

## **Online Supplement**

### **Title:**

Effects of influenza vaccination in patients with interstitial lung diseases: an epidemiological claims data analysis

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*Figure E1 Detailed participant flow of the season 2014/15*

*Figure E2 Detailed participant flow of the season 2015/16*

*Figure E3 Detailed participant flow of the season 2016/17*

*Figure E4 Detailed participant flow of the season 2017/18*

*Figure E5 Cumulative incidence curves for all-cause hospitalization with 95% confidence intervals*

Cumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence intervals

*Figure E6 Cumulative incidence curves for respiratory-related hospitalization with 95% confidence intervals*

Cumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence interval

*Figure E7 Sensitivity analyses for residual confounding by dividing the influenza season into periods of pre-, in- and post-season*

*Horizontal bars represent 95% confidence intervals*

*Pre-season: From September 1 until 10% of specimen were positive for influenza viruses according to the RKI influenza surveillance data*

*In-season: From 10% positive specimens until calendar week 20 of the following year*

*Post-season: From calendar week 20 until August 31*

*Table E1 Treatment-related codes of the physician's fee scale (EBM) and ICD-10 codes to identify treatments and procedures*

<b>Treatment</b>	<b>Codes</b>
Palliative Care	EBM-codes: 01425, 01426, 03370 ,03371, 03372, 03373, 04370, 04372, 04371, 04373, 37300, 37305, 37306, 37318 ICD-codes: Z51.5
Influenza vaccine	EBM-codes: 89111, 89112

*Table E2 Influenza season divided in pre-, in- and post-season periods identified by national surveillance data of the Robert-Koch-Institute for each season*

<b>Season</b>	<b>Pre-season</b>	<b>In-season</b>	<b>Post-season</b>
Main analysis: influenza viruses continuously detected			
2014/15	Sep 1 - Oct 19, 2014	Oct 20, 2014 - May 17, 2015	May 18 - Aug 31, 2015
2015/16	Sep 1 - Nov 08, 2015	Nov 09, 2015 - May 22, 2016	May 23 - Aug 31, 2016
2016/17	Sep 1 - Nov 06, 2016	Nov 07, 2016 - May 21, 2017	May 22 - Aug 31, 2017
2017/18	Sep 1 - Oct 29, 2017	Oct 30, 2017 - May 20, 2018	May 21 - Aug 31, 2018
Sensitivity analysis: 10% of the specimen positive			
2014/15	Sep 1 - Dec 12, 2014	Dec 13, 2014 - May 17, 2015	May 18 - Aug 31, 2015
2015/16	Sep 1 - Dec 18, 2015	Dec 19, 2015 - May 22, 2016	May 23 - Aug 31, 2016
2016/17	Sep 1 - Dec 09, 2016	Dec 10, 2016 - May 21, 2017	May 22 - Aug 31, 2017
2017/18	Sep 1 - Dec 15, 2017	Dec 16, 2017 - May 20, 2018	May 21 - Aug 31, 2018

