared to the unvaccinated
376 group, significant risk reductions (24%) were observed in the group that received both
377 vaccines. However, those who only received the influenza vaccine had no significant risk
378 decrease (RR 1.07; 95% CI, 0.87-1.37) when compared to the unvaccinated group. Receiving

379 both vaccines was associated with a significant reduction of 29% in the risk of hospitalization
380 for CHF when compared to receiving influenza vaccine alone. Hedlund *et al.* [59]
381 investigated prospectively the health effects of a large-scale programme of PPV23 vaccination
382 in individuals aged 65 years and older. The incidence of hospital admissions was not lower in
383 the vaccinated cohort compared to the unvaccinated cohort for cardiac failure (RR = 0.95
384 95% CI: 0.87-1.05). During the time period when influenza virus was circulating in the
385 community, December 1998 through May 1999, the incidence of hospital treatment was lower
386 in the vaccinated as in the unvaccinated cohort for cardiac failure (RR = 0.90 95% CI: 0.80-
387 1.01). Also during the time period without influenza, June through November 1999, the
388 incidence of hospital treatment for cardiac failure was not significantly lower in the
389 vaccinated cohort (1.02 95% CI: 0.93- 1.11)). Futher more, in Hung *et al.* [47], subjects who
390 received PPV alone had no significant heart failure reduction (0.99 95% CI: 0.78-1.27)
391 compared to the unvaccinated group.

392 3.7.3. Impact of Herpes zoster vaccine
393 Zona vaccine effect on the occurrence of CHF wasn't evaluated in the literature.

394 3.8. Impact of vaccines on the occurrence of stroke

395 3.8.1. Impact of influenza vaccine
396 The effect of influenza vaccination on stroke was retrieved in 11 studies.

397 Piñol-Ripoll *et al.* [60] evaluated the importance of acute infections and chronic bronchitis
398 (CB; as a chronic inflammatory state) in several subtypes of ischemic stroke, and investigated
399 whether the influenza vaccination was independently associated with a reduced probability of
400 stroke. Influenza vaccination during the last campaign (OR = 1.02, 95% CI = 0.77–1.36) or
401 during every campaign within the last 5 years was not associated with a lower risk of
402 ischemic stroke in any subgroup of age or subtype of stroke. Additionally, Lavallée *et al.* [43]
403 didn't show that the risk of stroke was reduced by prior influenza vaccination for people over
404 75 years old. Also Chiang *et al.* [39] have determined the protective effect of influenza
405 vaccine against ischemic stroke. When comparing the vaccinated and unvaccinated groups,
406 vaccination had significant protective effects in ischemic stroke subgroups (aOR 0.80, 95%
407 CI 0.77-0.82, P <0.001). When comparing No ILI or vaccination, ILI without vaccination and
408 ILI with vaccination, ILI significantly increased the risks of ischemic stroke (aOR 1.16, 95%
409 CI 1.10-1.22, P < 0.001). Vaccination neutralized the increased risk of ischemic stroke due to
410 ILI (aOR 0.96, 95% CI 0.89-1.05, P = 0.398). After adjustment for the traditional risk factors
411 for stroke and other potential confounding factors, Lavallée *et al.* [61] reported the inverse

412 association between brain infarction and influenza vaccination that was statistically
413 significant during the preceding vaccination campaign (OR 0.45 ; 95% CI, 0.24 to 0.84;
414 P=0.012) and every year in the last 5 years (OR 0.37 ; 95% CI, 0.19 to 0.70; P=0.002) . The
415 strength of the association was similar in men and women. When the analyses were restricted
416 to patients and controls without any cerebrovascular or cardiovascular history, an even
417 stronger negative association between brain infarction and influenza vaccination was
418 observed. Grau *et al.* [62] investigated whether influenza vaccination was associated
419 independently with reduced odds of stroke and whether effects were confined to stroke
420 subgroups and winter seasons and were shared by other vaccinations. Recent influenza
421 vaccination was associated with a reduced risk of stroke and transient ischemic attack (TIA)
422 in older subjects by 36%. Moreover, Siriwardena et al. 2014 [63] investigated whether
423 influenza or pneumococcal vaccination were associated with reduced risk of stroke or
424 transient ischaemic attack (TIA). Influenza vaccination given within the same season (as the
425 index date) was associated with a significant 26% reduction in the risk of stroke for those
426 aged 65 years old and over (adjusted OR 0.74, 95% CI 0.70-0.78) after adjusting for
427 confounding variables. Stroke risk was significantly lower with early influenza vaccination
428 (September to mid-November: 0.73, 95% CI: 0.69 -0.77) but less important with late
429 vaccination (mid-November onwards: 0.89, 95% CI: 0.80- 0.98). Influenza vaccination
430 within-season was not associated with a reduction in the risk of TIA. Lin *et al.* [64]
431 determined whether influenza vaccination was associated with a reduced risk of
432 hospitalization for stroke among the elderly. Already vaccinated individuals in the current
433 vaccination season were associated with a reduced risk of stroke admissions (Primary
434 Intracerebral Hemorrhagic stroke (PIH) + Ischemic Stroke (IS)) OR (OR = 0.80, 95% CI =
435 0.64–0.98). When they analyzed the data separating PIH and IS, a significant inverse
436 association was observed only for IS (OR = 0.76, 95% CI = 0.60– 0.97). When exposure was
437 categorized by cumulative number of influenza vaccinations within the previous 5 years, the
438 adjusted ORs were 0.93 (95% CI = 0.72–1.22) for the group with one or two vaccinations,
439 0.70 (95% CI = 0.53–0.92) for the group with 3 or 4 vaccinations, and 0.59 (95% CI = 0.42–
440 0.83) for the group with five vaccinations compared with never-vaccinated individuals. There
441 was a significant trend of decreasing risk of hospitalization for stroke with increasing number
442 of vaccinations (chi-square for linear trend = 12.61; p for trend < 0.001). The estimated ORs
443 for IS by cumulative number of influenza vaccinations within the previous 5 years, were 0.92
444 (95% CI = 0.68–1.23), 0.73 (95% CI = 0.54–1.00), and 0.56 (95 CI = 0.38–0.83), respectively
445 (chi-square for linear trend = 9.97; p for trend = 0.001). Again, the association for PIH was

