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Original Research

Difference in survival between COPD patients with an impaired immune reaction versus an adequate immune reaction to seasonal influenza vaccination: The COMIC study

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ABSTRACT

Aim: To study the hypothesis that COPD patients who do not achieve seroprotective levels after influenza vaccination, are a less immune-competent group with a higher risk of morbidity and mortality.
Methods: 578 patients included in the COMIC cohort had pre- and post-vaccination stable state blood samples in which influenza-vaccine specific antibodies were measured. Post-vaccination titers of ≥40 were considered protective and indicative of being immuno-competent. Primary outcome was all-cause mortality. Morbidity was defined as time till first severe acute exacerbation in COPD (severe AECOPD) and time till first community acquired pneumonia (CAP).
Results: 42% of the patients achieved seroprotective levels to *both* H1N1 and H3N2 after vaccination. Seroprotective levels to H3N2 were markedly higher (96%) than to H1N1(43%). Having seroprotective levels to *both* H1N1 and H3N2 was not associated with less morbidity (severe AECOPD HR 0.91 (95% 0.66–1.25; p = 0.564) (CAP HR 1.23 (95% 0.75–2.00; p = 0.412)) or lower mortality (HR 1.10(95% 0.87–1.38; p = 0.433)).
Conclusion: In a large well-characterized COPD cohort only the minority of patients achieved seroprotective titers to H1N1 and H3N1 after the yearly influenza vaccination. While achieving seroprotection after vaccination can be considered a surrogate marker of being immunocompetent, this was not associated with lower morbidity and mortality. Whether this means that the immune status is not a relevant pheno/endotype in COPD patients for the course of their disease or that seroprotection is not an adequate (surrogate) marker to define the immune status in COPD needs to be further studied.

1. Introduction

Since COPD is a major burden of morbidity and mortality, the assessment of prognostic factors to determine the probability of (the time-to) death and other clinically relevant outcomes such as risk of exacerbations, pneumonia and accelerated lung function decline is a topic of major interest. Our understanding of COPD is shifting to a personalized approach in which we have a better appreciation of the multiple factors involved in its course.

Although several multi-component prognostic indices are available, they still lack in accuracy. One of the indices is the 2019 revised GOLD classification that assesses COPD patients using three different domains: severity of airflow limitation (spirometric grade), its impact on dyspnea (mMRC) or symptoms (CAT), and their history of moderate and severe exacerbations (including prior hospitalization) [1]. Well known multidimensional tools are the BODE-index (based on the body mass index

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(BMI), airflow Obstruction (FEV_1), Dyspnea (mMRC), and 6-min-walk distance(6MWD) [2], and the ADO index (which combines age, mMRC and FEV_1) [3]. Both are internationally validated and updated [3].

None of these multi-component prognostic indices, however, addresses the systemic aspect of COPD. Although multiple biomarkers have shown some promise in predicting risk of morbidity and mortality, (e.g. CC16, SP-D, IL-6 [4], hsCRP [5], sRAGE [6], fibrinogen [7] and MR-proADM [8]), not all biomarkers remain prognostic when studied in validation cohorts [9]. More importantly, their prediction of major outcomes (morbidity, mortality) remains rather poor.

An aspect that is under-exposed in COPD is the status of the immune system. The immune system, both the humoral and cellular response, is vitally important to protect against pathogens, without overshoot or immune deviation. However, COPD is often associated with bacterial colonization of the airways and severe bacterial and viral infections [10]. This suggests an impairment of the immune system, either innate, acquired, or both. Specific immune deviations in COPD have been suggested previously [11]. Since mortality in COPD is related to acute and severe exacerbations, when patients are hospitalized, and since roughly one third of these exacerbations is associated with bacterial and one third with viral infections [12], it is attractive to postulate a direct link between increased morbidity and mortality and impaired immune responses. However, it is difficult to assess these immune responses in individual patients and over repeated exacerbations due to the variety of triggers that cause these exacerbations. A more standardized trigger to assess immune-competence is the annual influenza vaccination as recommended to COPD patients in the international guidelines. Influenza vaccinations can reduce the incidence and severity of lower respiratory tract infections and is associated with reduced later AECOPD risk including hospitalizations [13–15]. However, it is unclear whether it leads to a survival benefit [13,14]. Parpaleix et al. showed that both the humoral and the cellular responses to influenza vaccination were impaired in patients with COPD [16]. Also Nath et al. observed that the humoral immune response to the 2010 influenza vaccine was lower in persons with COPD compared to non-COPD controls [17]. Both studies were very small (n = 15 and n = 34) and did not report an association with disease outcome.

Seroconversion to the seasonal influenza vaccination is difficult to interpret in COPD patients since pre-vaccination antibody titers can be elevated because of previous vaccinations and/or influenza infections [17,18]. Seroprotection is another method to determine vaccination effectiveness. Eagan et al. showed varying percentages of COPD patients with protective titers (>40). Furthermore, they showed that having high titers at baseline did not impact later risk for exacerbations, but seemed to be associated with higher all-cause mortality, even after adjustment for COPD disease characteristics. The authors themselves already indicated some methodological issues, one being the use of self-reported vaccination status as a proxy for actual vaccination. Furthermore, accurate data on the time of vaccination were lacking, while it is preferred to measure antibody titers before and after vaccination at fixed time intervals [18].

In the COMIC cohort, a large well-characterized COPD cohort [8, 19–25] in which patients received the influenza vaccination yearly through their GP, we were able to check the actual date of vaccination. By this we could measure antibody titers before and after vaccination at fixed time intervals. We investigated the humoral response to the influenza vaccination, to study our hypothesis that COPD patients who do not achieve seroprotective levels after influenza vaccination reflect a less immune-competent group and have a higher risk of morbidity, defined as time to first severe AECOPD and time to first CAP, and mortality.

Table 1
Composition of the seasonal influenza vaccines 2006–2011[a].