Table E3 Patient characteristics in the matched population for each season

	Season 2014/15			Season 2015/16			Season 2016/17			Season 2017/18		
	Un-vaccinated	Vaccinated	SMD	Un-vaccinated	Vaccinated	SMD	Un-vaccinated	Vaccinated	SMD	Un-vaccinated	Vaccinated	SMD
Number of patients	7503	7503		10318	10318		12723	12723		13927	13927	
Age (years), mean (SD)	68.9 (11.7)	69.0 (11.7)	0.012	69.4 (11.6)	69.5 (11.6)	0.017	69.8 (11.7)	69.9 (11.6)	0.013	69.8 (11.8)	70.0 (11.7)	0.017
Age groups (years), n (%)			<0.001			<0.001			<0.001			<0.001
20-29	23 (0.3)	23 (0.3)		13 (0.1)	13 (0.1)		22 (0.2)	22 (0.2)		20 (0.1)	20 (0.1)	
30-39	101 (1.3)	101 (1.3)		105 (1.0)	105 (1.0)		135 (1.1)	135 (1.1)		163 (1.2)	163 (1.2)	
40-49	359 (4.8)	359 (4.8)		499 (4.8)	499 (4.8)		558 (4.4)	558 (4.4)		573 (4.1)	573 (4.1)	
50-59	1079 (14.4)	1079 (14.4)		1470 (14.2)	1470 (14.2)		1743 (13.7)	1743 (13.7)		1912 (13.7)	1912 (13.7)	
60-69	1669 (22.2)	1669 (22.2)		2445 (23.7)	2445 (23.7)		3081 (24.2)	3081 (24.2)		3456 (24.8)	3456 (24.8)	
70-79	2998 (40.0)	2998 (40.0)		3770 (36.5)	3770 (36.5)		4400 (34.6)	4400 (34.6)		4616 (33.1)	4616 (33.1)	
80-89	1261 (16.8)	1261 (16.8)		1970 (19.1)	1970 (19.1)		2717 (21.4)	2717 (21.4)		3109 (22.3)	3109 (22.3)	
90+	13 (0.2)	13 (0.2)		46 (0.4)	46 (0.4)		67 (0.5)	67 (0.5)		78 (0.6)	78 (0.6)	
Sex (male), n (%)	3613 (48.2)	3613 (48.2)	<0.001	4909 (47.6)	4909 (47.6)	<0.001	6090 (47.9)	6090 (47.9)	<0.001	6632 (47.6)	6632 (47.6)	<0.001
ILD diagnosis, n (%)			<0.001			<0.001			<0.001			<0.001
Idiopathic interstitial pneumonia	3306 (44.1)	3306 (44.1)		4443 (43.1)	4443 (43.1)		5440 (42.8)	5440 (42.8)		5767 (41.4)	5767 (41.4)	
Other fibrosing ILDs	853 (11.4)	853 (11.4)		1428 (13.8)	1428 (13.8)		2004 (15.8)	2004 (15.8)		2380 (17.1)	2380 (17.1)	
Sarcoidosis	2866 (38.2)	2866 (38.2)		3678 (35.6)	3678 (35.6)		4284 (33.7)	4284 (33.7)		4631 (33.3)	4631 (33.3)	
Drug-associated ILDs	6 (0.1)	6 (0.1)		10 (0.1)	10 (0.1)		22 (0.2)	22 (0.2)		25 (0.2)	25 (0.2)	
Pneumoconiosis	212 (2.8)	212 (2.8)		286 (2.8)	286 (2.8)		311 (2.4)	311 (2.4)		318 (2.3)	318 (2.3)	
Radiation-associated pneumonitis	6 (0.1)	6 (0.1)		18 (0.2)	18 (0.2)		19 (0.1)	19 (0.1)		20 (0.1)	20 (0.1)	
Eosinophilic pneumonia	24 (0.3)	24 (0.3)		71 (0.7)	71 (0.7)		115 (0.9)	115 (0.9)		155 (1.1)	155 (1.1)	
Hypersensitivity pneumonitis	162 (2.2)	162 (2.2)		249 (2.4)	249 (2.4)		304 (2.4)	304 (2.4)		336 (2.4)	336 (2.4)	
Connective tissue-associated ILD	68 (0.9)	68 (0.9)		135 (1.3)	135 (1.3)		224 (1.8)	224 (1.8)		295 (2.1)	295 (2.1)	
Care dependency, n (%)			<0.001			<0.001			<0.001			<0.001
No care level	6953 (92.7)	6953 (92.7)		9408 (91.2)	9408 (91.2)		11342 (89.1)	11342 (89.1)		12150 (87.2)	12150 (87.2)	
Care level 1	463 (6.2)	463 (6.2)		736 (7.1)	736 (7.1)		1088 (8.6)	1088 (8.6)		86 (0.6)	86 (0.6)	
Care level 2	83 (1.1)	83 (1.1)		172 (1.7)	172 (1.7)		279 (2.2)	279 (2.2)		1205 (8.7)	1205 (8.7)	
Care level 3	4 (0.1)	4 (0.1)		2 (0.0)	2 (0.0)		14 (0.1)	14 (0.1)		403 (2.9)	403 (2.9)	

