Vaccine 36 (2018) 5556–5564

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Impact of repeated influenza vaccinations in persons over 65 years of age: A large population-based cohort study of severe influenza over six consecutive seasons, 2011/12–2016/17

Åke Örtqvist [a,*], Mia Brytting [b], Amy Leval [c,d,e], Maria-Pia Hergens [a,*]

[a] Department of Communicable Disease Control and Prevention, Stockholm County Council, and Karolinska Institutet, Department of Medicine Karolinska Solna, Unit of Infectious Diseases, Stockholm, Sweden
[b] Unit for Laboratory Surveillance of Viral Pathogens and Vaccine Preventable Diseases, Department of Microbiology, The Public Health Agency of Sweden, Solna, Sweden
[c] Janssen-Cilag AB, Solna, Sweden[1]
[d] Department of Communicable Disease Control and Prevention, Stockholm County Council, Sweden[2]
[e] Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 18 April 2018
Received in revised form 14 July 2018
Accepted 22 July 2018
Available online 31 July 2018

Keywords:
Seasonal influenza
Repeated vaccinations
Vaccine effectiveness
Older persons

ABSTRACT

Background: A forty-year debate on the potential negative effects of repeated seasonal influenza vaccination has been inconclusive, with multiple observational studies of various design providing heterogeneous results too inadequate to inform vaccination policy.
Methods: A large population-based cohort study including over one-million observations in individuals over age 65 from six consecutive seasons (2011/12 –2016/17) in Stockholm County, Sweden. Current season vaccine effectiveness (VE) against severe, mostly hospital-attended, influenza was assessed using Cox multivariate regression analyses adjusting for demographic variables, comorbidities and previous seasonal influenza vaccination status.
Results: In none of the six seasons was VE significantly different in persons vaccinated in the current season only, compared to those who had been vaccinated in both the current and the previous season. Neither were there any differences in VE during the seasons 2014/15–2016/17 when comparing persons vaccinated during the current season only vs. those vaccinated during one-three or four-five previous influenza seasons. In contrast, persons only vaccinated during one or more previous years had no protection during the current season.
Conclusions: Persons above 65 years are the largest group at risk for severe or complicated influenza and policy should support their yearly seasonal influenza vaccination, which is to-date the best preventive measure available for all risk groups. No negative effects of repeated seasonal vaccination were seen in this large population-based cohort of older persons with severe influenza, which strengthens the recommendation that persons belonging to this age group should be vaccinated yearly.

1. Introduction

During the last forty years, there has been a debate whether protection from seasonal influenza vaccine may be attenuated by vaccination in prior seasons [1–14]. The major concern has been that prior vaccination or vaccinations may attenuate the effectiveness of the influenza vaccine during the current seasons, particularly for Influenza A(H3N2) and B strains [4,5,9,10], but also for influenza A(H1N1)pdm09 [4,13]. An often-used model for explaining the possible mechanism for such interaction is the antigen distant hypothesis (ADH), described by Smith et al in the late 1990s [15]. The ADH predicts that there may be negative interference from a prior season's vaccine on the current season's vaccine effectiveness, when the antigenic distance is small between the two vaccines but large between the prior vaccine and the current season's epidemic strain [15]. However, most recent studies indicating a negative interference of prior vaccinations have mainly included children, adolescents and non-elderly adults seeking outpatient care, and there is a lack of data on the possible impact in older persons with severe influenza.

* Corresponding authors.
E-mail addresses: ake.ortqvist@sll.se (Å. Örtqvist), maria-pia.hergens@sll.se (M.-P. Hergens).
[1] Present address.
[2] Former address.

https://doi.org/10.1016/j.vaccine.2018.07.052
0264-410X/

In Stockholm County, a catchment area that encompasses 2.3 million individuals, seasonal influenza vaccination has been offered free-of-charge to persons 65 years and older since 2001, and data on all vaccine exposures for this age group have been recorded in a web-based vaccination register since 2009. We have previously shown that vaccine effectiveness (VE) is possible to estimate using population-based registers [16,17]. The aim of this study was to use this method to investigate the impact of prior vaccinations on the VE of seasonal influenza vaccine during six seasons, 2011/2012 to 2016/2017, in older persons (>65 years). In this age group the risk for severe influenza is substantial and, in Stockholm County, a majority of older persons with laboratory-confirmed influenza will be hospitalized.

2. Methods

2.1. Study population

Six annual closed cohorts each comprising all individuals ≥66 years of age (n ~ 300.000 persons yearly), registered in Stockholm at the start of each season, 2011/12–2016/17. In Stockholm County influenza vaccination is offered free-of-charge and entered in the vaccine register from 65 years, irrespective of whether the vaccination is performed by the county's primary health care, outpatient care, or in private vaccination clinics.

The present study included persons from 66 years of age, so that all those included could have received an influenza vaccination free-of-charge in at least one prior season. The influenza season was defined as starting on October 1 and ending on May 31 the following year.

2.2. Data sources

As has been described earlier [17], age, sex, diagnoses of influenza and comorbidities were collected using Stockholm County's central database (VAL) and the Stockholm Mosaic system [18] was used as a proxy for living conditions and socioeconomic status. Immigration and death dates were not available in VAL, necessitating the design of a closed cohort for each season.

VAL has over 99% coverage for inpatient care [19] and the validity of the diagnostic coding has been estimated to 85–95%, depending on the diagnosis [20]. The validity of VAL was confirmed for influenza by the present study, since 95% of inpatients discharged with an influenza diagnosis (International Classification of Diseases, 10th revision (ICD-10) J09-J11) had a laboratory-confirmed influenza (LCI) during the two seasons (2015/16 and 2016/17) when such data were available.

Comorbidities were extracted from VAL using ICD-10 codes for tumours (C00-D48), diabetes (E10–14), circulatory (I00-I99) and non-acute respiratory illness (J40-J99) registered for a period of up to three years before the start of the respective season.

Vaccinera, the County's vaccination register, contains all data on seasonal and pandemic influenza vaccination of persons ≥65 years of age, since the influenza pandemic in 2009 [21]. The regional coverage of the Vaccinera database can be assumed to be 100% as vaccination is free-of-charge for the patient, and registration is mandatory and required for reimbursements to the healthcare provider.

SmiNet is the national electronic surveillance system for the reporting of communicable diseases [22]. Since December 1, 2015, it is mandatory for all Swedish laboratories to report findings of influenza (reported as influenza A or B) to SmiNet.

Data from VAL, Vaccinera and SmiNet were linked using the same personal identification numbers (PIN).

2.3. Case definition

During 2011/12 to 2014/15 seasons, a case was defined as being treated in hospital with a clinical diagnosis of influenza (ICD-10 codes J09 - J11). These cases were obtained from VAL (see above).