Year	viruses
2006–2007	– an A/New Caledonia/20/99(H1N1)-like virus – an A/Wisconsin/67/2005 (H3N2)-like virus – a B/Malaysia/2506/2004-like virus
2007–2008	– an A/Solomon Islands/3/2006 (H1N1)-like virus – an A/Wisconsin/67/2005 (H3N2)-like virus – a B/Malaysia/2506/2004-like virus
2008–2009	– an A/Brisbane/59/2007 (H1N1)-like virus – an A/Brisbane/10/2007 (H3N2)-like virus – a B/Florida/4/2006-like virus
2009–2010	– an A/Brisbane/59/2007 (H1N1)-like virus – an A/Brisbane/10/2007 (H3N2)-like virus – a B/Brisbane/60/2008-like virus
2010–2011	– an A/California/7/2009 (H1N1)-like virus – an A/Perth/16/2009 (H3N2)-like virus – a B/Brisbane/60/2008-like virus

[a] As recommended by the World Health Organization.

2. Methods

2.1. Setting and study population

The COMIC study (Cohort of Mortality and Inflammation in COPD) is a single center cohort study from Enschede, the Netherlands. From December 2005 till April 2010, 795 patients were included. All patients were followed-up for at least three years.

Patients included in the COMIC study had to meet the following criteria; a) a clinical diagnosis of COPD according to the GOLD guidelines; b) current or former smoker; c) age ≥40 years; d) no medical condition compromising survival within the follow-up period or serious psychiatric morbidity; e) absence of any other active lung disease (e.g. sarcoidosis); f) no maintenance therapy with antibiotics; g) ability to communicate in Dutch. Patients were enrolled when hospitalized for an acute exacerbation of COPD (AECOPD group) or when visiting the outpatient clinic in stable state (stable state group). To be included in the AECOPD group, patients had to be hospitalized for an AECOPD and be able to produce an adequate sputum sample at the day of hospitalization. To be included in the stable state group patients had to meet the following criteria: no use of an antibiotic and/or prednisolone 4 weeks prior to enrolment and no exacerbation less than 4 weeks before study entry.

The study was approved by the Medical Ethics Committee Twente in 2005 (study number P05-49) and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

2.2. Influenza vaccination

Patients received their annual influenza vaccination through their GP. The compositions of the influenza vaccination were all based on the WHO recommendation [26] and are shown in Table 1.

2.3. Antibody response

Influenza-vaccine specific antibodies were measured with the hemagglutination inhibition (HAI) assay [27–29], performed on blood samples collected in a stable state pre-vaccination serum sample in the preceding month(s) or week(s) and a post-vaccination serum sample obtained 4–6 weeks after vaccination. Post-vaccination titers reaching an antibody titer of 40 or above were considered indicative of being immunized, either by vaccination or infection (i.e. protective titers) [30]. Patients were divided into two groups based on their post-vaccination titers. Patients were considered to be more immune-competent if they had a protective titer (≥40) to both H1N1 and H3N2 and less immune-competent if they had no or only one

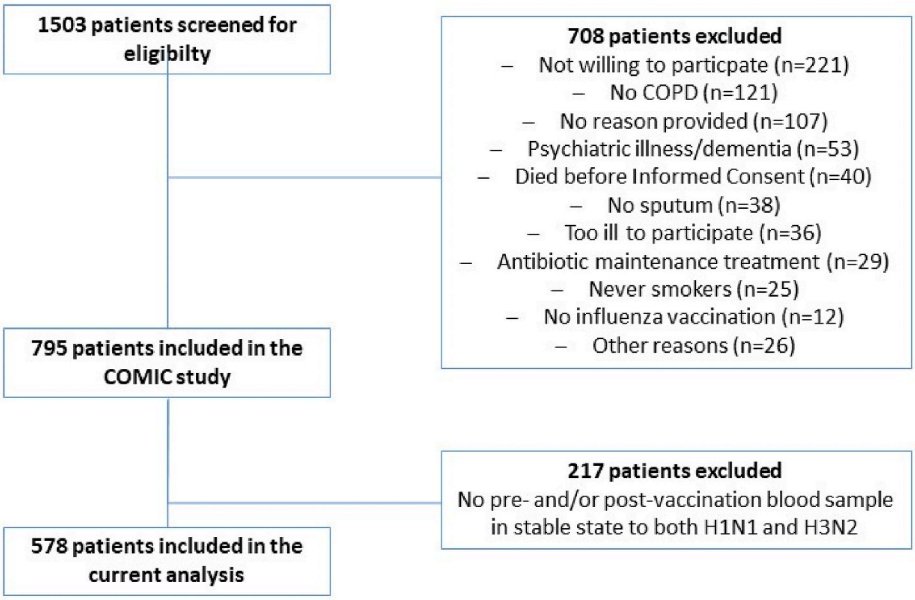

Fig. 1. Flowchart patient inclusion.

protective titer to H1N1 and H3N2.

2.4. Outcomes

The primary outcome parameter was survival, based on all-cause mortality. Date of death was verified from public registries.

Morbidity was defined as both time till first hospitalization for an acute exacerbation in COPD (severe AECOPD) and as time till first community acquired pneumonia (CAP).

AECOPD was defined as an acute negative change from baseline, reported by the patient, in dyspnea and/or sputum volume and/or color of sputum (yellowish or greenish sputum) and/or cough, which warranted additional treatment with prednisolone with or without antibiotics by a physician in a patient with underlying COPD [31]. Pneumonia was defined as an acute respiratory tract illness associated with radiographic shadowing on a chest radiograph consistent with infection which was neither pre-existing nor of any other known cause [32]. All X-rays were double read by a radiologist and a pulmonary physician. In case of doubtful shadows in the report, the X-ray was presented to another independent pulmonary physician for final judgment.