Care level 4	-	-		-	-		0 (0.0)	0 (0.0)		79 (0.6)	79 (0.6)	
Care level 5	-	-		-	-		0 (0.0)	0 (0.0)		4 (0.0)	4 (0.0)	
Nursing Home Residency, n (%)	15 (0.2)	15 (0.2)	<0.001	47 (0.5)	47 (0.5)	<0.001	77 (0.6)	77 (0.6)	<0.001	80 (0.6)	80 (0.6)	<0.001
Federal state, n (%)			<0.001			<0.001			<0.001			<0.001
Baden-Wuerttemberg	928 (12.4)	928 (12.4)		1303 (12.6)	1303 (12.6)		1644 (12.9)	1644 (12.9)		1860 (13.4)	1860 (13.4)	
Bavaria	835 (11.1)	835 (11.1)		1561 (15.1)	1561 (15.1)		1964 (15.4)	1964 (15.4)		2193 (15.7)	2193 (15.7)	
Berlin	189 (2.5)	189 (2.5)		230 (2.2)	230 (2.2)		290 (2.3)	290 (2.3)		301 (2.2)	301 (2.2)	
Brandenburg	262 (3.5)	262 (3.5)		356 (3.5)	356 (3.5)		453 (3.6)	453 (3.6)		475 (3.4)	475 (3.4)	
Bremen	38 (0.5)	38 (0.5)		47 (0.5)	47 (0.5)		64 (0.5)	64 (0.5)		65 (0.5)	65 (0.5)	
Hamburg	21 (0.3)	21 (0.3)		50 (0.5)	50 (0.5)		97 (0.8)	97 (0.8)		104 (0.7)	104 (0.7)	
Hesse	428 (5.7)	428 (5.7)		596 (5.8)	596 (5.8)		726 (5.7)	726 (5.7)		761 (5.5)	761 (5.5)	
Lower Saxony	946 (12.6)	946 (12.6)		1168 (11.3)	1168 (11.3)		1333 (10.5)	1333 (10.5)		1514 (10.9)	1514 (10.9)	
Mecklenburg-Vorpommern	213 (2.8)	213 (2.8)		276 (2.7)	276 (2.7)		344 (2.7)	344 (2.7)		365 (2.6)	365 (2.6)	
North Rhine-Westphalia	1294 (17.2)	1294 (17.2)		1791 (17.4)	1791 (17.4)		2231 (17.5)	2231 (17.5)		2423 (17.4)	2423 (17.4)	
Rhineland-Palatinate	145 (1.9)	145 (1.9)		218 (2.1)	218 (2.1)		295 (2.3)	295 (2.3)		317 (2.3)	317 (2.3)	
Saarland	30 (0.4)	30 (0.4)		43 (0.4)	43 (0.4)		56 (0.4)	56 (0.4)		47 (0.3)	47 (0.3)	
Saxony	1067 (14.2)	1067 (14.2)		1370 (13.3)	1370 (13.3)		1596 (12.5)	1596 (12.5)		1742 (12.5)	1742 (12.5)	
Saxony-Anhalt	480 (6.4)	480 (6.4)		534 (5.2)	534 (5.2)		654 (5.1)	654 (5.1)		703 (5.0)	703 (5.0)	
Schleswig-Holstein	148 (2.0)	148 (2.0)		192 (1.9)	192 (1.9)		254 (2.0)	254 (2.0)		319 (2.3)	319 (2.3)	
Thuringia	479 (6.4)	479 (6.4)		583 (5.7)	583 (5.7)		722 (5.7)	722 (5.7)		738 (5.3)	738 (5.3)	
Comorbidities Elixhauser score, mean (SD)	3.6 (2.0)	3.6 (2.0)	<0.001	3.8 (2.1)	3.8 (2.1)	<0.001	4.0 (2.1)	4.0 (2.1)	<0.001	4.0 (2.2)	4.0 (2.2)	<0.001
Comorbidities Elixhauser categories, n (%)												
Congestive heart failure	1459 (19.4)	1513 (20.2)	0.018	2228 (21.6)	2168 (21.0)	0.014	2786 (21.9)	2759 (21.7)	0.005	3096 (22.2)	3107 (22.3)	0.002
Cardiac arrhythmias	1601 (21.3)	1618 (21.6)	0.006	2367 (22.9)	2405 (23.3)	0.009	3096 (24.3)	3145 (24.7)	0.009	3450 (24.8)	3478 (25.0)	0.005
Valvular disease	895 (11.9)	918 (12.2)	0.009	1367 (13.2)	1359 (13.2)	0.002	1794 (14.1)	1757 (13.8)	0.008	2026 (14.5)	2015 (14.5)	0.002
Pulmonary circulation disorders	530 (7.1)	565 (7.5)	0.018	747 (7.2)	830 (8.0)	0.030	942 (7.4)	1055 (8.3)	0.033	1052 (7.6)	1141 (8.2)	0.024
Peripheral vascular disorders	1180 (15.7)	1127 (15.0)	0.020	1794 (17.4)	1779 (17.2)	0.004	2326 (18.3)	2370 (18.6)	0.009	2691 (19.3)	2618 (18.8)	0.013
Hypertension, uncomplicated	4540 (60.5)	4499 (60.0)	0.011	6225 (60.3)	6192 (60.0)	0.007	7708 (60.6)	7598 (59.7)	0.018	8406 (60.4)	8325 (59.8)	0.012
Hypertension, complicated	920 (12.3)	890 (11.9)	0.012	1360 (13.2)	1317 (12.8)	0.012	1704 (13.4)	1672 (13.1)	0.007	1890 (13.6)	1921 (13.8)	0.006
Paralysis	91 (1.2)	83 (1.1)	0.010	158 (1.5)	166 (1.6)	0.006	213 (1.7)	214 (1.7)	0.001	231 (1.7)	238 (1.7)	0.004
Other neurological disorders	269 (3.6)	269 (3.6)	<0.001	440 (4.3)	420 (4.1)	0.010	551 (4.3)	553 (4.3)	0.001	617 (4.4)	603 (4.3)	0.005
Chronic pulmonary disease	4084 (54.4)	4150 (55.3)	0.018	5537 (53.7)	5692 (55.2)	0.030	6851 (53.8)	7005 (55.1)	0.024	7285 (52.3)	7594 (54.5)	0.044
Diabetes, uncomplicated	1144 (15.2)	1164 (15.5)	0.007	1566 (15.2)	1564 (15.2)	0.001	1846 (14.5)	1824 (14.3)	0.005	1974 (14.2)	1830 (13.1)	0.030