446 not significant. Liu *et al.* [65] investigated the association of influenza vaccination with the
447 risk of haemorrhagic stroke to develop an efficient strategy for reducing this risk in patients
448 with AF. The adjusted HRs (aHRs) of haemorrhagic stroke significantly decreased in the
449 vaccinated patients during the noninfluenza season (influenza season aHR = 0.97, 95% CI :
450 0.59-1.60, noninfluenza season 0.51, 95% CI : 0.30-0.87 and all seasons 0.72, 95% CI 0.50-
451 1.03). Furthermore, the stratified analysis revealed that aHRs decreased significantly in the
452 vaccinated patients during the noninfluenza season and all seasons (aHRs = 0.44 and 0.61; P
453 $< .05$ and $< .05$, respectively), particularly in the patients aged ≥ 75 years, irrespective of sex.
454 Frequent vaccination significantly reduced the risk of haemorrhagic stroke. During the
455 noninfluenza season and all seasons, the aHRs indicated that vaccination significantly reduced
456 the risk of haemorrhagic stroke in a dose-dependent way, in patients aged ≥ 75 years old.
457 (noninfluenza season ≥ 4 vaccinations: aHR = 0.29, 95% CI : 0.09-0.99 ; and all seasons aHR
458 = 0.45, 95% CI : 0.22-0.94) and male patients (noninfluenza season ≥ 4 vaccinations: aHR =
459 0.24, 95% CI : 0.07-0.83; and all seasons aHR = 0.24, 95% CI : 0.09-0.62). Christiansen *et*
460 *al.* [48], reported that the 1-year risk of hospitalization for stroke was 2.9% in the vaccinated
461 patients and 3.3% in the unvaccinated patients, with a corresponding adjusted HR of 0.84
462 (95% CI 0.78–0.92). Nichol *et al.* [35] showed that influenza vaccination was associated with
463 reductions in the odds of hospitalization for cerebrovascular diseases (reduction of 16%
464 during the 1998–1999 season and 23% during the 1999–2000 season). Similar protective
465 results have been reported in elderly patients with AF [66], and with elderly women with
466 COPD [67]. Finally by Hung *et al.* [47], dual-vaccines (PPV+TIV) had a 33% reduction in
467 ischemic stroke compared to the unvaccinated group. In contrast, the TIV-alone had no
468 significant reduction in ischemic stroke (HR 0.85; 95% CI: 0.61–1.17; $P=0.31$).

469 3.8.2. Impact of Pneumococcal vaccines

470 According to Marra's meta-analysis, the impact of PPV23 on cerebrovascular disease
471 (stroke/TIA) was evaluated in five studies: four cohort studies and one case control study. A
472 significant reduction in the risk of having cerebrovascular disease following pneumococcal
473 vaccination was not observed (RR: 0.96; 95% CI: 0.83–1.10; $I^2 = 74.3\%$; $P < 0.001$) [38].

474 3.8.3. Impact of herpes zoster vaccines

475 The effect of zona vaccination on stroke was retrieved in 2 studies.

476 Klaric *et al.* [68] investigated the hypothesis of decreased odds of stroke in persons who have
477 received zoster vaccine. They have carried out several types of analyses in which those
478 without zoster vaccination were significantly at higher risk of stroke compared to those

479 receiving zoster vaccination. Adjusted odds ratios (aOR) indicated that people in the 65-69
480 years' age group who were not vaccinated against shingles were 50% more likely to report a
481 stroke than those who were vaccinated (OR = 1.51, 99% CI: 1.21, 1.88). Also, Yang *et al.*
482 [69] examined the effect of Zoster vaccine live on risk of stroke among adults aged 66 years
483 or older who enrolled in the Medicare fee-for-service program during 2008 to 2017 in the
484 United States. Adjusted HRs comparing vaccinated to unvaccinated beneficiaries were 0.84
485 (95% CI; 0.83–0.85), 0.83 (95% CI; 0.82–0.84), and 0.88 (95% CI; 0.85–0.91) for all stroke,
486 AIS, and haemorrhagic stroke, respectively.

487 4. DISCUSSION

488 In this review, we summarized for the first time the impact of vaccines specifically
489 recommended in elderly exposed to cardio-vascular events. Indeed, a growing body literature
490 has looked at the impact of each vaccine separately on these types of non-infectious outcomes
491 in the general population. Clar *et al.* [70], realised a systematic review and a meta-analysis to
492 assess the potential benefits of influenza vaccination for primary and secondary prevention of
493 cardiovascular diseases. Marra *et al.* [38], realized a meta-analysis summarizing available
494 evidence on the impact of PPV23 on cardiovascular diseases, across all ages. More recently,
495 several publications have been issued regarding the cardioprotective impact of vaccinations in
496 the general population [71]–[75]. In this current work, the prevention of cardio-vascular
497 events associated to influenza, pneumococcal and zoster vaccines among elderly was
498 reviewed, as this population is particularly concerned by these vaccine preventable diseases.
499 A search on the impact of Covid19 vaccination on cardiovascular events was also conducted
500 but the studies identified referred to thrombotic events. This allows to have an overview for
501 the healthcare provider that wants to advice elderly patients and inform them about the
502 benefits of vaccines beyond their preventive action against infectious diseases as summarized
503 in Table 7.