During the 2015/16 and 2016/17 seasons, when it was possible to link to SmiNet, a case was defined as having been diagnosed with LCI by polymerase chain reaction (PCR). PCR is the only method used for influenza diagnoses in Sweden since 2009.

2.4. Vaccination status

Vaccination dates and vaccine types were derived from Vaccinera. Two tri-valent inactivated split-virus vaccines, Vaxigrip® (Sanofi Pasteur MSD) and Fluarix® (GSK) accounted for more than 99% of the vaccinations performed. No high-dose, adjuvanted, or quadrivalent vaccines were used.

During each "current" season, 2011/12–2016/17, individuals with influenza infection before vaccination, or up to 13 days post-vaccination, were considered to be unvaccinated, as were those who did not receive the seasonal vaccine. Those with influenza infection ≥14 days post vaccination were considered to be vaccinated.

During each "previous" season, 2010/11 to 2015/16, a person was defined as vaccinated (exposed) if at least one influenza vaccination was noted in the vaccine register during that previous season. We did not include the 2009/2010 seasonal vaccine in the analysis because about 60% of persons ≥65 years received the pandemic AS04-adjuvanted monovalent influenza A(H1N1)pdm09 (Pandemrix®,GSK) vaccine during October – December 2009 [21], with much fewer later vaccinated with the 2009/10 seasonal vaccine. However, vaccination with Pandemrix® 2009–2010 was included as a covariate in the statistical analysis because this adjuvanted vaccine induced a better protection, and at least in children also a protection of longer duration, than ordinary seasonal vaccine [21,23].

2.5. Influenza epidemiology

The dominating circulating seasonal influenza strains and levels of influenza activity in Sweden during the six seasons are shown in Table 1. Mismatch between the vaccine strain and the dominating strain or strains was seen in 2011/12 (A(H3N2)), 2012/13 (B), 2014/15 (A(H3N2) and B), 2015/16 (B), and 2016/17 (A(H3N2)). During 2016/17, mutations in the egg-adapted vaccine for A (H3N2) as well as in the circulating 3C.2a1 and 3C.2a subclades resulted in mismatch [16,24–26].

2.6. Statistical analyses

Vaccine effectiveness (VE) was assessed using Cox regression analyses. Hazard rate ratios (HRR) were calculated comparing the hazard rates of influenza cases among vaccinated and unvaccinated individuals. VE was calculated as (1 – adjusted HRR) × 100 % and reported with 95% confidence intervals (CI). Vaccination status during the study season was modelled as a time-varying exposure, so individuals could contribute to both vaccinated and unvaccinated risk-time.

Two models were used [5]. In model 1, VE for each season was estimated for all combinations of vaccine exposure in the current and previous season: 1. Not vaccinated in either season (reference group), 2. vaccinated in the current season only, 3. vaccinated in the previous season only, and 4. vaccinated in both seasons.

In model 2, VE was estimated for the seasons 2014/15, 2015/16 and 2016/17 for all combinations of seasonal influenza vaccine exposure in the current season and 4-year (season 2014/15) or

Table 1
Influenza epidemiology in Sweden 2011/12 to 2016/17. National data, based on annual influenza reports from the Public Health Agency of Sweden, except for weeks of peak influenza activity and starting weeks for the vaccination campaigns which are regional for Stockholm County.

	Total No. of laboratory confirmed influenza (LCI) (all age groups), in Sweden	Incidence / 100000 of LCI in persons ≥65 years, in Sweden	Dominating influenza strain/s, in Sweden	Percentage of laboratory findings, in Sweden	Week/s of peak activity in Stockholm County	Start of vaccination campaign (week) in Stockholm County	Vaccine strain/s*, in Sweden	Influenza strain - vaccine match, in Sweden
2011/12	4840	130	A(H3N2)	94	9	41	A/Perth/16/2009	Poor
2012/13	8197	138	A(H3N2)	35	6–7	43	A/Victoria/361/2011*	Poor
			A(H1N1) pdm09	30	5–7		A/California/7/2009	Good
			B Yamagata	33	8		B/Wisconsin/1/2010 (Y)*	Poor
2013/14	2585	36	A(H3N2)	24	6	42	A/Texas/50/2012*	Poor
			A(H1N1) pdm09	67	6–8		A/California/7/2009	Good
2014/15	10 389	285	A(H3N2)	58	6–8	43	A/Texas/50/2012	Poor
			B Yamagata	35	12–14		B/Massachusetts/2/2012 (Y)*	Poor
2015/16	9150	127	A(H1N1) pdm09	63	4–5	44	A/California/7/2009	Good
2016/17	13 069	412	A(H3N2)	94	51–1	45	A/Hong Kong/4801/2014*	Poor

* Change of vaccine strain from previous season marked with an asterix.

5-year (2015/16 and 2016/17 seasons) vaccination history. This model included only persons ≥70 years, since individuals in the cohort had to have been at least 65 and living in Stockholm County to be offered vaccination free-of-charge during at least four previous seasons. Infrequent and frequent vaccinees were defined as persons who had been vaccinated 1–3 and 4–5 times, respectively, during the past 4–5 seasons. Non-vaccinees were defined as not vaccinated in any of the preceding years. Model 2 included 6 categories of exposure: 1. No current-season vaccination and non-vaccinee (reference group), 2. current-season vaccination and non-vaccinee, 3. no current-season vaccination and infrequent vaccinee, 4. current-season vaccination and infrequent vaccinee, 5. no current-season vaccination and frequent vaccinee, and 6. current-season vaccination and frequent vaccinee.

In the final analyses adjustments were made for age, sex, socioeconomic status, co-morbidity, and Pandemrix® vaccination.

2.7. Ethical consideration

The analysis is part of an ongoing evaluation of vaccine programmes required by the Department of Communicable Disease Control and Prevention, Stockholm County Council, Sweden, and falls outside the mandate for the Regional Ethics committee. PINs were anonymised in the linking of Vaccinera to VAL and SmiNet, and no individual identification was retained.

3. Results

The population ≥66 years of age increased during the study period from 291 358 to 336 111 persons per season (Table 2A and B). Demographic data, vaccination coverage, and exposure to previous pandemic vaccination for the vaccinated and unvaccinated populations are shown in Tables 2A-C. Persons vaccinated during a current season and who had no prior vaccination were more often males, and when compared to frequent- or infrequent vaccinees in Model 2 they were also younger and healthier (Table 3A and B).