Demographic data was collected from medical records. Spirometry was performed by trained lung function technicians according to the American Thoracic Society guidelines [33]. Smoking status was determined by the Vlagtwedde questionnaire and pack-years were calculated [34]. Data on common co-morbidities like myocardial infarction, congestive heart failure and diabetes mellitus were obtained from medical records and/or during study visits. Number of previous moderate AECOPD in the year preceding inclusion was determined based on prescribed prednisolone courses as retrieved from pharmacy data. Previous severe AECOPD was defined as an hospitalization in the year preceding inclusion and was retrieved from hospital records. Patients completed the modified Medical Research Council dyspnea questionnaire (mMRC) [35] and the Clinical COPD Questionnaire (CCQ) [36] The BOD comprises BODE without the exercise capacity measurement. The components were scored according to the same cut-offs as in BODE [2]. The BOD therefore ranges from 0 to 7. The ADO score ranges, in increasing severity, from 0 to 10 [37]. All measurements were performed in stable state.

2.5. Sample size calculation

A predefined hazard ratio of 2.0 was assumed and a median survival time of the less immune-competent group of 60 months was estimated based on mortality data of Groenewegen et al. [38] and Almagro et al. [39]. Groenewegen et al. showed that 1 year after hospital admission approximately 22% of patients had died. According to Almagro et al., 36% had died after 24 months of follow-up. Since a reasonable amount of patients in the COMIC cohort will be included at admission to the hospital, we assumed a conservative median survival time of 60 months. We also estimated the proportion of less immune-competent patients to be 10%. With an inclusion period of 60 months, a minimal follow up of 24 months, an alpha of 0.05 and a power of 0.8, in total 600 patients needed to be included.

2.6. Statistical analyses

Continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IQR); categorical variables as counts with corresponding percentages.

Time to death, time till first hospitalization for AECOPD and time till first pneumonia were analyzed by Kaplan-Meier survival curves. Univariate and multivariate Cox proportional hazard regression models were used to establish the relationship between the humoral response to the influenza vaccination on the one hand, and time to all-cause death, time till first hospitalization for AECOPD, and time till first pneumonia on the other hand. In the multivariate Cox proportional hazard regression models potential confounders were taken into account based on a stepwise backward method. Potential confounders were baseline characteristic that were associated with both the humoral response and the outcome variable of interest (both $p < 0.10$).

All tests were two-sided and a p-value of 0·05 or lower was considered statistically significant. Data were analyzed using SPSS, version 25 (SPSS Inc. Chicago IL).

3. Results

Of the 795 included patients in the COMIC cohort, 578 patients had both a pre- and post-vaccination blood sample and could be included in the current analysis on the humoral response to the influenza vaccination (see flowchart in Fig. 1). Table 2 shows the baseline characteristics

Table 2
Baseline characteristics of the 578 patients, including the differences in baseline characteristics in patients with and without a protective antibody titer to both H1N1 and H3N2.

Characteristic	Post-vaccination titer			
	Total group N = 578	<40 to both H1N1 and H3N2 or to one of them (n = 334)	>40 to both H1N1 and H3N2 (n = 244)	p
Mean age (SD)	67.1 (9.1)	66.3 (9.2)	68.1 (8.9)	.019
Sex, male, N (%)	348 (60.2)	193(57.8)	155 (63.5)	.164
Smoker, N (%)				.814
Current smoker	144 (24.9)	82(24.6)	62(25.4)	
Ex-smoker	434 (75.1)	252 (75.4)	182(74.6)	
Mean BMI (SD)[a]	27.6 (5.4)	27.5 (5.0)	27.8 (5.8)	.429
Median Pack-years (IQR) [b]	35.0 (22.0–50.0)	34.1(21.9–48.4)	37.0 (22.0–53.1)	.282
Mean lung function (SD)[c]				
FEV_1 in l	1.5 (0.6)	1.52 (0.65)	1.40 (0.56)	.018
FEV_1% predicted	54.0 (18.9)	55.0 (19.3)	52.6 (18.4)	.127
FEV_1/VC ratio	44.9 (13.4)	45.4(13.4)	44.2 (13.3)	.297
GOLD (2007), N (%)[c]				.823
I-II	320 (55.5)	186 (55.9)	134 (54.9)	
III-IV	257 (44.5)	147 (44.1)	110 (45.1)	
Previous moderate AECOPD, N(%)[d]				.694
0-1 AECOPD	365 (63.1)	213 (68.3)	152 (66.7)	
≥2 AECOPD	175 (30.3)	99 (31.7)	76 (33.3)	
Previous severe AECOPD, N (%) ≥1 severe AECOPD	74 (12.8)	46 (13.8)	28(11.5)	.414
ICS use, yes, N (%)	492 (85.1)	279 (83.5)	213 (87.3)	.209
Mean mMRC (SD)[e]	1.7 (1.3)	1.60 (1.21)	1.81 (1.31)	.045
Comorbidities, N (%)				
Heart failure	98 (17.0)	53 (15.9)	45 (18.4)	.415
Diabetes Mellitus	38 (6.6)	25(7.5)	13(5.3)	.301
Myocardial Infarction	24 (4.2)	9 (2.7)	15(6.1)	.040
Mean CCQ score (SD)[f]	1.7 (1.0)	1.67 (0.98)	1.82 (0.99)	.083
Mean ADO score (SD)[g]	4.0 (1.8)	3.85 (1.75)	4.32 (1.76)	.002
Mean BOD score (SD)[g]	2.4 (1.7)	2.24 (1.67)	2.46 (1.78)	.135

[8] BOD score is missing of resp. 23, 15 and 8 patients in the total, <40 and ≥ 40 group.
Abbreviations: SD: standard deviation, N: number, IQR: interquartile range, BMI: body mass index, FEV_1: Forced expiratory volume in 1 s, mMRC: modified Medical Research Council dyspnea questionnaire, CCQ: Clinical COPD Questionnaire, ADO: age dyspnea, airflow obstruction, BOD: BMI, airflow obstruction, dyspnea.
[a] BMI missing of resp. 11, 9 and 2 patients in the total, <40 and ≥ 40 group.
[b] Pack-years is missing of resp. 35, 25 and 10 patients in the total, <40 and ≥ 40 group.
[c] Lung function and GOLD is missing of resp.1 patient in the total and <40 group.
[d] Previous AECOPD is missing of resp. 38, 22 and 16 patients in the total, <40 and ≥ 40 group.
[e] mMRC is missing of resp. 12, 6 and 6 patients in the total, <40 and ≥ 40 group.
[f] CCQ is missing of resp. 4, 2 and 2 patients in the total, <40 and ≥ 40 group.
[g] ADO is missing of resp. 13, 7 and 6 patients in the total, <40 and ≥ 40 group.

of the 578 patients.