504 Influenza and pneumococcal mortality in older adults appears to be well established [35],
505 [37], [76]–[79]. The impact of these vaccinations on specific cardiovascular mortality is also
506 known [40], [80]–[87]. Data about the impact of influenza on cardio-vascular events within
507 the elderly are numerous and are reported since the early 1900s. Moreover, Influenza vaccine
508 was shown to protect against major non-fatal cardiovascular events, with a significantly
509 lower risk of cardiovascular diseases [33], [37], [88], MACE [39], [40], MI [39], [44]–[46],
510 IHD occurrence secondary to COPD [49], ASC [50], [51], AF [52], CHF [35], [51]–[59] and
511 stroke [35], [39], [48], [61], [62], [64]–[67] in older adults. Observational and clinical studies

512 still show discordant results with regards to the protective association with AMI and MI
513 although the association with IHD is more consistent (Table 7). Finally, repeated vaccination
514 shows a consistent, dose-dependent, protective association with CHF [56] and stroke [39],
515 [61], [65], [66]. In fact, in a Danish study among adults with HF, influenza vaccination was
516 associated with a reduced risk of both all-cause and of cardiovascular death. Frequent
517 vaccination and early vaccination in the year were associated with larger reductions in the risk
518 of death compared to intermittent and late vaccination [89]. Although there are still some gray
519 areas, the studies on repeated vaccination fit with the observational studies and emphasize the
520 need for more robust clinical research to investigate the beneficial effects of influenza vaccine
521 in older adults. Accordingly, the seroprotection provided by influenza vaccination enables a
522 secondary immune response that neutralizes the virus, prevents host cell colonization, and
523 results in the elimination of the pathogen [90]. This widely accepted mechanism is
524 underpinned by a large number of epidemiological, clinical and experimental studies. It has
525 been suggested that the reduced short-term risk of cardiovascular events offered by the
526 influenza vaccination is due to a reduction of infection, which can be a trigger in the
527 inflammatory cascade that leads to the progression of atherosclerosis [91]. However, these
528 results do not explain the beneficial effects on the prevention of cardiovascular events
529 observed during generally virus-free periods (*i.e.* the summer months) [37], [39], [40], [92],
530 and the cumulative effect of repeated vaccination [39], [61]. Furthermore, Aidoud *et al.*
531 reported an emerging mechanism independent of influenza infection. (Aidoud *et al.*, 2020).
532 However, few studies of these mechanisms have been performed.

533 Other studies have shown that pneumococcal vaccination (PPV23) protects against
534 major non-fatal cardiovascular events, with a significantly lower risk of cardiovascular
535 diseases [38] and MI [38] in older adults. There is less literature on the effects of this
536 vaccination against cardiovascular events than there is for influenza. In the literature, the
537 effect of pneumococcal vaccination has not been studied on MACE, ACS and AF. It would be
538 interesting to explore these outcomes. No protective effect of this vaccination was shown for
539 CHF and stroke (Table 4). Unlike, the influenza and pneumococcal double vaccination that
540 was shown to protect against MI [47], IHD [47], CHF [47], [58] and stroke [47]. In addition,
541 co-administration was compared to administration of the influenza vaccine alone by Hung *et*
542 *al.* and Chang *et al.* on the occurrence of MI [47], IHD [47], CHF [58] and stroke [47]. The
543 dual-vaccines appears to be more protective than influenza alone. However, the impact of
544 PCV13 on the cardiovascular event was not studied yet as well as the currently recommended

545 vaccine regimen with PCV13 followed by PPV23. The link between cardiovascular events
546 and pneumococcal infections seems to be related to the phosphorylcholine lipid antigens of
547 the *S. pneumoniae* cell wall that induces the production of antibodies that cross-react with
548 oxLDL, a component of atherosclerotic plaques. These antibodies may bind and facilitate the
549 regression of the plaques. In fact, pneumococcal vaccination has been shown to induce anti-
550 oxLDL antibodies [93]. A significant association has also been observed between
551 pneumococcal IgG and anti-oxLDL titers [94]. It is therefore suggested that the PPV, by
552 inducing the production of anti-phosphorylcholine and anti-oxLDL antibodies that block the
553 uptake of LDL by macrophages, may have a protective effect on cardiovascular diseases in
554 humans [74], [93]

555 For shingles vaccination, only the protective effect against stroke has been studied with the
556 live attenuated herpes zoster vaccine (ZVL) but no studies were performed with the
557 recombinant subunit herpes zoster vaccine (RZV). Associations between VZV-induced
558 vasculopathy and stroke events have been reported since the early 1970's ; [95]–[98] clinical
559 associations have been extensively reviewed [20]. Several potential multifactorial physiologic
560 mechanisms have been proposed for this interaction between VZV activation and such
561 vascular events that can lead to stroke. Due to VZV's replication in human cerebral arteries,
562 one hypothesis postulates that shingles virus directly affects blood vessels as it spreads along
563 nerve fibers. [97] A second hypothesis is that higher levels of inflammation in the body
564 during a severe systemic infection leads to endothelial dysfunction resulting in the disruption
565 of atheromatous plaques and hypercoagulability [97], [98]. Results from the present review
566 suggests that vaccination against VZV by reducing zoster protects against these possible
567 disruptive events leading to stroke when administered to elderly adults at specific ages.