Depending on season, 69–83% of persons vaccinated in the current season had also been vaccinated during the previous season, compared to 11–22% among those who were unvaccinated during the current season (Table 4A). Among those vaccinated during the 2015/16 and 2016/17 seasons, nearly two-thirds were frequent and one-third infrequent vaccinees, while 5% had no previous vaccination registered during the 5-year period (Table 4B).

In total, 3623 persons ≥66 years were diagnosed with influenza; 1539 had a hospital discharge ICD-10 code of J09-J11 during 2011/12–2014/15 seasons and 2084 had LCI during the 2015/16–2016/17 seasons (Fig. 1A, Fig. 1B). The highest number of cases was seen in the influenza A(H3N2) dominated seasons, 2014/15 and 2016/17. A large majority of all LCI cases were hospitalized, 88% in 2015/16 and 86% in 2016/17. Of those, 41% received the ICD-10 code J09-J11 upon discharge, while the remaining 59% had different discharge diagnoses, most commonly J15.9 Unspecified bacterial pneumonia, J18.9 Pneumonia, unspecified organism, or J44.1 Chronic obstructive pulmonary disease with acute exacerbation. Conversely, 95% of all hospitalized persons discharged with ICD-10 codes J09-J11 in 2015/16 and 2016/17 had a LCI.

3.1. Repeated vaccinations and influenza VE

The estimated VEs for of the six seasons included in Model 1 are presented in (Fig. 1A, B). The overall VE was low to non-existent during influenza A(H3N2) seasons, 8% (95% CI −21–31) in 2011/12, 20% (95% CI 9–30) in 2014/15, and 24% (95% CI 15–31) in 2016/17, but it was of the same magnitude in persons vaccinated in the current season only, as in those who had received both the current and the previous year's vaccines.

During influenza A(H1N1)pdm09 seasons, VE was moderately high, 52% (95% CI 27–68) in 2013/14 and 54% (95% CI 40–65) in 2015/16, and with no significant difference between those vaccinated in the current seasons only, compared to those also vaccinated the year before.

During the 2012/13 season, when influenza A(H1N1)pdm09, A (H3N2) and B co-circulated, the overall VE was 56% (95% CI 40–68), 41% (95% CI, 4–64) in those vaccinated only in the current and 63% (95% CI, 46–74) in those vaccinated in both seasons.

There was no significant protection among persons vaccinated only during the previous season. Although the confidence intervals were wide in most seasons, the point estimates of VE in this group were always lower than those vaccinated in the current season, irrespective of the prior vaccination status of the latter.

In Model 2, significant VE's were observed for persons vaccinated during each of the three "current" seasons and who were infrequent or frequent vaccinees, 28% (95% CI, 12–42) and 29%

Table 2A and B
Demographic data for the populations included in the Model 1 analyses; sex, age-groups, socio-economic status, and co-morbidity, and exposure to previous pandemic vaccination, for the vaccinated and unvaccinated populations of persons 66 years of age, or above, living in Stockholm County, Sweden, during the 2011/12 to 2013/14 season (2A) and 2014/15 to 2016/17 seasons (2B).

A. Seasons 2011/12, 2012/13, 2013/14

Characteristic	Influenza season 2011/12			Influenza season 2012/13			Influenza season 2013/14		
	Total n	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)
Cohort total (66+)	291 358	167 677 (58%)	123 681 (42%)	301 404	155 209 (52%)	146 195 (48%)	311 735	163 405 (52%)	148 330 (48%)
Sex									
Male	126 444	72 432 (57%)	54 012 (43%)	131 721	67 483 (51%)	64 238 (49%)	137 168	71 103 (52%)	66 065 (48%)
Female	164 914	95 245 (58%)	69 669 (42%)	169 683	87 726 (52%)	81 957 (48%)	174 567	92 302 (53%)	82 265 (47%)
Age group in years									
66–70	101 293	50 059 (49%)	51 234 (51%)	107 378	46 385 (43%)	60 993 (57%)	111 283	48 215 (43%)	63 068 (57%)
71–80	113 651	70 279 (62%)	43 372 (38%)	117 705	65 880 (56%)	51 825 (44%)	123 902	70 834 (57%)	53 068 (43%)
≥ 81	76 414	47 339 (62%)	29 075 (38%)	76 321	42 944 (56%)	33 377 (44%)	76 550	44 356 (58%)	32 194 (42%)
Mosaic income/education categories									
Highest	124 971	75 910 (61%)	49 061 (39%)	130 726	71 482 (55%)	59 244 (45%)	135 902	75 543 (56%)	60 359 (44%)
Middle	52 872	30 219 (57%)	22 653 (43%)	54 590	27 725 (51%)	26 865 (49%)	55 896	29 394 (53%)	26 502 (47%)
Lowest	111 351	60 568 (54%)	50 783 (46%)	115 076	55 634 (48%)	59 442 (52%)	118 452	57 900 (49%)	60 552 (51%)
Missing	2 164	980 (45%)	1 184 (55%)	1 012	368 (36%)	644 (64%)	1 485	568 (38%)	917 (62%)
Comorbidity									
Yes	206 164	126 098 (61%)	80 066 (39%)	215 971	118 893 (55%)	97 078 (45%)	225 583	126 231 (56%)	99 352 (44%)
No	85 194	41 579 (49%)	43 615 (51%)	85 433	36 316 (43%)	49 117 (57%)	86 152	37 174 (43%)	48 978 (57%)
Pandemrix in 2009/2010									
Yes	162 460	124 168 (76%)	38 292 (24%)	166 997	116 345 (70%)	50 652 (30%)	171 597	120 887 (70%)	50 710 (30%)
No	128 898	43 509 (34%)	85 389 (66%)	134 407	38 864 (29%)	95 543 (71%)	140 138	42 518 (30%)	97 620 (70%)