The percentage of patients with a protective antibody titer to H1N1 and H3N2 itself, to either H1N1 or H3N2, and to both H1N1 and H3N2 is displayed in Table 3. Most patients had a protective titer to H3N2, while more than half of the patients did not have a protective titer to H1N1.

Table 3
Percentage of patients with a protective antibody titer to H1N1 and H3N2.

Antibody titer	H1N1	H3N2	H1N1 and H3N2
≥40, n (%)	250 (43.3)	555 (96.0)	244 (42.2)

Comparison of the pre- and post-vaccination antibody titers to H1N1 (Table 4a) and H3N2 (Table 4b), shows that also prevaccination titers to H3N2 (in 94.5% of patients) were more often ≥ 40 than prevaccination titers to H1N1 (in 40.1% of patients).

Baseline differences in patients with and without a protective antibody titer to both H1N1 and H3N2.

Patients with protective titers to both H1N1 and H3N2 were somewhat older, had a worse lung function and a higher mMRC and ADO score (see Table 2).

3.1. Mortality

Patients with a protective response to both H1N1 and H3N2 had 1.26 times higher risk of dying than patients with either one or no protective titer to H1N1 and H3N2 (HR 1.26; 95%CI 1.01–1.58; p = 0.043), see also Fig. 2. After correction for the confounders BOD, CCQ total score and age the corrected HR was no longer significant (HR 1.10(95% 0.87–1.38; p = 0.433).

3.2. Morbidity

There was no difference in time till first hospitalization between patients with a protective titer to both H1N1 and H3N2 vs patient with no or only one protective titer to H1N1 and H3N2(Fig. 3; p = 0.53, HR 1.11 (95% 0.81–1.52)). After correction for the confounders age, FEV_1 in liters, myocardial infarction, CCQ total score the corrected HR was 0.91 (95% 0.66–1.25; p = 0.564).

Neither was there a difference in time to first pneumonia between patients with a protective titer to both H1N1 and H3N2 vs patient with no or only one protective titer to H1N1 and H3N2 (Fig. 4; HR 1.45 (95% 0.89–2.35) p = 0.135). After correction for the confounders age, FEV_1 in liters, myocardial infarction, mMRC and CCQ total score the corrected HR was 1.23 (95% 0.75–2.00; p = 0.412).

4. Discussion

The main outcome of our study is that 42% of the patients achieved seroprotective levels to both H1N1 and H3N2 after the influenza vaccination. The seroprotective levels to H3N2 were markedly higher (96%) than the seroprotective levels to H1N1(43%). Having seroprotective levels to both H1N1 and H3N2 was not associated with less morbidity or lower mortality compared to having no seroprotective levels or only seroprotective levels to either H1N1 or H3N2.

The yearly influenza vaccination has been recommended for a long time in the annual GOLD-report and different international guidelines. As concluded in the Cochrane review by Kosaftis et al. [40] and recently in a retrospective analyses [15] influenza vaccination in COPD patients lead to lower risk of AECOPD. Acquiring an adequate immune-response to vaccinations is essential for achieving this favorable outcome [41]. Our study however reveals that for COPD patients having seroprotective levels, as a surrogate marker for an adequate acquired immune-response after this annual vaccination, or not is apparently not a major factor to be taken into account for achieving this favorable outcome. Furthermore, in the ongoing discussion whether the annual vaccination leads to better survival as well, our hypothesis that this may be true for the patients being able to achieve seroprotective levels could not be demonstrated with this study. These are surprising but relevant outcomes.

Because COPD patients often experience recurrent bacterial and viral infections, it has been proposed that they may be relatively immune-

Table 4a
the change in absolute pre- and post-vaccination antibody titers to H1N1 per patient.

		Post-vaccination titer									
		1	8	16	32	64	128	256	512	1024	Total
Pre-vaccination titer	**1**	30	13	5	6	–	–	–	–	–	54
	8	2	11	18	4	2	1	–	–	–	38
	16	5	5	50	31	11	2	–	–	–	104
	32	2	1	12	93	37	2	1	–	–	148
	64	2	1	5	26	82	14	2	–	–	132
	128	–	–	2	4	12	32	6	1	–	57
	256	–	–	–	–	1	2	30	2	–	35
	512	–	–	–	–	–	–	3	6	–	9
	1024	–	–	–	–	–	–	–	1	–	1
	Total	41	31	92	164	145	53	42	10	0	578

Table 4b
the change in absolute pre- and post-vaccination antibody titers to H3N2 per patient.

		Post-vaccination titer									
		1	8	16	32	64	128	256	512	1024	Total
Pre-vaccination titer	**1**	–	–	–	–	–	–	–	–	–	0
	8	–	1	–	–	–	–	–	–	–	1
	16	–	–	–	–	1	–	–	–	–	1
	32	–	–	–	20	4	1	4	1	–	30
	64	–	–	–	2	100	4	4	2	1	113
	128	–	–	–	–	14	77	18	6	8	123
	256	–	–	–	–	–	13	50	43	10	116
	512	–	–	–	–	–	1	16	58	38	113
	1024	–	–	–	–	1	–	3	18	59	81
	Total	0	1	0	22	120	96	95	129	116	578