568 Despite scientific evidence on the effectiveness, safety and benefits of the vaccines
569 recommended, doubts about vaccine necessity or efficacy and concerns about possible
570 adverse effects have always followed , including in elderly [99], [100] . ‘Vaccine hesitancy’
571 refers to delayed acceptance or refusal of vaccines despite their availability [101]. The reasons
572 for vaccine hesitancy are complex and involve socio-demographic, contextual, physical, and
573 psychosocial factors [99]. This psychosocial factors are amenable to change through
574 intervention [102]. Moreover, vaccination related knowledge and receiving advice or
575 recommendations, by healthcare providers or relatives, as well as participants’ general
576 vaccination attitudes, also appear important [103], [104] but all of these elements are often not
577 considered in the researches investigating older adults’ vaccine hesitancy.

578 Greater awareness and targeted education around disease risk and vaccine benefits
579 may be required to increase vaccine coverage, particularly regarding influenza, pneumococcal
580 and shingles vaccines. Informing elderly patients of the substantial risk of cardiovascular
581 events following an infection and its modification by vaccination may constitute a simple,
582 effective, costless and time-saving method of changing many patients' negative attitudes
583 towards vaccination. We postulate that this may reduce complacency component of vaccine
584 hesitancy. Schattner *et al.* [105] have shown that a short physician-administered verbal
585 instruction on the risk of 'heart-attack and stroke' following influenza, results in the changing
586 of behaviour and an increase in seasonal influenza vaccination in a population of over 65
587 years.

588 This study has a potential limitation, we have not studied the link between
589 cardiovascular events and the COVID-19 vaccine. It has been reported that pre-existing CVD
590 may contribute to adverse early clinical outcomes and that COVID19 infection may have
591 longer terms of implications for overall cardiovascular (CV) health.[106] The American
592 College of Cardiology and the European Society of Cardiology also pointed out that patients
593 with CV risk factors and established CVD represent a vulnerable population when suffering
594 from COVID-19.[107], [108] Recent studies have showed that the risk of in-hospital death
595 among patients with severe COVID-19 was significantly associated with elderly,
596 inflammatory response and CV comorbidities.[109] Tessitore *et al.* [110] found that Patients
597 with a history of CVD, had their COVID-19 Hospitalisation significantly associated to an
598 increased risk of MACE and death. COVID-19-triggered AMI in individuals with high
599 coronary risks may become a public health issue. Interestingly, during Covid19 pandemic,
600 Mahmud et al [111] analysed the benefits of influenza vaccination in preventing AMI and
601 estimated that the effectiveness of flu vaccines in AMI prevention was 29%. The merits of
602 vaccination goes beyond preventing the original viral infection to its possible prevention of
603 cardiovascular complications. We did not include the dTP vaccine in our review, as it is not a
604 vaccine specific to the elderly Also, it is considered as well followed by the older adults.

605 There is growing evidence of a link between influenza, pneumococcal and herpes zoster
606 vaccinations and a reduction in the incidence of cardiovascular events. This is firstly based on
607 prevention of the cardiovascular complications of infections. We also suggest that vaccination
608 has other infection-independent cardioprotective effects. The scientific interest in vaccination
609 and its cardiovascular protection is and will continue to grow. In the literature, the protective
610 effect of the vaccine against influenza, pneumococci and shingles goes beyond cardiovascular

611 events such as dementia, falls, fractures and loss of quality of life. This is why we must look
612 for other protective effects of vaccination and communicate these benefits to the ageing
613 population and health professionals in order to improve the vaccination coverage in this
614 population.