B. Seasons 2014/15, 2015/16, 2016/17

Characteristic	Influenza season 2014/15			Influenza season 2015/16			Influenza season 2016/17		
	Total n	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)
Cohort total (66+)	321 408	165 789 (52%)	155 619 (48%)	329 384	174 409 (53%)	154 975 (47%)	336 111	155 882 (46%)	180 229 (54%)
Sex									
Male	142 111	72 590 (51%)	69 521 (49%)	146 203	76 440 (52%)	69 763 (48%)	149 829	68 681 (46%)	81 148 (54%)
Female	179 297	93 199 (52%)	86 098 (48%)	183 181	97 969 (53%)	85 212 (47%)	186 282	87 201 (47%)	99 081 (53%)
Age group in years									
66–70	112 484	47 134 (42%)	65 350 (58%)	110 918	46 737 (42%)	64 181 (58%)	108 095	39 758 (37%)	68 337 (63%)
71–80	132 350	73 979 (56%)	58 371 (44%)	141 968	81 484 (57%)	60 484 (43%)	151 207	75 911 (50%)	75 296 (50%)
≥ 81	76 574	44 676 (58%)	31 898 (42%)	76 498	46 188 (60%)	30 310 (40%)	76 809	40 213 (52%)	36 596 (48%)
Mosaic income/education categories									
Highest	140 381	77 000 (55%)	63 381 (45%)	144 571	81 747 (57%)	62 824 (43%)	148 461	73 800 (50%)	74 661 (50%)
Middle	57 274	29 736 (52%)	27 538 (48%)	58 535	31 113 (53%)	27 422 (47%)	59 948	27 614 (46%)	32 334 (54%)
Lowest	121 714	58 136 (48%)	63 578 (52%)	124 263	60 628 (49%)	63 635 (51%)	126 787	54 232 (43%)	72 555 (57%)
Missing	2 039	917 (45%)	1122 (55%)	2 015	921 (46%)	1 094 (54%)	915	236 (26%)	679 (74%)
Comorbidity									
Yes	227 626	125 821 (55%)	101 805 (45%)	244 097	137 830 (56%)	106 267 (44%)	237 995	117 845 (50%)	120 150 (50%)
No	93 782	39 968 (43%)	53 814 (57%)	85 287	36 579 (43%)	48 708 (57%)	98 116	38 037 (39%)	60 079 (61%)
Pandemrix in 2009/2010									
Yes	175 443	120 098 (68%)	55 345 (32%)	178 509	125 850 (71%)	52 659 (29%)	181 028	111 791 (62%)	69 237 (38%)
No	145 965	45 691 (31%)	100 274 (69%)	150 875	48 559 (32%)	102 316 (68%)	155 083	44 091 (28%)	110 992 (72%)

(95% CI, 12–43) in 2014/15, 60% (95% CI, 35–76) and 62% (95% CI, 42–75) in 2015/16, and 17% (95% CI, 1–31) and 23% (95% CI, 10–34) in 2017/18 (Fig. 2). In contrast, persons vaccinated only during these "current" seasons, but in none of the previous seasons, had non-significant VE's and lower point estimates, 19% (95% CI, <0–46), 24% (95% CI, <0–67), and 11% (95% CI, <0–40), respectively.

4. Discussion

We found no negative effects of one or more previous vaccinations on the VE of a "current" seasonal vaccine against severe, mostly hospital-attended, influenza among persons ≥ 66 years of age in our comprehensive population-based cohort study during six consecutive seasons. In contrast, no significant VE was seen in any of the "current" seasons in persons who only had been vaccinated during one or more previous years, and not in the current season.

VE was low to non-existent during seasons dominated by influenza A(H3N2), and moderately high in those dominated by influenza A(H1N1)pdm09. The point estimate of VE in persons vaccinated both the current and the prior season was slightly, but non-significantly, higher in five of the six seasons (Fig. 1A, B), compared to those who had been vaccinated only the current season. In contrast, two previous studies demonstrated that persons vaccinated only during 2014/15 influenza A(H3N2) season had much higher VE, than in persons vaccinated also in the 2013/14 season [9,10]. The A(H3N2) components of the seasonal vaccine were the same in those two seasons, while the A(H3N2) virus drifted in Sweden, the rest of Europe and in Canada, resulting in a mismatch between the 2014/15 vaccine and circulating strains, thus meeting the conditions of the antigen distant hypothesis (ADH) [15]. Neither did we find any negative impact of more than

Table 2C
Demographic data for the populations included in the Model 2 analyses; sex, age-groups, socio-economic status, and co-morbidity, and exposure to previous pandemic vaccination, for the vaccinated and unvaccinated populations of persons 70 years of age, or above, living in Stockholm County, Sweden, during the 2014/15 to 2016/17 seasons.

C. Seasons 2014/15, 2015/16 and 2016/17

Characteristic	Influenza season 2014/15			Influenza season 2015/16			Influenza season 2016/17		
	Total n	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)
Cohort total (70+)	227 192	127 696 (56%)	99 496 (44%)	235 719	136 191 (58%)	99 528 (42%)	244 868	123 243 (50%)	121 625 (50%)
Sex									
Male	97 250	55 320 (57%)	41 930 (43%)	101 683	59 241 (58%)	42 442 (42%)	106 345	54 036 (51%)	52 309 (49%)
Female	129 942	72 376 (56%)	57 566 (44%)	134 036	76 950 (57%)	57 086 (43%)	138 523	69 207 (50%)	69 316 (50%)
Age group in years									
70–79	142 954	78 324 (55%)	64 630 (45%)	151 463	85 158 (56%)	66 305 (44%)	159 539	78 324 (49%)	81 3215 (51%)
≥ 80	84 238	49 372 (59%)	34 866 (41%)	84 256	51 033 (61%)	33 223 (39%)	85 329	44 919 (53%)	40 410 (47%)
Mosaic income/education categories									
Highest	97 240	58 121 (60%)	39 119 (40%)	102 006	62 815 (62%)	39 191 (38%)	107 075	57 580 (54%)	49 495 (46%)
Middle	41 097	23 140 (56%)	17 957 (44%)	42 263	24 412 (58%)	17 851 (42%)	43 931	21 836 (50%)	22 095 /50%)
Lowest	87 529	45 771 (52%)	41 758 (48%)	90 226	48 331 (54%)	41 895 (46%)	93 324	43 667 (47%)	49 657 (53%)
Missing	1 326	664 (50%)	662 (50%)	1 224	633 (52%)	591 (48%)	538	160 (30%)	378(70%)
Comorbidity									
Yes	170 787	100 544 (59%)	70 243 (41%)	184 140	111 093 (60%)	73 047 (40%)	183 359	96 519 (53%)	86 840 (47%)
No	56 405	27 152 (48%)	29 253 (52%)	51 579	25 098 (49%)	26 481 (51%)	61 509	26 724 (43%)	34 785 (57%)
Pandemrix in 2009/2010									
Yes	128 301	93 345 (73%)	34 956 (27%)	132 924	99 678 (75%)	33 246 (25%)	137 286	89 782 (65%)	47 504 (35%)
No	98 891	34 351 (35%)	64 540 (65%)	102 795	36 513 (36%)	66 282 (64%)	107 582	33 461 (31%)	74 121 (69%)

Table 3A and B
A and B Gender, age and presence of co-morbidities in different exposure categories in Model 1 (A) and Model 2 (B). For categorical variables sex and comorbidity, chi-square tests were used for group comparisons. For continuous variable mean age, ANOVA was used to test differences in means.