Diabetes, complicated	1269 (16.9)	1331 (17.7)	0.022	1961 (19.0)	2067 (20.0)	0.026	2593 (20.4)	2657 (20.9)	0.012	2806 (20.1)	2930 (21.0)	0.022
Hypothyroidism	876 (11.7)	827 (11.0)	0.021	1292 (12.5)	1222 (11.8)	0.021	1687 (13.3)	1672 (13.1)	0.003	1962 (14.1)	1956 (14.0)	0.001
Renal failure	957 (12.8)	1007 (13.4)	0.020	1548 (15.0)	1626 (15.8)	0.021	2247 (17.7)	2273 (17.9)	0.005	2642 (19.0)	2757 (19.8)	0.021
Liver disease	932 (12.4)	948 (12.6)	0.006	1446 (14.0)	1392 (13.5)	0.015	1821 (14.3)	1760 (13.8)	0.014	2075 (14.9)	1965 (14.1)	0.022
Peptic ulcer disease, excluding bleeding	106 (1.4)	111 (1.5)	0.006	144 (1.4)	149 (1.4)	0.004	175 (1.4)	184 (1.4)	0.006	179 (1.3)	195 (1.4)	0.010
AIDS	6 (0.1)	5 (0.1)	0.005	8 (0.1)	10 (0.1)	0.007	9 (0.1)	19 (0.1)	0.024	15 (0.1)	20 (0.1)	0.010
Lymphoma	125 (1.7)	123 (1.6)	0.002	168 (1.6)	160 (1.6)	0.006	216 (1.7)	224 (1.8)	0.005	253 (1.8)	250 (1.8)	0.002
Metastatic cancer	122 (1.6)	110 (1.5)	0.013	179 (1.7)	164 (1.6)	0.011	249 (2.0)	226 (1.8)	0.013	307 (2.2)	294 (2.1)	0.006
Solid tumour without metastasis	818 (10.9)	808 (10.8)	0.004	1242 (12.0)	1163 (11.3)	0.024	1540 (12.1)	1505 (11.8)	0.008	1771 (12.7)	1694 (12.2)	0.017
Rheumatoid arthritis/collagen vascular diseases	1060 (14.1)	1046 (13.9)	0.005	1489 (14.4)	1482 (14.4)	0.002	1878 (14.8)	1907 (15.0)	0.006	2149 (15.4)	2135 (15.3)	0.003
Coagulopathy	211 (2.8)	240 (3.2)	0.023	302 (2.9)	319 (3.1)	0.010	408 (3.2)	439 (3.5)	0.014	506 (3.6)	489 (3.5)	0.007
Obesity	1493 (19.9)	1486 (19.8)	0.002	2238 (21.7)	2163 (21.0)	0.018	2935 (23.1)	2900 (22.8)	0.007	3215 (23.1)	3242 (23.3)	0.005
Weight loss	83 (1.1)	87 (1.2)	0.005	121 (1.2)	153 (1.5)	0.027	161 (1.3)	167 (1.3)	0.004	234 (1.7)	203 (1.5)	0.018
Fluid and electrolyte disorder	126 (1.7)	120 (1.6)	0.006	218 (2.1)	201 (1.9)	0.012	313 (2.5)	304 (2.4)	0.005	330 (2.4)	341 (2.4)	0.005
Blood loss anemia	26 (0.3)	21 (0.3)	0.016	35 (0.3)	38 (0.4)	0.005	56 (0.4)	50 (0.4)	0.007	56 (0.4)	50 (0.4)	0.005
Deficiency anaemia	306 (4.1)	282 (3.8)	0.016	421 (4.1)	443 (4.3)	0.011	550 (4.3)	558 (4.4)	0.003	645 (4.6)	654 (4.7)	0.003
Alcohol abuse	162 (2.2)	156 (2.1)	0.006	271 (2.6)	255 (2.5)	0.010	372 (2.9)	331 (2.6)	0.020	462 (3.3)	366 (2.6)	0.041
Drug abuse	40 (0.5)	36 (0.5)	0.008	70 (0.7)	70 (0.7)	<0.001	123 (1.0)	109 (0.9)	0.012	143 (1.0)	120 (0.9)	0.017
Psychoses	62 (0.8)	65 (0.9)	0.004	110 (1.1)	111 (1.1)	0.001	142 (1.1)	157 (1.2)	0.011	142 (1.0)	129 (0.9)	0.010
Depression	1652 (22.0)	1540 (20.5)	0.036	2418 (23.4)	2390 (23.2)	0.006	3122 (24.5)	3020 (23.7)	0.019	3410 (24.5)	3358 (24.1)	0.009
Radiotherapy or chemotherapy in three month before matching, n (%)	10 (0.1)	10 (0.1)	<0.001	39 (0.4)	39 (0.4)	<0.001	80 (0.6)	80 (0.6)	<0.001	106 (0.8)	106 (0.8)	<0.001

SD: Standard deviation; SMD: Standardized mean difference

*Table E4 Hospitalization rates per 100 person-years for vaccinated and unvaccinated patients for all-cause and respiratory-related hospitalization*

	Season 2014/15	Season 2015/16	Season 2016/17	Season 2017/18
<b>All-cause hospitalization</b>				
Vaccinated	53.4 (50.5; 56.5)	55.9 (53.3; 58.6)	56.8 (54.4; 59.3)	53.2 (51.1; 55.4)
Unvaccinated	55.4 (52.4; 58.6)	56.3 (53.4; 59.1)	56.8 (54.5; 59.3)	54.8 (52.7; 57.1)
<b>Respiratory-related hospitalization</b>				
Vaccinated	14.6 (13.2; 16.1)	14.2 (13.1; 15.5)	14.8 (13.7; 16.0)	14.0 (12.9; 15.0)
Unvaccinated	15.7 (14.2; 17.3)	15.2 (14.3; 16.9)	14.9 (13.8; 16.1)	14.2 (13.2; 15.3)