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964

FIGURES



PRISMA 2009 Flow Diagram – Cardio-vascular Event

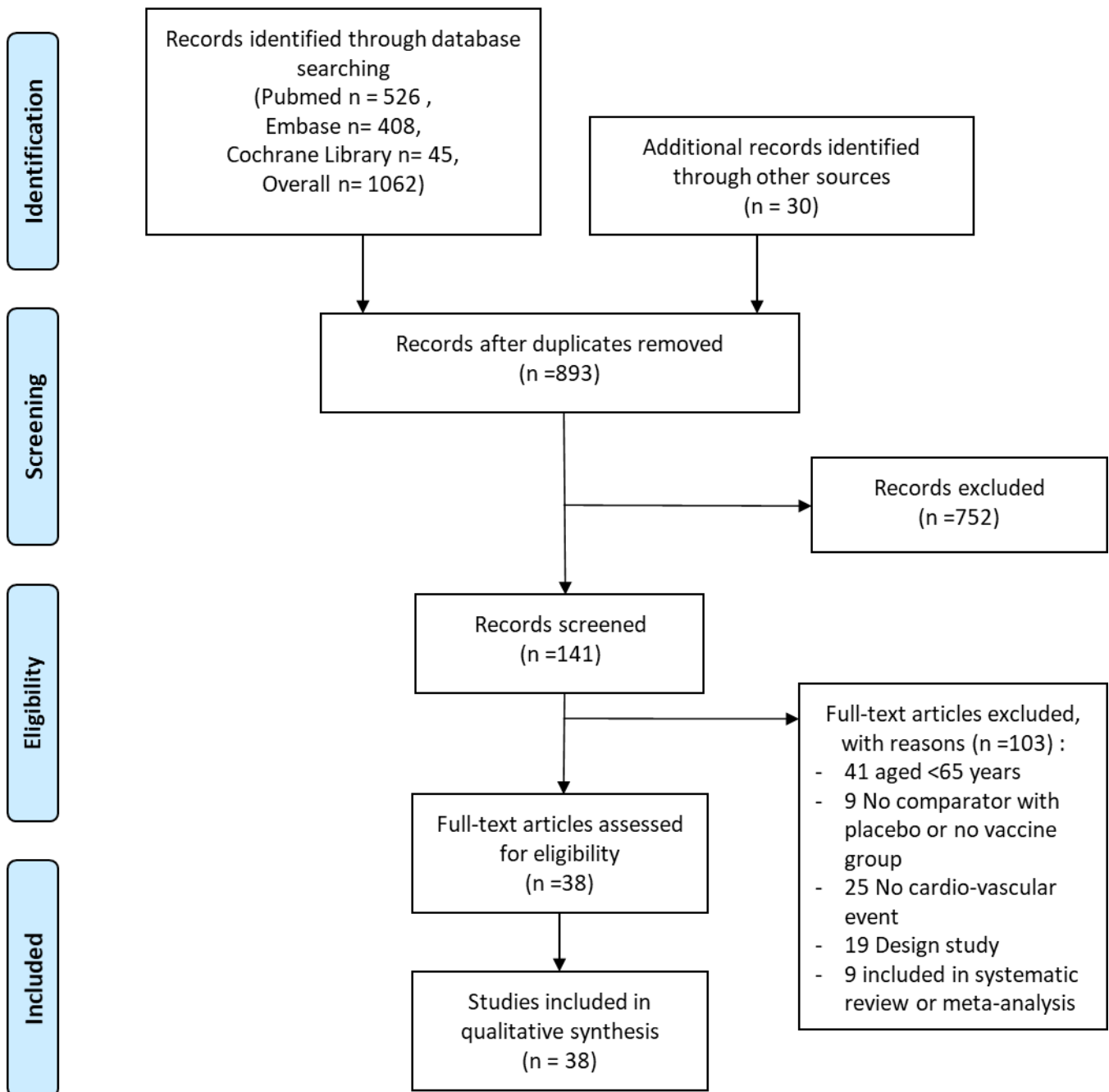


Figure 1 – Flow Diagram – Cardio-Vascular Event

TABLES

	Author	Year of publication	Journal	Study design	Country	Follow-up	Specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)
1	Chang et al.	2012	The Journal of infection	Retrospective cohort study	Taiwan	12 m	/	16284	≥75y	8142	CHF	Y
2	Chang et al. (a)	2016	Heart Rhythm	Case-control study	Taiwan	/	/	56 870	70.9 ± 13.4	11 374	AF	Y
3	Chang et al. (b)	2016	Scientific reports	Retrospective cohort study	Taiwan	1y	Systemic Lupus Erythematosus	10 125	subgroup analysis (≥65y)	1 765	CVD	N
4	Chen et al.	2013	Journal of Experimental and Clinical Medicine	Retrospective cohort study	Taiwan	8y	COPD	25609	subgroup analysis (≥65y)	3345	CHF	Y
5	Chen et al.	2022	Frontiers in Medicine	Retrospective cohort study	Taiwan	/	chronic obstructive pulmonary disease	6681	≥ 65 y	3768	Stroke	Y
6	Chiang et al.	2017	American Heart Journal	Case-control study	Taiwan	13 y	ILI	160 726	≥65y	62 331	MACE, MI, Stoke	Y

	Author	Year of publication	Journal	Study design	Country	Follow-up	Specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)
7	Christiansen et al.	2019	Intensive Care Medicine	Retrospective cohort study	Denmark	1y	/	89 818	≥65y	34 871	MI, Stroke, CHF	Y
8	de Abajo et al.	2022	Heart	Case-control study	Spain	/	/	144 930	subgroup analysis (≥65y)	45 296	MI	Y
9	Fang et al.	2016	Acta Cardiologica Sinica	Retrospective cohort study	Taiwan	12y	Chronic Kidney Disease	4406	≥65y	2254	CHF	Y
10	Grau et al.	2005	Stroke	Case-control study	Germany	18 m	ischemic or hemorrhagic stroke or TIA	740	subgroup analysis (≥65y)	187	Stroke	Y
11	Heffelfinger et al.	2006	Human Vaccines	case-control study	USA	/	/	1 735	≥65y	1 145	MI	N
12	Hsu et al.	2016	Medicine	Retrospective cohort study	Taiwan	1 y	/	202 058	≥65y	93 051	MI	Y
13	Huang et al.	2013	Computer Methods and Programs in Biomedicine	Prospective cohort study	Taiwan	8 y	COPD	29 178	subgroup analysis (≥65y)	6 713	IHD	Y

Author	Year of publication	Journal	Study design	Country	Follow-up	Specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)	
14	Hung et al.	2010	Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America	Prospective cohort study	Hong Kong	64w	/	36 636	≥65y	7292 (19.9%) received both PPV and TIV, 2076 (5.7%) received TIV alone, 1875 (5.1%) received PPV alone, and 25,393 (69.3%) were unvaccinated	Stroke, IHD, MI, CHF	Y
15	Ishigami et al.	2020	American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation	Retrospective cohort study	USA	1y	with and without reduced kidney function	91520	75,5	54856	ACS, CHF	Y
16	Kao et al.	2017	Oncotarget	Retrospective cohort study	Taiwan	8 y	atrial fibrillation	5068	subgroup analysis (≥65y)	2233	Stroke	Y
17	Lavallée et al.	2002	Stroke	Case-control study	France	/	/	270	subgroup analysis (≥75y)	90	Stroke	Y