A

	Females (%)	Age, mean (years)	Age, median (years)	Co-morbidity (%)
Season 2011-2012				
Vaccinated and no vaccination prior season	56	75	74	75
Vaccinated and vaccination prior season	57*	76*	75	75*†
Season 2012-2013				
Vaccinated and no vaccination prior season	56	75	74	76
Vaccinated and vaccination prior season	57*	76	75	77
Season 2013-2014				
Vaccinated and no vaccination prior season	56	75	73	76
Vaccinated and vaccination prior season	57*	76	75	78
Season 2014-2015				
Vaccinated and no vaccination prior season	55	75	73	74
Vaccinated and vaccination prior season	56*	76	75	77
Season 2015-2016				
Vaccinated and no vaccination prior season	56	75	74	78
Vaccinated and vaccination prior season	56*	76	75	80
Season 2016-2017				
Vaccinated and no vaccination prior season	56	75	73	74
Vaccinated and vaccination prior season	56*	76	75	76

B

	Females (%)	Age, mean (years)	Age, median (years)	Co-morbidity (%)
Season 2014-2015				
Vaccinated current no vaccination prior season	53	72	70	68
Vaccinated current and 1-3 prior seasons	56	76	74	75
Vaccinated current and 4 prior seasons	57*	78*	76	79*
Season 2015-2016				
Vaccinated current no vaccination prior season	53	72	69	72
Vaccinated current and 1-3 prior seasons	56	75	72	76
Vaccinated current and 4-5 prior seasons	57*	78*	77	82*
Season 2016-2017				
Vaccinated current no vaccination prior season	53	72	70	66
Vaccinated current and 1-3 prior seasons	55	75	73	73
Vaccinated current and 4-5 prior seasons	57*	78*	77	79*

† 74.57% in vaccinated and no vaccination in prior season vs. 75.34% in those vaccinated both seasons.
* $p < 0.001$.

Table 4A
Exposure to influenza vaccination during a prior season in vaccinated and unvaccinated persons 66 years, and above, during six influenza seasons, 2011/12 to 2016/17 (Model 1).

	Influenza season 2011/12			Influenza season 2012/13			Influenza season 2013/14		
	Total n	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)
Vaccinated prior season	165 726 (57%)	138 869 (83%)	26 857 (22%)	152 446 (51%)	123 329 (79%)	29 117 (20%)	128 762 (41%)	112 587 (69%)	16 175 (11%)
No vaccination prior season	125 632 (43%)	28 808 (17%)	96 824* (78%)	148 958 (49%)	31 880 (21%)	117 078* (80%)	182 973 (59%)	50 818 (31%)	132 155* (89%)
	Influenza season 2014/15			**Influenza season 2015/16**			**Influenza season 2016/17**		
	Total n	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)
Vaccinated prior season	139 114 (43%)	117 338 (71%)	21 776 (14%)	145 398 (44%)	125 489 (72%)	19 909 (13%)	146 380 (44%)	116 199 (75%)	30 181 (17%)
No vaccination prior season	182 294 (57%)	48 451 (29%)	133 843* (86%)	183 986 (56%)	48 920 (28%)	135 066* (87%)	189 731 (56%)	39 683 (25%)	150 048* (83%)

* Used as reference in the model.

Table 4B
Exposure categories to influenza vaccination during prior seasons in vaccinated and unvaccinated persons 70 years, and above, during three influenza seasons, 2014/15 to 2016/17 (Model 2).

	Influenza season 2014/15			**Influenza season 2015/16**			Influenza season 2016/17		
	Total n	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)	Total n (%)	Vaccinated n (%)	Unvaccinated n (%)
Vaccinated ≥1 previous season									
(a) 1-3 seasons[a]	96 096 (42%)	62 244 (49%)	33 852 (34%)	74 801 (32%)	44 146 (32%)	30 655 (31%)	76 267 (31%)	40 609 (33%)	35 658 (29%)
(b) 4-5 seasons[a]	65 465 (29%)	58 148 (46%)	7317 (7%)	95 329 (40%)	85 710 (63%)	9619 (10%)	92 608 (38%)	76 171 (62%)	16 437 (14%)
No previous vacc	65 631 (29%)	7304 (6%)	58 327 (59%)*	65 589 (29%)	6335 (5%)	59 254 (60%)*	75 993 (31%)	6463 (5%)	69 530 (57%)*

[a] For the 2014/15 season only the four previous seasons were included (2010/11-2013/14) because of the pandemic season 2009/2010. Therefore, group (a) included 1–3 seasons and group (b) only 4 seasons.
* Used as reference in the analyses.

one previous vaccinations during a 4–5-year period. Significant VE's against influenza A(H3N2) in 2014/15 and 2016/17, and against influenza A(H1N1)pdm09 in 2015/16, was seen for the seasonal vaccine in persons who were infrequent or frequent vaccinees, but not in those vaccinated only during the "current" season, who also had lower point estimates of VE all three seasons (Fig. 2). These findings are in contrast to earlier studies [5,13]. McLean et al 2014 [5] studied oupatients during eight seasons dominated by influenza A(H3N2) or B and found significantly higher VE in persons vaccinated in the current season only, than in those who also were frequent vaccinees (vaccinated 4–5 out of the last 5 seasons). In a Spanish study, during four influenza A (H1N1)pdm09 seasons, VE was significantly lower in persons vaccinated during the current season if they had been vaccinated more than 2, compared to 1–2 prior seasons [13]. Our study included persons ≥66 years, where individuals in most cases required hospital treatment. In contrast, the four studies discussed above [5,9,10,13] included children, adolescents and adults, but few elderly persons. Three of the four studies included only patients seeking outpatient care [5,9,10] and in two vaccination history was partly based on self-reporting [9,10]. A negative impact of repeated vaccinations on VE has been indicated in other [4,6,12], but not all [7,8] out-patient studies and an Australian case-control study of individuals ≥9 years hospitalized with LCI 2010–2015 found significantly higher VE in persons vaccinated in both the current and previous season compared to those vaccinated in the current season only [14].

In two recent meta-analyses, one found variable results but which suggested that repeat vaccination may adversely affect vaccine-induced protection in some seasons, particularly for A (H3N2) (27), while the other found no overall evidence that prior season vaccination negatively impacts current season VE [28]. Belongia et al. [27] pointed out, that population heterogeneity made comparisons difficult and pooling analyses across multiple seasons, as many studies do, may not be appropriate. Comparisons of results will be difficult depending on whether analyses are based on a single year versus pooled over several years, a single country versus multiple countries, or if a single strain, the dominant strain or all circulating influenza strains are examined. Other methodological differences may also influence results, for example, odds ratio estimates obtained from standard case-control studies, such as those used in TND potentially inflate risks, particularly when the outcomes are more prevalent as in the case of influenza. Cohort studies, modelling time-to-events with hazard or incident rate ratios, would be more accurate than odds ratios in approximating relative-risks when the outcome is prevalent [29].