CI: confidence interval

*Table E5 Sensitivity analysis of influenza in-season Risk Ratio estimates for influenza effectiveness*

	Season 2014/15	Season 2015/16	Season 2016/17	Season 2017/18
	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>
<b>Mortality</b>	<b>0.80 (0.64; 0.99), p = 0.04</b>	<b>0.67 (0.54; 0.81), p &lt; 0.001</b>	0.95 (0.80; 1.12), p = 0.51	0.98 (0.82; 1.17), p = 0.79
<b>All-cause hospitalization</b>	0.99 (0.91; 1.08), p = 0.86	1.01 (0.94; 1.08), p = 0.80	1.00 (0.94; 1.06), p = 0.99	0.98 (0.93; 1.04), p = 0.55
<b>Respiratory-related hospitalization</b>	0.96 (0.82; 1.12), p = 0.60	0.92 (0.81; 1.05), p = 0.23	0.99 (0.88; 1.11), p = 0.81	1.00 (0.89; 1.12), p = 0.99

CI: confidence interval, RR: Risk Ratio

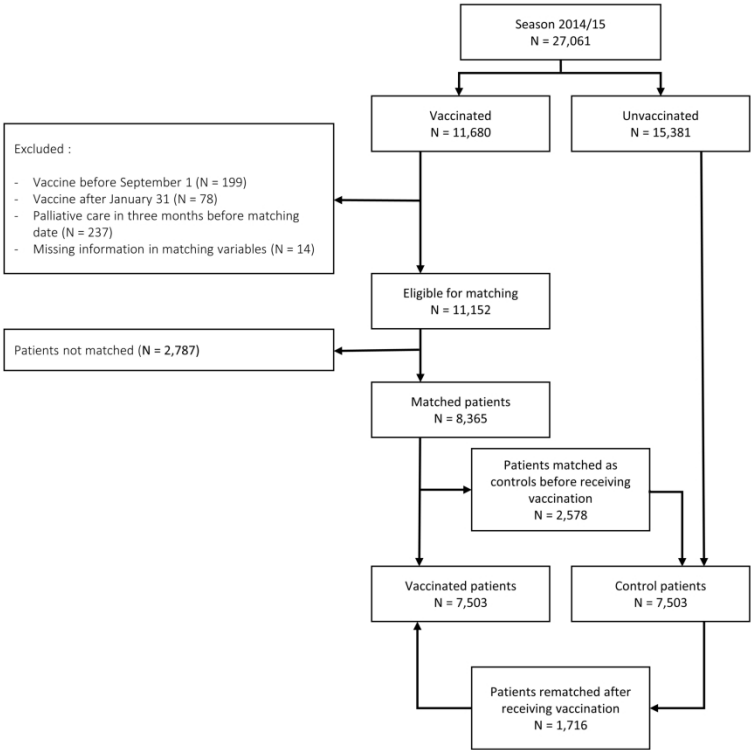


Figure E1 Detailed participant flow of the season 2014/15

254x190mm (300 x 300 DPI)

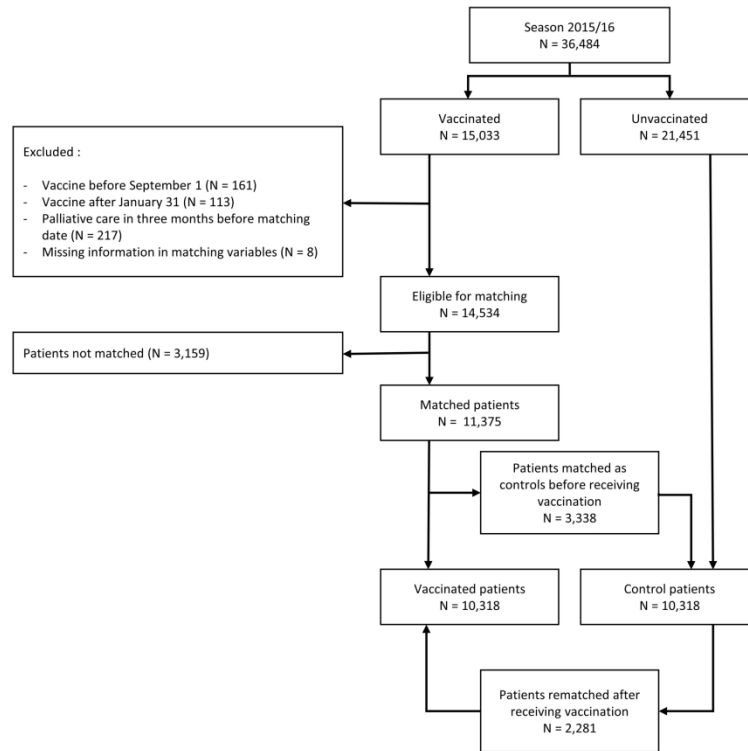


Figure E2 Detailed participant flow of the season 2015/16

254x190mm (300 x 300 DPI)