Author	Year of publication	Journal	Study design	Country	Follow-up	Specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)	
18	Lavallée et al.	2014	Neurology	Prospective cohort study	multinational	/	/	2 497	subgroup analysis (≥75y)	1 217	MI, Stroke	N
19	Lin et al.	2014	International Journal of Environmental Research and Public Health	Case-control study	Taiwan	/	/	3 120	≥65y	2 890	Stroke	Y
20	Liu et al.	2017	International Journal of Cardiology	Case-control study	Taiwan	8y	atrial fibrillation	6 570	73,39	2 547	Stroke	Y
21	Liu et al.	2012	Preventive Medicine	Prospective cohort study	Taiwan	4y	Ischemic Heart Disease	5 048	Non-vaccinated 75,7y Vaccinated 74,8y	2 760	CVD	Y
22	Meyers et al.	2004	Heart drug	Case-control study	USA	/	/	534	subgroup analysis (≥65y)	303	MI	N
23	Nichol et al.	2003	The New England Journal of Medicine	Prospective cohort study	USA	1 y	/	146 328	≥65y	87 357	CVD, IHD, CHF, Stroke	Y
24	Nichol et al.	1994	The New England Journal of Medicine	Retrospective cohort study	USA	/	/	78 527	≥65y	41 418	CHF	Y

Author	Year of publication	Journal	Study design	Country	Follow-up	Specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)	
25	Phrommintikul et al.	2011	European Heart Journal	prospective randomized open with blinded endpoint (PROBE) study	Thailand	360d	ACS	439	66y	221	MACE, ACS, CHF, Stroke	Y
26	Piñol-Ripoll et al.	2008	Cerebrovascular Diseases (Basel, Switzerland)	Case-control study	Spain	/	Chronic Bronchitis and Acute infections	794	cases : 73,5y controls : 73,2	431	Stroke	N
27	Seo et al.	2014	Human Vaccines & Immunotherapeutics	Case-control study	Korean	/	cardiopulmonary disease	602	subgroup analysis (≥65y)	430	IHD, CHF	Y
28	Siriwardena et al.	2010	CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne	Case-control study	England and Wales	/	/	78 706	subgroup analysis (≥65y)	15 575	MI	Y
29	Siriwardena et al.	2014	Vaccine	Case-control study	England and Wales	/	/	94 022	subgroup analysis (≥65y)	7 021	Stroke	Y

Author	Year of publication	Journal	Study design	Country	Follow-up	Specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)
30	Song et al.	PloS One	Prospective cohort study	Korean	1y	cardiopulmonary disease	2 119	76	2119 (vaccinated)/ 817(unvaccinated)	Acute Exacerbation of chronic heart disease	Y
31	Sung et al.	Vaccine	Retrospective cohort study	Taiwan	12y	COPD	7 722	subgroup analysis (≥65y)	3 027	ACS	Y
32	Wang et al.	Vaccine	Prospective cohort study	Taiwan	12m	Peritoneal dialysis patients	2 351	≥65y	1 326	CVD	Y
33	Wu et al.	PloS One	Retrospective cohort study	Taiwan	5y	/	29 066	≥65y	4 554	CHF	Y

Table 1 - Summary of relevant observational studies and clinical trials of the efficacy/effectiveness of influenza vaccination on the prevention of cardiovascular events in older adults

	Author	Year of publication	Journal	Study design	Country	Follow-up	specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)
1	Chang et al.	2012	The Journal of infection	Retrospective cohort study	Taiwan	12 m	/	16284	≥75y	8142	CHF	Y
2	Hedlund et al.	2003	Vaccine	Prospective cohort study	Sweden	1y	/	259 627	≥65y	100 242	CHF, MI	N
3	Hung et al.	2010	Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America	Prospective cohort	Hong Kong	1,2y		36 636		PPV and TIV : 7292 , TIV alone : 2076 , PPV alone : 1875 (5.1%), and unvaccinated 25,393	IHD, CHF	N
4	Marra et al.	2020	International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases	meta-analysis	/	/	/	/	/	/	CVD, Mi, IHD,CHF,Stroke	Y
5	Song et al.	2018	PloS One	Prospective cohort study	Korean	1y	cardiopulmonary disease	2 119	76	2 119	Acute Exacerbation of chronic heart disease	N

Table 2 - Summary of relevant observational studies and clinical trials of the efficacy/effectiveness of pneumococcal vaccination on the prevention of cardiovascular events in older adults

Author	Year of publication	Journal	Study design	Country	Follow-up	specific-disease	N	Age (years)	Vaccination (yes)	Outcomes	Protective effect (Y/N)
Klaric et al.	2019	Military Medicine	Retrospective cohort study	USA	/	/	265 568	subgroup analysis (≥65y)	63 166	Strokes	Y
Yang et al.	2021	Stroke	Prospective cohort study	USA	5.1 y	/	3 206 812	≥65y	1 603 406	Stokes	Y

Table 3 - Summary of relevant observational studies and clinical trials of the efficacy/effectiveness of zona vaccination on the prevention of cardiovascular events in older adults