Our study population, being ≥66 years of age, probably had their first influenza episode when only influenza A(H1N1) was still circulating, which may partly explain the good VE against A(H1N1) pdm09 in their old age, while their response to A(H3N2) is poor. This is in accordance with the concept that it is the first hemagglutinin subtype encountered by an individual that leaves a defining immunological memory, and this significantly impacts the antibody cross-reactome which the individual eventually develops, the so called "Original Antigen Sin" [30,31]. The immune response is also known to decline with age [31,32]. This immunosenescence could explain why the response to influenza vaccination during a previous year in older persons does not have a significant impact on the VE in the current season. Thus, it is possible that the risk for a negative impact of previous vaccination under the conditions meeting the ADH may be valid in a younger population, such as that described in the study by Skowronski et al [9], but not in older persons such as those in the current study.

Major strengths of this study are the large and homogenous study population, including only older persons who most often required hospital treatment, and that VE during a "current" season

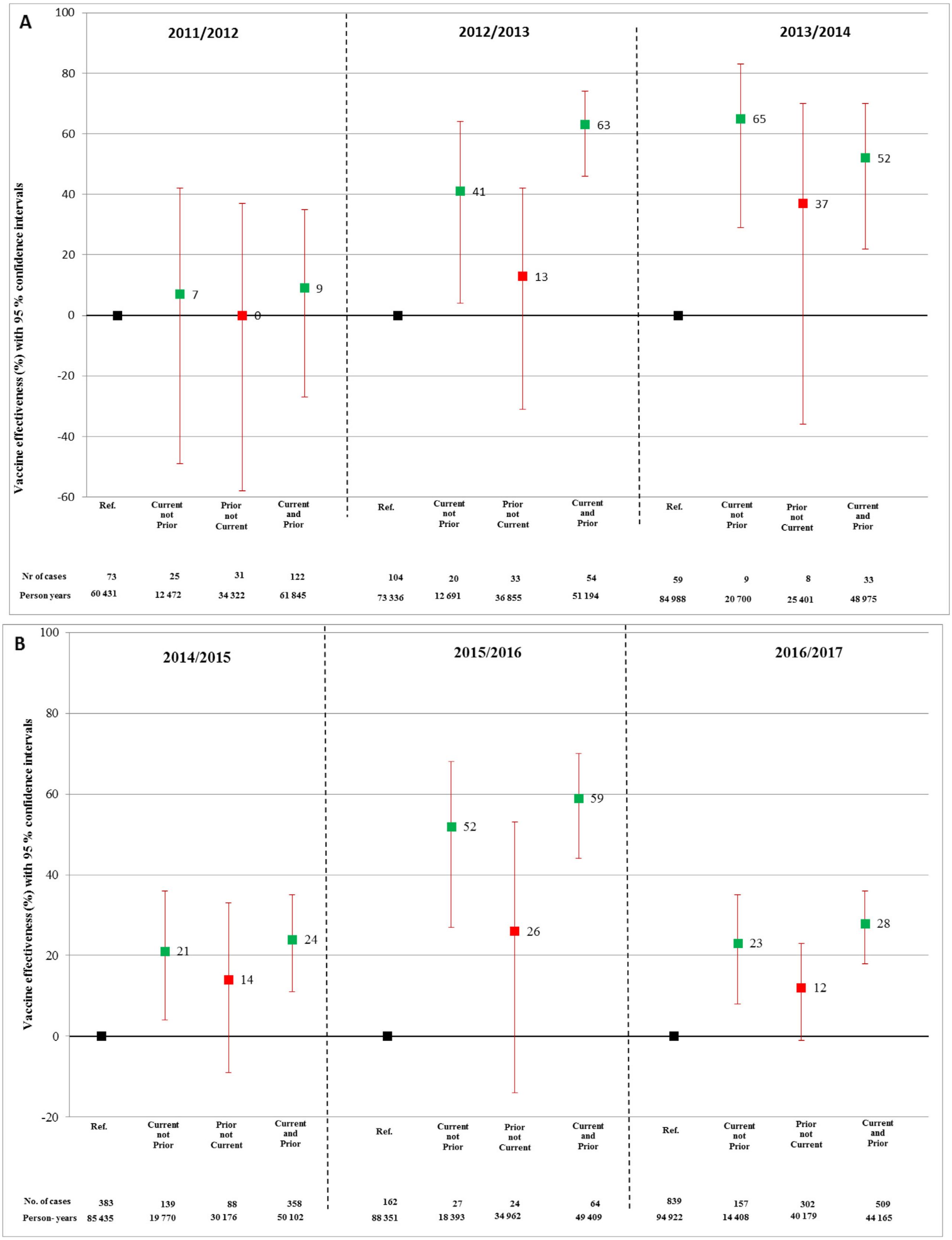

Fig. 1. Vaccine effectiveness (VE), with 95% confidence intervals, of seasonal influenza vaccine in persons 66 years, and above, who had received influenza vaccine in the current but not prior season, in the prior but not current season, in both the current and prior seasons, or in neither season (reference) (Model 1), during 2011/12 to 2013/14 (1A) and 2014/15 to 2016/17 (1B).