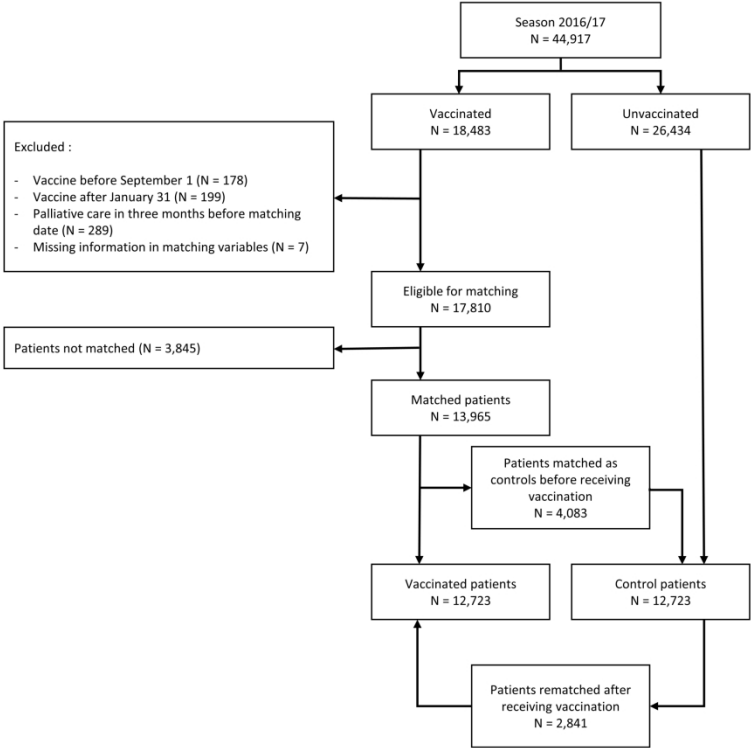


Figure E3 Detailed participant flow of the season 2016/17

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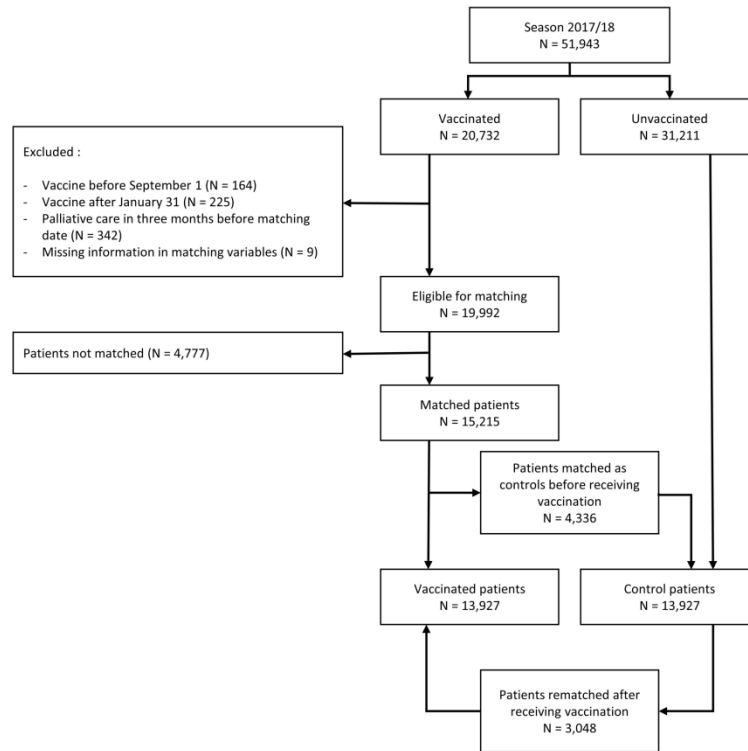