Vaccine	Study	Year of publication	Selection				Comparability	Exposure			Number of stars
			Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls		Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	
Influenza	Chang et al.	2016	a)*	a)*	b)	a)*	a)*	a)*	a)*	a)*	7
Influenza	Chiang et al.	2017	a)*	a)*	a)*	a)*	a)*	a)*	a)*	c)	7
Influenza	Grau et al.	2005	a)*	a)*	a)*	a)*	a)*	b)*	a)*	c)	7
Influenza	Heffelfinger et al.	2006	a)*	a)*	b)	a)*	a)*	d)	a)*	c)	5
Influenza	Lavallée et al.	2002	a)*	a)*	b)	a)*	a)**	d)	b)	c)	5
Influenza	Liu et al.	2017	a)*	a)*	a)*	a)*	**	a)*	a)*	a)*	9
Influenza	Lin et al.	2014	a)*	a)*	b)	a)*	**	a)*	a)*	a)*	8
Influenza	Seo et al.	2014	c)	a)*	b)	b)	**	d)	b)	c)	3
Influenza	Siriwardena et al.	2010	a)*	a)*	b)	b)	*	a)*	a)*	a)*	6
Influenza	Piñol-Ripoll et al.	2008	b)	a)*	b)	a)*	**	a)*	a)*	a)*	7
Influenza	Meyers et al.	2004	a)*	a)*	b)	a)*	**	d)	a)*	c)	6
Influenza	Abajo et al.	2021	a)*	a)*	b)	a)*	**	a)*	a)*	a)*	8

Table 4 - Quality assessment for case-control studies

			Selection				Comparability	Outcome			Number of star
Vaccine	Study	Year of publication	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Same method of ascertainment for cases and controls Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Influenza	Christiansen et al.	2019	a)*	a)*	a)*	a)*	**	a)*	a)*	d) pas de déclaration	8
Influenza	Hsu et al.	2016	a)*	a)*	a)*	b	*	d)	a)*	d) pas de déclaration	5
Influenza	Huang et al.	2013	a)*	a)*	a)*	a)*	0	d)	a)*	d) pas de déclaration	5
Influenza	Hung et al.	2010	b)*	a)*	a)*	b)	*	a)*	a)*	d) pas de déclaration	6
Influenza	Lavallée et al.	2014	b)*	a)*	a)*	a)*	**	d)	a)*	d) pas de déclaration	7
Influenza	Liu et al.	2012	a)*	a)*	a)*	a)*	**	d)	a)*	a)*	7
Influenza	Nichol et al.	1994	a)*	a)*	a)*	a)*	0	d)	a)*	a)*	6
Influenza	Nichol et al.	2003	a)*	a)*	a)*	a)*	**	d)	a)*	a)*	8
Influenza	Song et al.	2018	a)*	a)*	a)*	a)*	**	a)*	a)*	a)*	9
Influenza	Sung et al.	2014	a)*	a)*	a)*	a)*	**	d)	a)*	a)*	8
Influenza	Wang et al .	2002	b)*	a)*	b)*	b)	0	d)	a)*	d) pas de déclaration	4
Influenza	Wu et al.	2019	a)*	a)*	a)*	a)*	0	d)	a)*	d) pas de déclaration	5
Influenza	Chen et al.	2013	a)*	a)*	a)*	a)*	*	d)	a)*	d) pas de déclaration	6
Influenza	Fang et al.	2016	a)*	a)*	a)*	a)*	*	d)	a)*	d) pas de déclaration	6
Influenza	Kao et al.	2017	a)*	a)*	a)*	a)*	*	d)	a)*	d) pas de déclaration	6
Influenza	Chang et al.	2016	a)*	a)*	a)*	a)*	*	d)	a)*	d) pas de déclaration	6

Influenza	Chen et al.	2022	a)*	a)*	a)*	a)*	**	d)	a)*	d) pas de déclaration	7
Influenza	Ishigami et al.	2020	a)*	a)*	a)*	a)*	**	d)	a)*	d) pas de déclaration	7
Pneumococcal	Chang et al.	2012	a)*	a)*	a)*	a)*	**	d)	a)*	a)*	8
Pneumococcal	Hedlund et al.	2003	b)*	a)*	a)*	b)	0	d)	a)*	a)*	5
Pneumococcal	Song et al.	2018	a)*	a)*	a)*	b)	*	d)	a)*	a)*	6
Pneumococcal	Hung et al.	2010	a)*	a)*	a)*	a)*	*	d)	a)*		6
Herpes zoster	Klaric et al.	2019	c)	a)*	c)	b)	0	c)	a)*	a)*	3
Herpes zoster	Yang et la.	2021	b)*	a)*	a)*	a)*	**	a)*	a)*	a)*	10

Table 5 - Quality assessment for cohort studies

Vaccine	Autor	Years of Publication	Random sequence generation	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	Losses to follow-up/non-completers	intention to treat analyses	selective reporting	similarity at baseline	other bias
Influenza	Phrommintikul et al.	2011	+	?	-	+	+	+	+	+	?	+