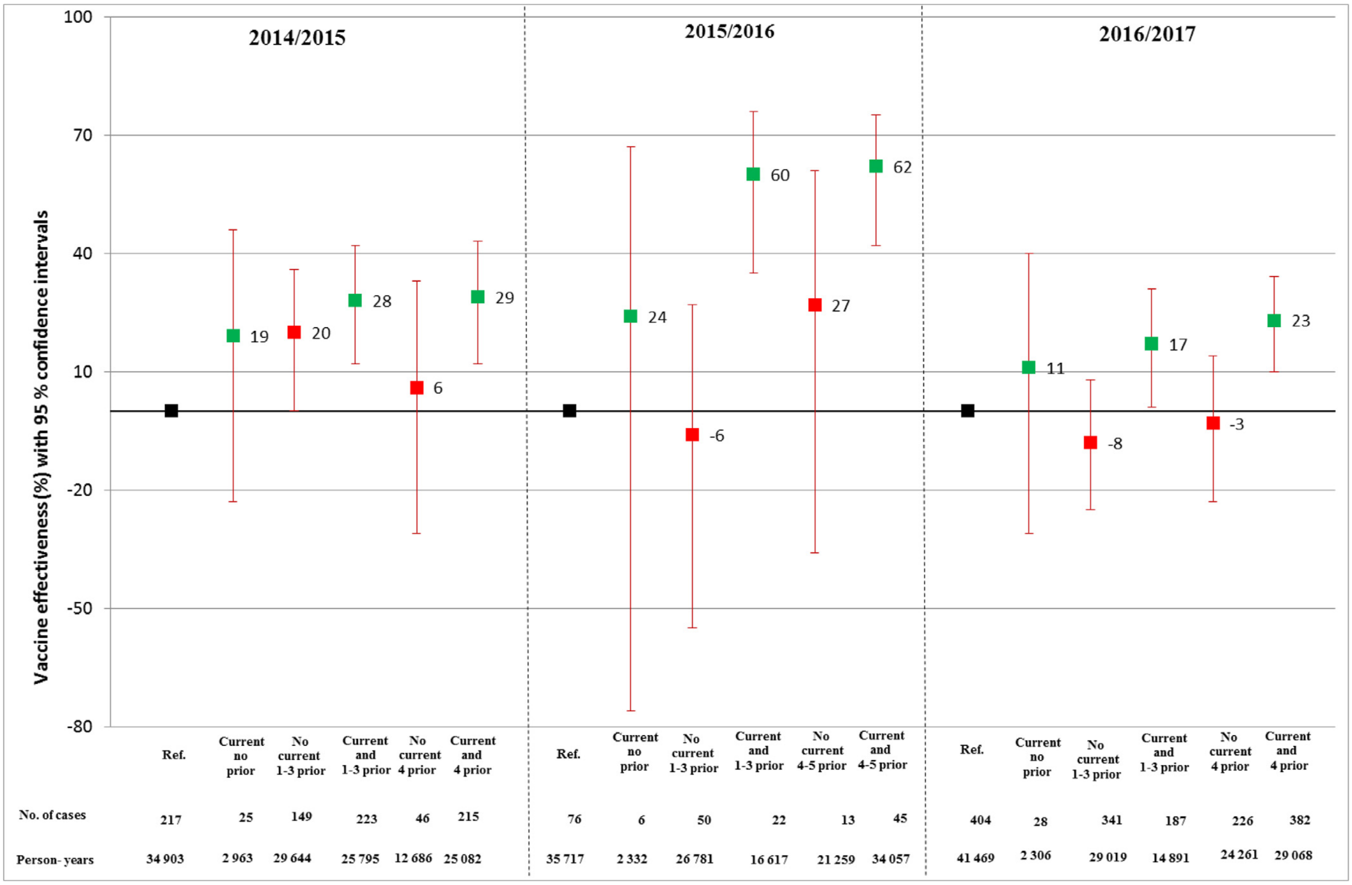

Fig. 2. Vaccine effectiveness (VE), with 95% confidence intervals, of seasonal influenza vaccine in persons 70 years, and above, who were vaccinated or unvaccinated during 2014/15 to 2016/17 and who were in-frequent or frequent vaccinees (see definitions), or not vaccinated either in a current or in prior seasons (reference) (Model 2).

was analyzed in a time-varying way, so that persons could contribute to both the unvaccinated and vaccinated population, thereby minimizing selection biases. This study has several limitations. In contrast to test-negative-design studies, health-care seeking- and sampling biases are often cited as limitations in cohort studies of VE. Such biases cannot be out-ruled in the present study. However, since nearly all persons in our study needed hospitalization, all had access to affordable health services, and influenza tests in hospital are consistently performed to allow cohort care due to a regular shortage of beds during the influenza season, we do not believe that such biases played a significant role for this severely ill patient group. In Stockholm County, the utilization of primary health care is low for older persons with acute illnesses, such as high fever or severe respiratory tract symptoms. Thus, our results may not be representative for those with mild disease not seeking care, or who saw their primary care doctor but were not sampled for influenza. Although there may be residual health seeking biases, these would not impact the effects of prior vaccinations, as examined here. Further, there is some misclassification of outcome in the earlier seasons due to the unavailability of LCI diagnoses, however this misclassification should be non-differential. The second model, comparing vaccination in multiple seasons vs. in the current season only, was somewhat underpowered due to dividing influenza patients into six categories. There may also be residual confounding despite adjustments, since persons who choose to become vaccinated for the first time were fewer and tended to be both younger and healthier than those who were infrequent/frequent vaccinees. However, comorbidity status and age were accounted for in the multivariate models and as such minimize differences between the groups.

In conclusion, no negative effects of repeated vaccination, or vaccinations, on the VE of the current seasonal vaccine were seen among large cohorts of persons over 65 years during six consecutive influenza seasons, 2011/12 to 2016/17. Although there is an urgent need for improved vaccines, especially against influenza A (H3N2), seasonal vaccination remains the best preventive measure currently available for all risk groups. Persons above 65 years are the largest group at risk for severe or complicated influenza and they should be offered yearly vaccination.

5. Role of the funding source

The study was performed as a part of the work at the Department of Communicable Disease Control and Prevention of Stockholm County Council. There was no external funding.

6. Author's contributions

ÅÖ, M-PH and AL designed the study, all authors participated in the analysis and writing of the manuscript of this study. M-PH had full access to all the data in the study and takes responsibility for the integrity of the data. M-PH and AL take responsibility for the accuracy of the data analyses. MB takes responsibility for all virologic data.

7. Declaration of interest

The authors' have nothing to disclose.