Figure E4 Detailed participant flow of the season 2017/18

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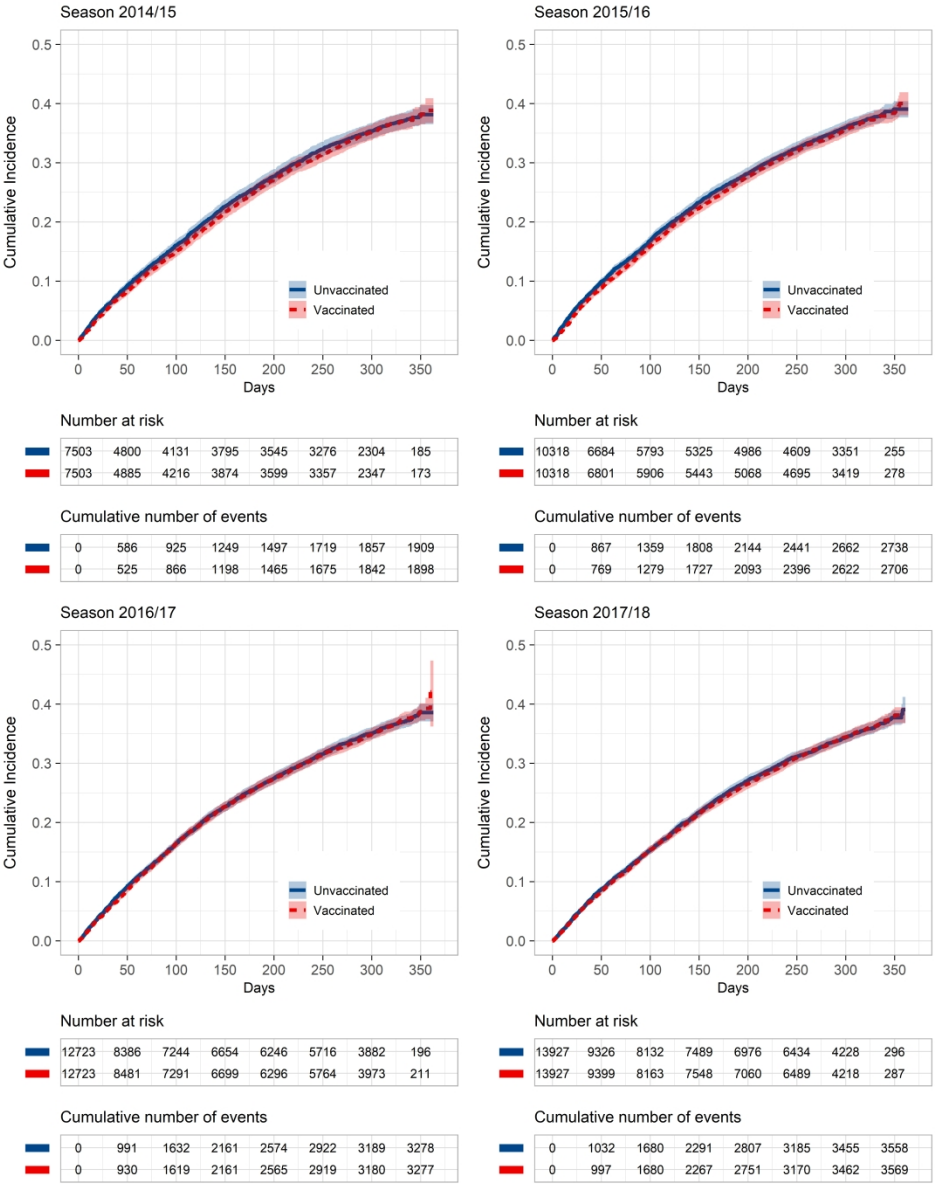


Figure E5 Cumulative incidence curves for all-cause hospitalization with 95% confidence intervals  
Cumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence intervals

481x608mm (276 x 276 DPI)