Table 6 - Quality assessment for RCT

Influenza vaccine				
	Protective effect		No evidence of protective effect	
Outcome	Study	Magnitudes of facts % [CI95%]	Study	Magnitudes of facts % [CI95%]
CVD	Liu et al. 2012 (with IHD)	-16% [-24%; -7%]	C-C Chang et al. 2016 (b) (Systemic Lupus Erythematosus)	-24% [-50% ; +13%]
	Song et al. 2018 (a) (exacerbation CVD)	-51% [-73%; -9%]		
	Wang et al. 2002 (hospitalisation)	-50% [-73%; -9%]		
	Nichol et al. 2003 (hospitalisation)	-19% [-23%; -11%]		
MACE	Chiang et al. 2017 (ILI)	-20% [-22%; -18%]		
	Phrommintikul et al. 2011 (with ACS)	-31% [-46%; -10%]		
MI	Abajo et al. 2021	-16% [-19%; -12%]	Christiansen et al. 2019 (hospitalisation)	-7% [-17%; +19%]
	Chiang et al. 2017 (ILI)	-20% [-24%; -16%]	Heffelfinger et al. 2006	-3% [-25%; +27%]
	Hsu et al. 2016	-32% [-50%; -9%] (men)	Hung et al. 2010 (TIV alone)	-13% [-41%; +33%]
	Hung et al. 2010 (double vaccination)	-48% [-29% ; -62%]	Lavallée et al. 2014	-50% [-78%; +22%]
	Siriwardena et al. 2010	-21% [-17% ; -25%]	Meyers et al. 2004	-44% [-75%; +27%]
IHD	Huang et al. 2013 (with COPD)	-26% [-7% ; -41%] (71-80 years old)	Hung et al. 2010 (TIV alone)	-13% [-34%; +13%]
	Hung et al. 2010 (double vaccination)	-35% [-22% ; -46%]		
	Nichol 2003	-20% [-9% ; -30%]		
ACS	Ishigami et al. 2020 (reduced kidney function)	-7% [-3% ; -12%]		
	Sung et al. 2014 (hospitalisation)	-52% [-39%; -63%] (65-74 years old) ; -59% [-43% ; -71%] (75 years and older)		
AF	Chang et al. 2016 (a)	-12% [-8% ; -17%]		
CHF	Chang et al. 2012 (TIV alone+ double vaccination)	-24% [-1% ; -42%] / -29% [-8% ; -46%]	Hung et al. 2010 (TIV alone)	-8% [-27%; +16%]
	Chen et al. 2013 (COPD)	-63% [-48%; -74%] (65-74y) ; -64% [-48%; -75%] (75 years and older)	Christiansen et al. 2019	-2% [-14%; +12%]
	Fang et al. 2016 (CKD)	-69% [-61% ; -74%]		
	Hung et al. 2010 (double vaccination)	-19% [-6% ; -30%]		
	Ishigami et al. 2020 (reduced kidney function)	-8% ; [-1% ; -14%]		
	Nichol et al. 1994	37% [NA]		
	Nichol et al. 2003 (Hospitalisation)	-19% [-8% ; -30%]		

	Seo et al. 2014 (AF+CHF)	-56% [-32% ; -71%]		
	Wu et al. 2019 (CVD)	-17% [-8% ; -26%]		
Stroke	Chen et al. 2022 (women COPD)	-40% [-33%;-46%]	Hung et al. 2010 (TIV alone)	-15%[-39%;+17%]
	Chiang et al.	-20% [-18% ; -23%]	Lavallée et al. 2014	-8%[-38%;+37]
	Christiansen et al. 2019 (hospitalisation)	-16% [-8% ; -22%]	Piñol-Ripoll et al. 2008	+2%[-23%;36%]
	Grau et al. 2005	-64% [-37% ; -80%]		
	Hung et al. 2010 (double vaccination)	-33% [-17%;-46%]		
	Kao et al. 2017 (AF) (65-74y) ; -55% [-47% ; -60%](75 years and older)	-52% [-39%;-61%] (65-74y) ; -55% [-47% ; -60%](75 years and older)		
	Lavallée et al. 2002	-55% [-16% ; -76%]		
	Lin et al. 2014 (hospitalisation)	-20% [-2% ; -36%]		
	Liu et al. 2017 (hemoragic) (75 years and older)	-39% [-1% ; -62%]		
	Nichol et al. 2003 (hospitalisation)	-16% [-3% ; -28%]		
	Siriwardena et al. 2014	-26% [-22% ; -30%]		
Pneumococcal vaccines				
	Protective effect		No evidence of protective effect	
Outcome	Study	Magnitudes of facts % [CI95%]	Study	Magnitudes of facts % [CI95%]
Cardio-vascular Disease	Marra et al. 2020	-6% [-1% ; -11%]	Song et al. 2018 (a)	-6%[-98%;+44%]
MI	Marra et al. 2020	-7% [-1% ; -12%]		
IHD	Hung et al. 2010 (double vaccination)	-35% [-22% ; -46%]	Hung et al 2010 (PPV alone)	-8%[-31%;+22%]
CHF	Chang et al. 2012 (double vaccination)	-29% [-8% ; -46%]	Chang et al. 2012(PPV alone)	+7%[-16%,+37%]
			Hung et al. 2010 (PPV alone)	-1%[-22%;27%]
			Hedlund et al. 2003 (double vaccination)	-5%[-13%;+5%]
Stroke			Marra et al. 2020	-8%[-19%;+4%]
Herpes zoster vaccine				
	Protective effect		No evidence of protective effect	
Outcome	Study	Magnitudes of facts	Study	Magnitudes of facts
Stroke	Klaric et al. 2019	-49% [-12% ; -79%]		
	Yang et al. 2021	-16%[-17% ; -15%]		

Table 7 – Summary of the effects of influenza, pneumococcal and herpes zoster vaccinations on cardio-vascular events in the literature