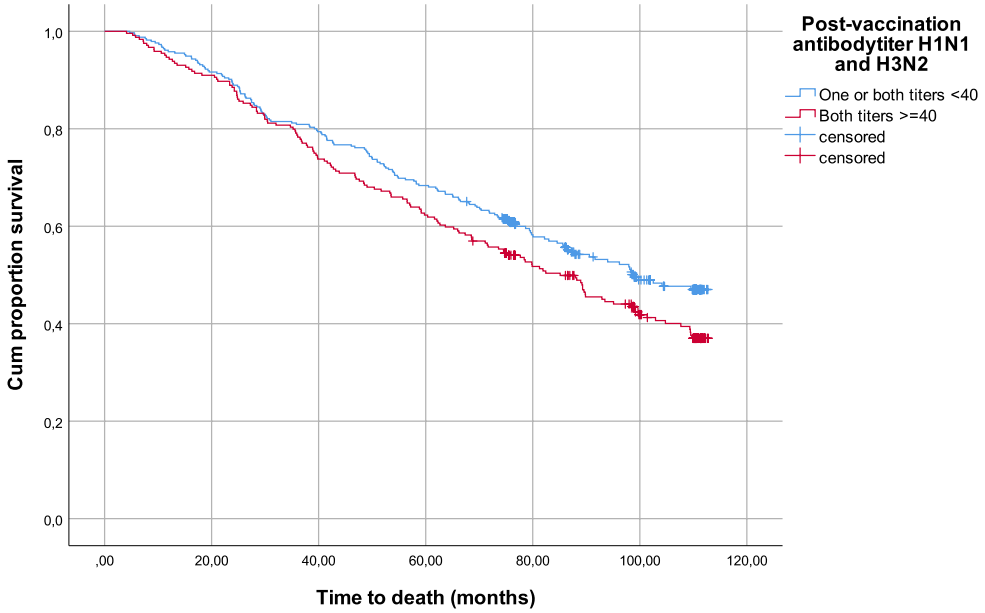

Fig. 2. Kaplan-Meier survival curve for patients with a protective titer to both H1N1 and H3N2 vs patient with no or only one protective titer to H1N1 and H3N2.

deficient compared to healthy persons, and as such may be less able to mount an effective immune response to vaccination. It is well established that the immunogenicity of influenza vaccine is lower in healthy elderly people than in healthy younger people [42]. However, only little information is available on the extent to which the influenza vaccination can induce an adequate adaptive immune response in COPD. There are indications that the immune response to influenza vaccination in COPD patients is impaired and therefore previous studies suggested adaptation of the influenza vaccination formulations for (subgroups) of patients with chronic (pulmonary) diseases because of this impaired immune response [16–18]. Although the COPD population is a somewhat older population in which the percentage of people with seroprotective titers is already somewhat lower (around 60%) [27], this percentage is still not comparable to the observed percentage of patients with seroprotective titers in the current cohort. Since almost 60% of our patients did not achieve seroprotective titers, adaptation or boosting of this vaccination might seem obvious for further studies [43]. However, our results show that the achieved levels of antibody post vaccination is not associated with relevant outcome parameters in COPD. Also in the Bergen COPD Cohort Study, seroprotective titers did not impact later risk for

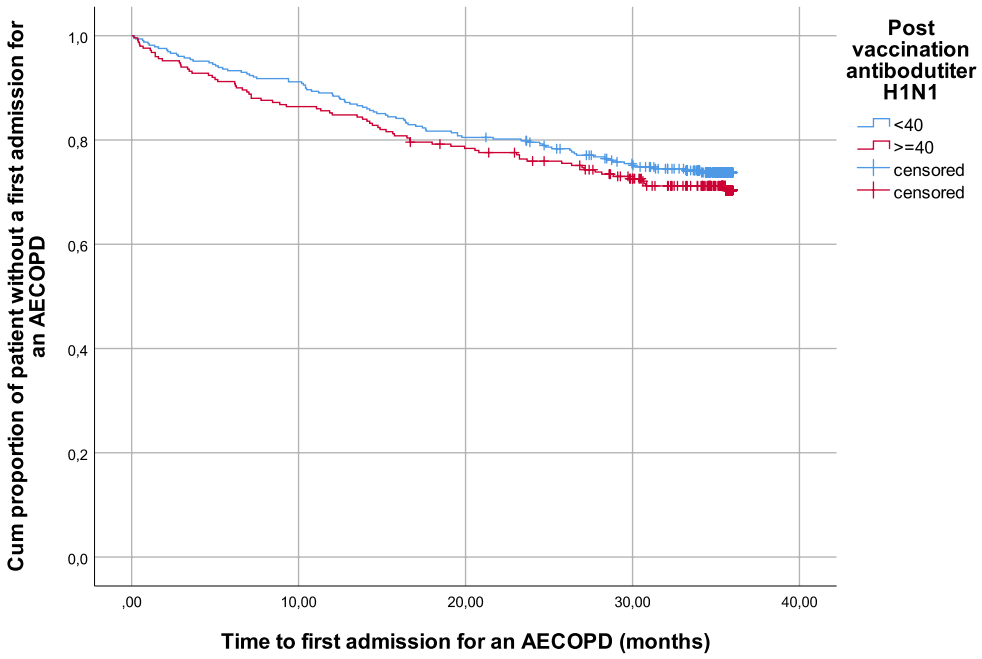

Fig. 3. Kaplan-Meier curve for a)time till first hospitalization for an AECOPD for patients with a protective titer to both H1N1 and H3N2 vs patient with no or only one protective titer to H1N1 and H3N2.