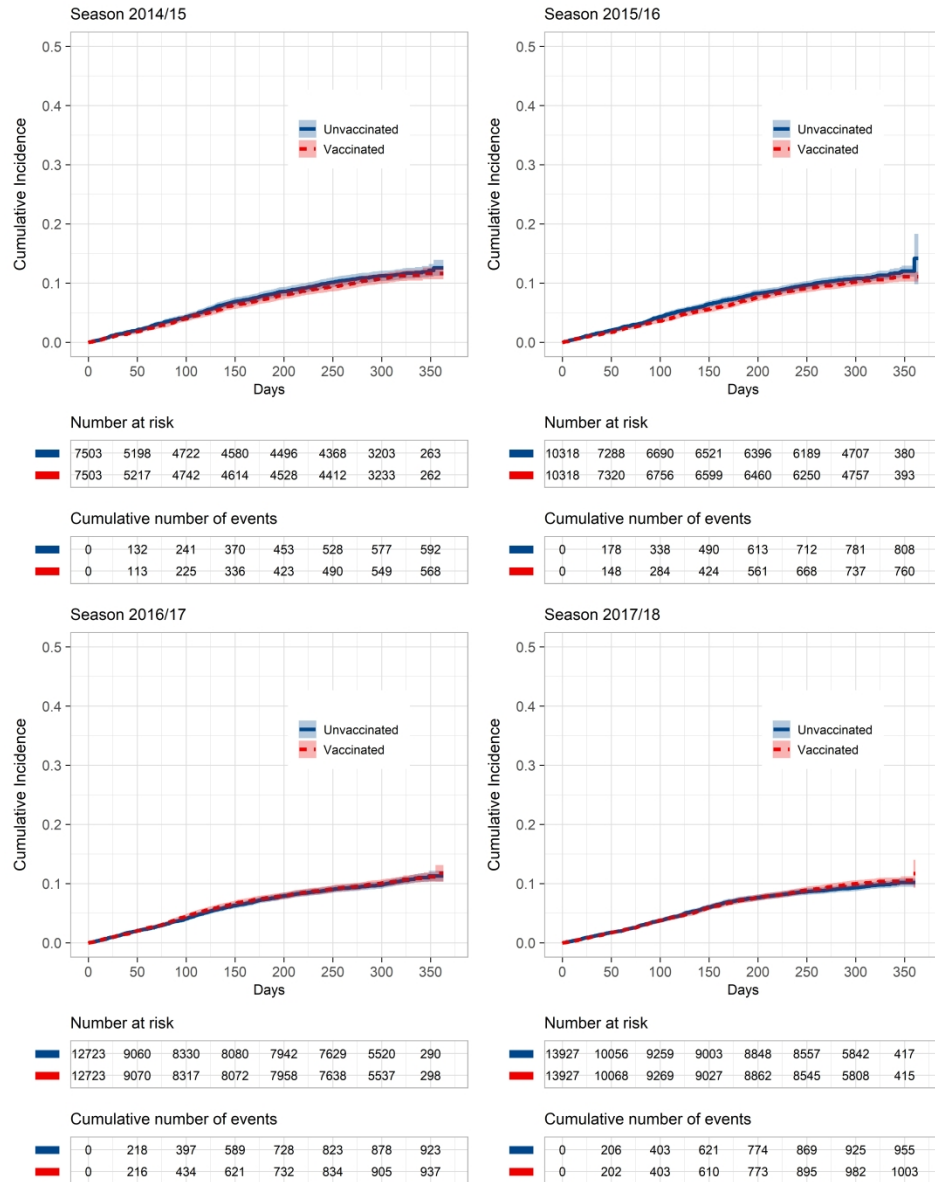


Figure E6 Cumulative incidence curves for respiratory-related hospitalization with 95% confidence intervals. Cumulative incidence curves (1 minus the Kaplan-Meier risk) depict the whole period from matching until end of follow-up (maximum June 30). Colored areas represent 95% confidence interval.

481x608mm (276 x 276 DPI)

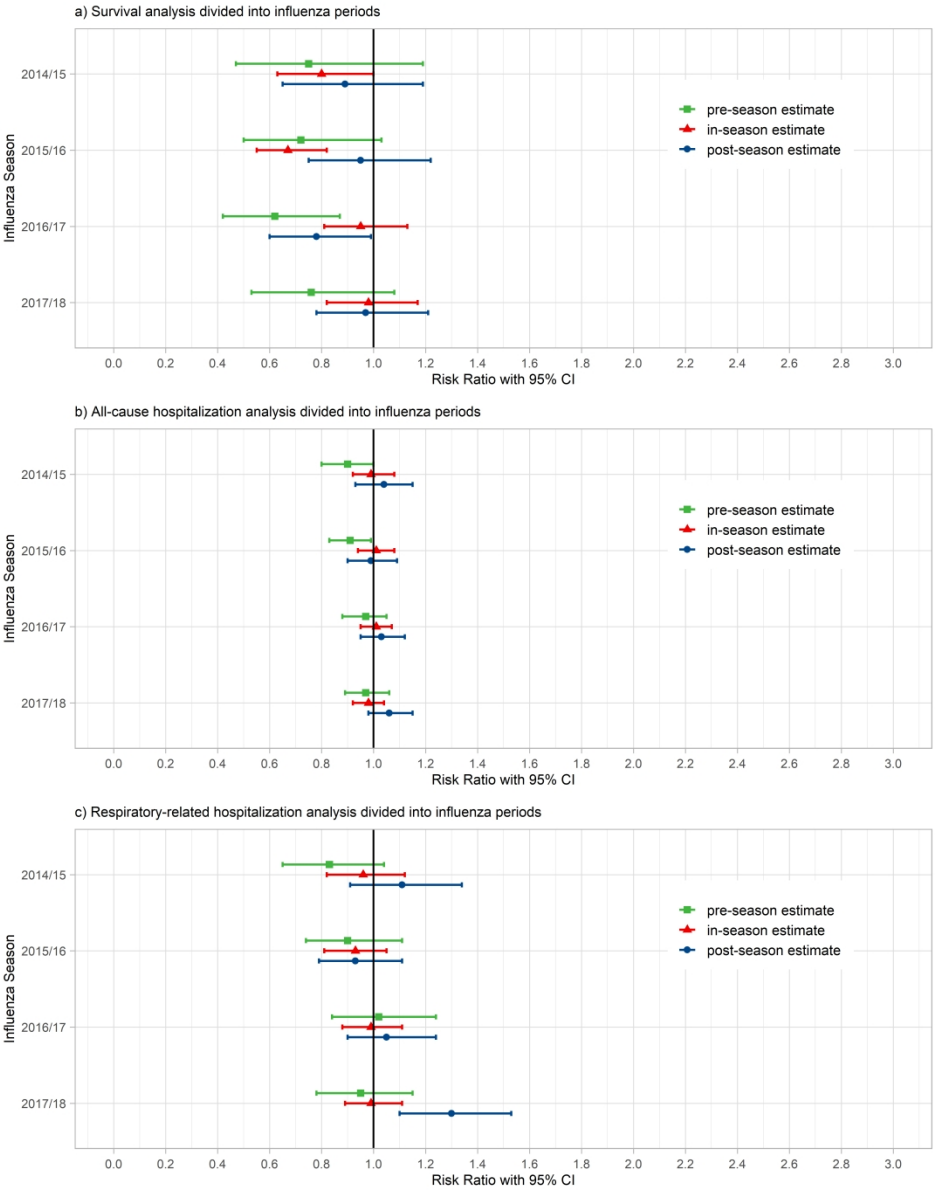


Figure E7 Sensitivity analyses for residual confounding by dividing the influenza season into periods of pre-, in- and post-season  
Horizontal bars represent 95% confidence intervals  
Pre-season: From September 1 until 10% of specimen were positive for influenza viruses according to the RKI influenza surveillance data  
In-season: From 10% positive specimens until calendar week 20 of the following year  
Post-season: From calendar week 20 until August 31

481x608mm (276 x 276 DPI)