References

[1] Hoskins TW, Davies JR, Smith AJ, Miller CL, Allchin A. Assessment of inactivated influenza-A vaccine after three outbreaks of influenza A at Christ's Hospital. Lancet 1979;1(8106):33–5.
[2] Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. Vaccine 1997;15(10):1114–22.
[3] Beyer WE, de Bruijn IA, Palache AM, Westendorp RG, Osterhaus AD. Protection against influenza after annually repeated vaccination: a meta-analysis of serologic and field studies. Arch Internal Med 1999;159(2):182–8.
[4] Ohmit SE, Petrie JG, Malosh RE, Cowling BJ, Thompson MG, Shay DK, et al. Influenza vaccine effectiveness in the community and the household. Clin Infect Dis: Off Publ Infect Dis Soc Am 2013;56(10):1363–9.
[5] McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clin Infect Dis: Off Publ Infect Dis Soc Am 2014;59(10):1375–85.
[6] Ohmit SE, Thompson MG, Petrie JG, Thaker SN, Jackson ML, Belongia EA, et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. Clin Infect Dis: Off Publ Infect Dis Soc Am 2014;58(3):319–27.
[7] Thompson MG, Li DK, Shifflett P, Sokolow LZ, Ferber JR, Kurosky S, et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010–2011 and 2011–2012 influenza seasons. Clin Infect Dis: Off Publ Infect Dis Soc Am 2014;58(4):449–57.
[8] Simpson CR, Lone NI, Kavanagh K, Ritchie LD, Robertson C, Sheikh A, et al. Trivalent inactivated seasonal influenza vaccine effectiveness for the prevention of laboratory-confirmed influenza in a Scottish population 2000 to 2009. Euro surveillance : bulletin Europeen sur les maladies transmissibles. Eur Commun Dis Bulletin 2015;20(8)..
[9] Skowronski DM, Chambers C, De Serres G, Sabaiduc S, Winter AL, Dickinson JA, et al. Serial vaccination and the antigenic distance hypothesis: effects on influenza vaccine effectiveness during A(H3N2) epidemics in Canada, 2010–11 to 2014–15. J Infect Dis 2017;215:1059–69.
[10] Valenciano M, Kissling E, Reuss A, Rizzo C, Gherasim A, Horvath JK, et al. Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case-Control Study, Europe 2014/15. Euro surveillance: bulletin Europeen sur les maladies transmissibles. Eur Commun Dis Bulletin 2016;21(7):pii=30139.
[11] Castilla J, Navascues A, Casado I, Diaz-Gonzalez J, Perez-Garcia A, Fernandino L, et al. Combined effectiveness of prior and current season influenza vaccination in northern Spain: 2016/17 mid-season analysis. Euro surveillance : bulletin Europeen sur les maladies transmissibles. Eur Commun Dis Bulletin 2017;22(7).
[12] Saito N, Komori K, Suzuki M, Morimoto K, Kishikawa T, Yasaka T, et al. Negative impact of prior influenza vaccination on current influenza vaccination among people infected and not infected in prior season: A test-negative case-control study in Japan. Vaccine 2017;35(4):687–93.
[13] Martinez-Baz I, Casado I, Navascues A, Diaz-Gonzalez J, Aguinaga A, Barrado L, et al. Effect of Repeated Vaccination With the Same Vaccine Component Against Influenza A(H1N1)pdm09. J Infect Dis 2017.
[14] Cheng AC, Macartney KK, Waterer GW, Kotsimbos T, Kelly PM, Blyth CC, et al. Repeated vaccination does not appear to impact upon influenza vaccine effectiveness against hospitalization with confirmed influenza. Clin Infect Dis: Off Publ Infect Dis Soc Am 2017;64(11):1564–72.
[15] Smith DJ, Forrest S, Ackley DH, Perelson AS. Variable efficacy of repeated annual influenza vaccination. PNAS 1999;96(24):14001–6.
[16] Hergens MP, Baum U, Brytting M, Ikonen N, Haveri A, Wiman A, et al. Mid-season real-time estimates of seasonal influenza vaccine effectiveness in persons 65 years and older in register-based surveillance, Stockholm County, Sweden, and Finland, January 2017. Euro surveillance: bulletin Europeen sur les maladies transmissibles. Eur Commun Dis Bulletin 2017;22(8).
[17] Leval A, Hergens MP, Persson K, Ortqvist A. Real-time real-world analysis of seasonal influenza vaccine effectiveness: method development and assessment of a population-based cohort in Stockholm County, Sweden, seasons 2011/12 to 2014/15. Euro surveillance : bulletin Europeen sur les maladies transmissibles. Eur Commun Dis Bulletin 2016;21(43).
[18] Szegö J. Bebyggelsens mosaik [The mosaic of the settlement]. Regionplanekontoret, Stockholm, report 2009(7):Available from: http://www.rufs.se/globalassets/h.-publikationer/2009-7_r_bebyggelsens_mosaik_91-112.pdf.
[19] Carlsson AC, Wandell P, Osby U, Zarrinkoub R, Wettermark B, Ljunggren G. High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden - a challenge for public health. BMC Publ Health 2013;13:670.
[20] Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Publ Health 2011;11:450.
[21] Ortqvist A, Berggren I, Insulander M, de Jong B, Svenungsson B. Effectiveness of an adjuvanted monovalent vaccine against the 2009 pandemic strain of influenza A(H1N1)v, in Stockholm County, Sweden. Clin Infect Dis: Off Publ Infect Dis Soc Am 2011;52(10):1203–11.
[22] Rolfhamre P, Jansson A, Arneborn M, Ekdahl K. SmiNet- 2: Description of an internet-based surveillance system for communicable diseases in Sweden. Euro surveillance: bulletin Europeen sur les maladies transmissibles. Eur Commun Dis Bulletin 2006;11(5):103–7.
[23] Ortqvist A, Bennet R, Hamrin J, Rinder MR, Lindblad H, Ohd JN, et al. Long term effectiveness of adjuvanted influenza A(H1N1)pdm09 vaccine in children. Vaccine 2015;33(22):2558–61.
[24] Melidou A, Broberg E. European region influenza surveillance n. Predominance of influenza A(H3N2) virus genetic subclade 3C.2a1 during an early 2016/17 influenza season in Europe - Contribution of surveillance data from World Health Organization (WHO) European Region to the WHO vaccine composition consultation for northern hemisphere 2017/18. Vaccine 2017;35(37):4828–35.
[25] Wu NC, Zost SJ, Thompson AJ, Oyen D, Nycholat CM, McBride R, et al. A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine. PLoS Pathog 2017;13(10):e1006682.
[26] Zost SJ, Parkhouse K, Gumina ME, Kim K, Diaz Perez S, Wilson PC, et al. H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. PNAS 2017;114(47):12578–83.
[27] Belongia EA, Skowronski DM, McLean HQ, Chambers C, Sundaram ME, De Serres G. Repeated annual influenza vaccination and vaccine effectiveness: review of evidence. Expert Rev Vaccines 2017;16(7):1–14.
[28] Ramsay LC, Buchan SA, Stirling RG, Cowling BJ, Feng S, Kwong JC, et al. The impact of repeated vaccination on influenza vaccine effectiveness: a systematic review and meta-analysis. BMC Med 2017;15(1):159.
[29] Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? Brit Med J 1998;316(7136):989–91.
[30] Kim JH, Skountzou I, Compans R, Jacob J. Original antigenic sin responses to influenza viruses. J Immunol 2009;183(5):3294–301.
[31] Nunez IA, Carlock MA, Allen JD, Owino SO, Moehling KK, Nowalk P, et al. Impact of age and pre-existing influenza immune responses in humans receiving split inactivated influenza vaccine on the induction of the breadth of antibodies to influenza A strains. PloS One 2017;12(11):e0185666.
[32] Rumke HC, Richardus JH, Rombo L, Pauksens K, Plassmann G, Durand C, et al. Selection of an adjuvant for seasonal influenza vaccine in elderly people: modelling immunogenicity from a randomized trial. BMC Infect Dis 2013;13:348.