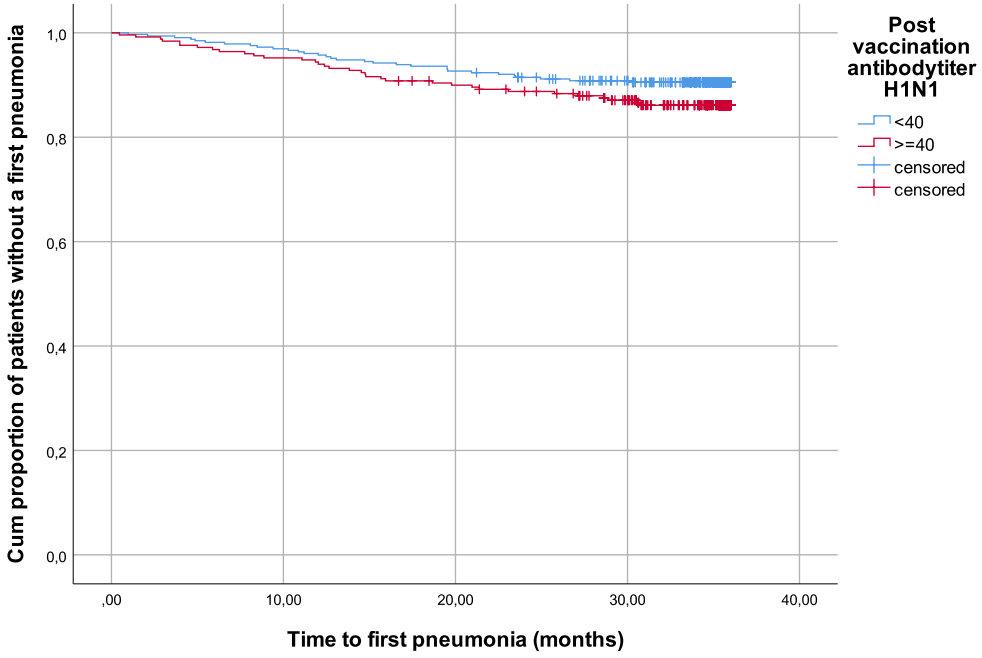

Fig. 4. Kaplan-Meier curve for time till first pneumonia for patients with either an protective titer to both H1N1 and H3N2 vs patient with no or only one protective titer to H1N1 and H3N2.

AECOPD, but this study was in patients with self-reported influenza vaccination. Furthermore, those researchers used a baseline influenza titer that could be determined at any moment in the year [18]. In our study, the antibody titers were determined in patients at fixed time intervals in which actual date of vaccination was checked at their GP, and yet we observed similar results.

With our study we used seroprotection as a marker to distinguish within our COPD population a more immune-competent group vs. a less immune-competent group. Indeed we found different baseline patient characteristics that were associated with achieving seroprotection. Patients with protective titers to both H1N1 and H3N2 were somewhat older, had a worse lung function and a higher mMRC and ADO score. Seroprotection status, as determined by the international accepted cut-off values, was however not associated with outcome. We have to keep in mind that there is no gold standard test to define a person's immune status, and achieving seroprotection is only a surrogate marker, which may only inform us for a small part of the complexity of our immune system as a whole. Besides, various other factors are known to be associated with the immune system and its competence such as nutritional status, use of immunosuppressive medication and (hemato-)

oncological disease. Unfortunately, data on nutritional status are lacking in our study, patients were however not allowed to use additional immunosuppressive medication and have another medical condition compromising survival. For many vaccines and diseases the true correlates of protection have not been established, despite the fact that threshold antibody levels have been defined. For influenza, as for COVID-19 and other infections, next to attained antibody levels, T cell immunity and B cell memory do ultimately contribute to protection against the disease.

Another possible explanation why higher seroprotective levels did not lead to better outcome could be the 'original antigenic sin', whereby immunological memory from prior (influenza) vaccinations prevents the immune system from mounting an effective response to subsequent vaccine strains of the influenza virus [44]. Imprinting of the specific molecular image of a given protein antigen into immunological memory is one of the hallmarks of immunity and the underlying principle for vaccination. A later contact with the same, for example in the form of a second contact with the virus, would trigger specific memory B- and T-lymphocytes and would result in a faster, higher and better immune response. In case the virus is mutated and one or more surface protein are changed, the memory cells would not be triggered. In case the specific memory cells would be triggered, resulting antibodies may be able to bind to the surface proteins, but not lead to virus neutralization. In that case those antibodies could block and render the response ineffective, a phenomenon termed the 'original antigenic sin' [45]. It is possible that the influenza virus can use this aspect of the original antigenic sin as a potential way of escaping from the host's immune system [46].

A remarkable finding in our study is that we observed a large difference in the humoral response between H1N1 and H3N2, with higher post-vaccination titers of H3N2. This could possibly be explained by the finding of Nath et al. who observed lower responses in those who had received the same influenza vaccine in the past [17]. In our cohort the H1N1 virus, that was used for the development of the vaccine and that was provided at the start of our cohort, when the majority of the patients were included, was similar to the virus included in the vaccines in the previous years. This was not the case for the H3N2 virus. However, we would then also expect a higher pre-vaccination titer to H1N1 compared to the pre-vaccination response to H3N2 and this was not the case.

Limitations of the current study include that the patients in our cohort were more severe, due to including a large number of patients during a severe COPD exacerbation, which limits the generalization to the more mild COPD patients. Another factor that could influence the results is the use of inhaled corticosteroids (ICS). Nath et al. showed that absolute post-vaccination titers were significantly lower in persons using ICS. While this might be explained by the systemic absorption of ICS, it is also feasible that use of ICS may be simply a marker of COPD severity [17]. In the current cohort we could not study this finding for ICS use, since almost all patients in our cohort were on ICS (>80%). Therapy adherence to ICS in our overall COMIC cohort was dependent on the type of medication prescribed, inhalation device and several disease-specific and quality of life factors [22,23,25]. The overall adherence to the different ICS prescribed in our study was optimal (≥75-≤125%) in 59% of patients, sub-optimal ≥50-<75% in 17%, poor (<50%) in 10% and we observed overuse (>125%) to ICS medications in 14%. Due to the small number of patient with a low exposure to ICS, we were not able to perform any subgroup analyses on ICS dosage. Based on the sample size calculation we needed 600 patients for this study, and although we included 795 patients within the cohort, for the current analyses we could only include 578 patients. This small difference in sample size does by no means lower the power far enough to explain the non-significant p-values.

We should also keep in mind that we have measured the response to vaccination when they first entered the cohort. The follow up extends to over 8 years. It can be assumed that they were vaccinated every year. We do not know whether they remained in their initial response group. Finally, our study lacks information about influenza associated morbidity and mortality. Therefore, we cannot exclude that achieving seroprotective titers could lead to lower influenza associated AECOPD, CAP and mortality, which then did not lead to lower overall morbidity/mortality. This was, however, not the main purpose of our study since we were interested in immune competence as a marker for overall morbidity and mortality.

In conclusion, in the COMIC study, a large well-characterized COPD cohort study, about 40% of the patients achieved seroprotective titers to H1N1 and H3N1 after the yearly influenza vaccination. Achieving seroprotection, as a surrogate marker of being immune-competent, was not associated with lower morbidity and mortality. Whether this means that the immune status is not a relevant pheno/endotype in COPD patients for the course of their COPD or that seroprotection to the influenza strains tested is just not a good (surrogate) marker to define the immune status in COPD patients needs to be further studied.

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CRediT authorship contribution statement

M. Brusse-Keizer: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **E. Citgez:** Writing – review & editing. **M. Zuur-Telgen:** Investigation, Writing – review & editing. **H. A.M. Kerstjens:** Conceptualization, Writing – review & editing. **G. Rijkers:** Methodology, Writing – review & editing. **P.D.L.P.M. VanderValk:** Conceptualization, Writing – review & editing. **J. van der Palen:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

References

[1] From the Global Strategy for the diagnosis, management and prevention of Copd, Global initiative for chronic obstructive lung diease (GOLD) 2019, Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf, 2019.

[2] B. Celli, C.G. Cote, J.M. Marín, C. Casanova, M. Montes de Oca, R.A. Méndez, et al., The body-mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease, N. Engl. J. Med. 350 (2004) 1005–1012.

[3] M.A. Puhan, J. Garcia-Aymerich, M. Frey, G. ter Riet, J.M. Antó, A.G. Agustí, et al., Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index, Lancet (London, England) 374 (9691) (2009 Aug) 704–711.

[4] B.R. Celli, N. Locantore, J. Yates, R. Tal-Singer, B.E. Miller, P. Bakke, et al., Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 185 (10) (2012 May) 1065–1072.

[5] M. Thomsen, T.S. Ingebrigtsen, J.L. Marott, M. Dahl, P. Lange, J. Vestbo, et al., Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease, JAMA 309 (22) (2013 Jun) 2353–2361.

[6] H.O. Coxson, A. Dirksen, L.D. Edwards, J.C. Yates, A. Agusti, P. Bakke, et al., The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study, Lancet Respir. Med. 1 (2) (2013 Apr) 129–136.

[7] D.M. Mannino, R. Tal-Singer, D.A. Lomas, J. Vestbo, R. Graham Barr, K. Tetzlaff, et al., Plasma fibrinogen as a biomarker for mortality and hospitalized exacerbations in people with COPD, Chronic Obstr. Pulm. Dis. (Miami, Fla) 2 (1) (2015) 23–34.

[8] M. Brusse-Keizer, M. Zuur-Telgen, J. Van Der Palen, P. Vandervalk, H. Kerstjens, W. Boersma, et al., Adrenomedullin optimises mortality prediction in COPD patients, Respir. Med. (2015).

[9] R.L. Zemans, S. Jacobson, J. Keene, K. Kechris, B.E. Miller, R. Tal-Singer, et al., Multiple biomarkers predict disease severity, progression and mortality in COPD, Respir. Res. (2017).

[10] J.M. Leung, P.Y. Tiew, M. Mac Aogáin, K.F. Budden, V.F.L. Yong, S.S. Thomas, et al., The role of acute and chronic respiratory colonization and infections in the pathogenesis of COPD, Respirology 22 (4) (2017 May) 634–650.

[11] M. Berger, B. Geng, D.W. Cameron, L.M. Murphy, E.S. Schulman, Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease, Respir. Med. 132 (2017 Nov) 181–188.
[12] M. Bafadhel, S. McKenna, S. Terry, V. Mistry, C. Reid, P. Haldar, et al., Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers, Am. J. Respir. Crit. Care Med. 184 (6) (2011) 662–671.
[13] S. Schembri, S. Morant, J.H. Winter, T.M. MacDonald, Influenza but not pneumococcal vaccination protects against all-cause mortality in patients with COPD, Thorax 64 (7) (2009 Jul) 567–572.
[14] Z. Kopsaftis, R. Wood-Baker, P. Poole, Influenza vaccine for chronic obstructive pulmonary disease (COPD), Cochrane Database Syst. Rev. 2018 (6) (2018).
[15] S. Mulpuru, L. Li, L. Ye, T. Hatchette, M.K. Andrew, A. Ambrose, et al., Effectiveness of influenza vaccination on hospitalizations and risk factors for severe outcomes in hospitalized patients with COPD, Chest 155 (1) (2019) 69–78.
[16] A. Parpaleix, L. Boyer, A. Wiedemann, C. Lacabaratz, L. Margarit, V. Enouf, et al., Impaired humoral and cellular immune responses to influenza vaccination in chronic obstructive pulmonary disease patients, J. Allergy Clin. Immunol. 140 (2017) 1754–1757.e6. United States.
[17] K.D. Nath, J.G. Burel, V. Shankar, A.L. Pritchard, M. Towers, D. Looke, et al., Clinical factors associated with the humoral immune response to influenza vaccination in chronic obstructive pulmonary disease, Int. J. COPD 9 (2013) 51–56.
[18] T.M. Eagan, J.A. Hardie, Jul-Larsen, T.B. Grydeland, P.S. Bakke, R.J. Cox, Self-reported influenza vaccination and protective serum antibody titers in a cohort of COPD patients [Internet], Respir. Med. 115 (2016) 53–59, https://doi.org/10.1016/j.rmed.2016.04.008. Available from:.
[19] E. Citgez, M. Zuur-Telgen, J. van der Palen, P. van der Valk, D. Stolz, M. Brusse-Keizer, Stable-state midrange proadrenomedullin is associated with severe exacerbations in COPD, Chest (2018).
[20] M.C. Zuur-Telgen, E. Citgez, A.T. Zuur, P. VanderValk, J. van der Palen, H.A. M. Kerstjens, et al., Predicting mortality in COPD with validated and sensitive biomarkers; fibrinogen and mid-range-proadrenomedullin (MR-proADM), COPD (2021 Dec) 1–7.
[21] E. Citgez, J. Van Der Palen, K. Koehorst-Ter Huurne, K. Movig, P. Van Der Valk, M. Brusse-Keizer, Statins and morbidity and mortality in COPD in the COMIC study: a prospective COPD cohort study, BMJ Open Respir Res. 3 (1) (2016).
[22] K. Koehorst-Ter Huurne, K. Movig, P. Van Der Valk, J. Van Der Palen, M. Brusse-Keizer, The influence of type of inhalation device on adherence of COPD patients to inhaled medication, Expet Opin. Drug Deliv. 13 (4) (2016).
[23] K. Koehorst-Ter Huurne, S. Kort, J. Van Der Palen, W.J.C. Van Beurden, K.L. L. Movig, P. Van Der Valk, et al., Quality of life and adherence to inhaled corticosteroids and tiotropium in COPD are related, Int. J. COPD (2016).
[24] M. Brusse-Keizer, M. Klatte, M. Zuur-Telgen, K. Koehorst-ter Huurne, J. van der Palen, P. VanderValk, Comparing the 2007 and 2011 GOLD classifications as predictors of all-cause mortality and morbidity in COPD, COPD 14 (1) (2017).
[25] K. Koehorst-ter Huurne, K. Movig, P. van der Valk, J. van der Palen, M. Brusse-Keizer, Differences in adherence to common inhaled medications in COPD, COPD (2015).
[26] WHO recommendations on the composition of influenza virus vaccines, Available from: https://www.who.int/influenza/vaccines/virus/recommendations/en/.
[27] L. Wijnans, B. Voordouw, A review of the changes to the licensing of influenza vaccines in Europe, Influenza Other Respi. Viruses 10 (1) (2016 Jan) 2–8.
[28] B. Brandenburg, W. Koudstaal, J. Goudsmit, V. Klaren, C. Tang, M.V. Bujny, et al., Mechanisms of hemagglutinin targeted influenza virus neutralization, PLoS One 8 (12) (2013), e80034.
[29] C.M. Trombetta, E. Montomoli, Influenza immunology evaluation and correlates of protection: a focus on vaccines, Expert Rev. Vaccines 15 (8) (2016 Aug) 967–976.
[30] D. Hobson, R.L. Curry, A.S. Beare, A. Ward-Gardner, The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses, J. Hyg. 70 (4) (1972 Dec) 767–777.
[31] K.F. Rabe, S. Hurd, A. Anzueto, P.J. Barnes, S.A. Buist, P. Calverley, et al., Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary, Am. J. Respir. Crit. Care Med. 176 (6) (2007) 532–555.
[32] W.S. Lim, M.M. van der Eerden, R. Laing, W.G. Boersma, N. Karalus, G.I. Town, et al., Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study, Thorax 58 (5) (2003 May) 377–382.
[33] R. Pellegrino, G. Viegi, V. Brusasco, R.O. Crapo, F. Burgos, R. Casaburi, et al., Interpretative strategies for lung function tests, Eur. Respir. J. 26 (5) (2005 Nov) 948–968.
[34] N. Taghizadeh, J.M. Vonk, H.M. Boezen, Lifetime smoking history and cause-specific mortality in a cohort study with 43 years of Follow-up, PLoS One 11 (4) (2016) 1–18.
[35] D.A. Mahler, C.K. Wells, Evaluation of clinical methods for rating dyspnea, Chest 93 (3) (1988) 580–586.
[36] T. van der Molen, B.W.M. Willemse, S. Schokker, N.H.T. ten Hacken, D.S. Postma, E.F. Juniper, Development, validity and responsiveness of the clinical COPD questionnaire [Internet], Health Qual. Life Outcome 1 (2003) 13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12773199%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/12773199.
[37] M.A. Puhan, N.N. Hansel, P. Sobradillo, P. Enright, P. Lange, D. Hickson, et al., Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts, BMJ Open 2 (6) (2012).
[38] K.H. Groenewegen, A.M.W.J. Schols, E.F.M. Wouters, Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD, Chest 124 (2) (2003) 459–467.
[39] P. Almagro, E. Calbo, A. Ochoa de Echagüen, B. Barreiro, S. Quintana, J.L. Heredia, et al., Mortality after hospitalization for COPD, Chest 121 (5) (2002) 1441–1448.
[40] Z. Kopsaftis, R. Wood-Baker, P. Poole, Influenza vaccine for chronic obstructive pulmonary disease (COPD), Cochrane Database Syst. Rev. 6 (6) (2018 Jun) CD002733.
[41] K.B. Wiggins, M.A. Smith, S. Schultz-Cherry, The nature of immune responses to influenza vaccination in high-risk populations [Internet], Viruses 13 (6) (2021 Jun 9) 1109. Available from: https://pubmed.ncbi.nlm.nih.gov/34207924.
[42] K. Goodwin, C. Viboud, L. Simonsen, Antibody response to influenza vaccination in the elderly: a quantitative review, Vaccine 24 (8) (2006 Feb) 1159–1169.
[43] K. Wilkinson, Y. Wei, A. Szwajcer, R. Rabbani, R. Zarychanski, A.M. Abou-Setta, et al., Efficacy and safety of high-dose influenza vaccine in elderly adults: a systematic review and meta-analysis, Vaccine 35 (21) (2017 May) 2775–2780.
[44] R.G. Webster, J.A. Kasel, R.B. Couch, W.G. Laver, Influenza virus subunit vaccines. II. Immunogenicity and original antigenic sin in humans, J. Infect. Dis. 134 (1) (1976 Jul) 48–58.
[45] G.T. Rijkers, F.J. van Overveld, The “original antigenic sin” and its relevance for SARS-CoV-2 (COVID-19) vaccination [Internet], Clin Immunol Commun 1 (2021), 13-6, https://www.sciencedirect.com/science/article/pii/S2772613421000068.
[46] J.H. Kim, I. Skountzou, R. Compans, J. Jacob, Original antigenic sin responses to influenza viruses, J. Immunol. 183 (5) (2009 Sep) 3294–3301.