


Research Article

An Independent Analysis of a Retrospective Cohort of 30,423 Covid-19 Patients Treated at IHU-Mediterranean in Marseille, France: Part 2, a Real-life Assessment of Covid-19 Vaccination efficacy

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Abstract

A cohort of 30,423 Covid-19 patients treated between March 2020 and December 2021 at the IHU-Méditerranée Infection in Marseille (France) was retrospectively analyzed in terms of treatment attempted and disease worsening factors to quantify vaccination efficacy with respect to the composite endpoint of transfer to intensive care unit or death, within a couple of months (56 days) from admission. Within limitations of the data and of the models, after adequate adjustment for sampling biases, multivariate logistic regression analyses were performed to determine unadjusted and adjusted odds ratios (ORs) for the subset of patients admitted after the Covid-19 vaccination program was started early 2021 (16,063 pts) (vaccination unadjusted OR = 0.498, 95%CI = [0.313 ; 0.794], $p = 0.003$ and adjusted OR = 0.462, 95%CI = [0.307 ; 0.670], $p < 0.001$). Statistically significant interactions ($p < 0.05$) were detected between vaccination and some covariates : favorable with the virus variant Delta and possibly obesity as well ($p=0.084$), and unfavorable with age > 89 years, Covid-19 disease severity, immunodeficiency and possibly chronic obstructive pulmonary disease (COPD) as well ($p=0.072$), confirming its capacity to worsen the Covid-19 disease condition not only in some cases of severe underlying chronic illness but also in the elderly patients and when the disease severity necessitated patient's hospital admission. Additionally, sensitivity analysis showed that vaccination had no efficacy below 50 years of age (adjusted OR = 1.35 ; 95% CI = [0.09 ; 8.84], $p = 0.781$).

Keywords: Covid-19, observational cohort, vaccination, multivariate analysis, logistic regression, propensity score matching, monocentric study, university medical institute, IHU-Méditerranée Infection

Introduction

About a year and a half after the end of the acute phase of the COVID-19 pandemic, reassessing the effectiveness of COVID-19 vaccination against severe outcomes using real-world data remains of keen interest for the scientific community and the broad public. Indeed, it turned out at the end of 2021 that vaccination did not hampered the virus inter-human transmission, as it was initially claimed by the manufacturers and their television affiliates [1-4]. The only potential benefit expected from mass vaccination was thus to reduce the number of aggravated disease conditions with the necessity of

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repeated injections at few months interval due to rapid waning of immunologic markers that were expected to reflect vaccine efficacy [5]. A retrospective cohort study conducted in the UK between December 8, 2020, and February 24, 2021 showed that at 28 days post vaccination with Oxford/AstraZeneca and Pfizer/BioNTech vaccines: “A very low proportion of hospital admissions were seen in vaccinated individuals who tested positive for SARS-CoV-2 (288/389,587, 0.07% of all patients vaccinated) providing evidence for vaccination effectiveness after a single dose” [6]. A preprint article in MedRxiv of October 2021 that has not yet been reviewed by a journal claimed that “among individuals infected with COVID-19, vaccination significantly reduced the risk of death (adj. HR: 0.20 [0.08 – 0.49])” [7].

However, the “announced” efficacy of COVID-19 vaccines proved to wane rapidly with an effectiveness on severe case of COVID-19 dropping to about 50 to 60% after 4 months [8]. Moreover, there was “some evidence for lower vaccine effectiveness in men than in women and in older individuals than in younger individuals” [8]. A critical appraisal of the marketed effectiveness of COVID-19 vaccines in reducing severe form of COVID-19 and death is all the more urgently needed since severe unwanted side effects have been associated with them. For instance, a nationwide, population-based, retrospective cohort study was conducted in Korea showing that the ChAdOx1, BNT162b2, mRNA-1273 vaccines significantly increased by a factor comprised between 1.4 and 2.6 the risk of ptosis both in the early (within 60 days) and late phase (61 – 180 days) post-vaccination [9]. The benefit/risk analysis of the vaccination appears to have moved towards increasing real life risks that would outweigh the “marketed benefits”. At the present time, it is difficult to appraise the proportion of severe adverse effects resulting from the mass vaccination in Europe and in other westernized countries due to the reluctance of general practitioners to declare to the pharmacovigilance units unexpected and expected suspected severe side effects following vaccine injection. The tip of the iceberg is revealed in the Eudravigilance database of the European Medical Agency (EMA), covering 32 countries, where 11 448 cases of Covid-19 vaccination with fatal outcomes, along with about 1 million adverse side effects, were reported by December 2022 [10]. In an observational study, from Dec 14, 2020, to June 14, 2021, the US vaccine adverse event report system (VAERS) processed 340 522 reports for 298 792 852 doses of mRNA vaccines administered in the USA: 313 499 (92.1%) were non-serious, 22 527 (6.6%) were serious (non-death), and 4496 (1.3%) were deaths [11]. A review of peer-reviewed published autopsy reports of vaccine-induced myocarditis has identified 28 deaths that have a clear causal link with COVID-19 vaccination [12]. What might very well be the tip of an iceberg of severe adverse events [13], is an

unacceptable safety record for a vaccination that is intended to be administered, even mandated, to healthy individuals, especially when there was a safe and effective treatment option at hand, as shown in Part 1 (see Part 1 [14]).

In Part 1 of our study [14], we provided an overview of the research profile of IHU-Méditerranée Infection in Marseilles (France), and explained the circumstances and need for an independent analysis of the published data set [15] of 30,423 COVID-19 patients treated between March 2020 and December 2021 to ascertain the treatment efficacy of the innovative protocols used by the IHU-Méditerranée medical teams. Part 1 has confirmed [14] the recently published results by the IHU Méditerranée group [16] in support of demonstrating treatment efficacy, using a more comprehensive statistical approach, combining propensity score matching with logistic regression analysis. Because the vaccination status of a significant proportion of the patients in the IHU Méditerranée dataset is known, in Part 2 we shall analyze the same database using the same statistical methodology to investigate whether vaccination has any efficacy towards reducing deaths or admissions to the ICU, while controlling for demographic variables and choice of treatment.

Methods

The monocentric retrospective cohort of 30,423 COVID-19 patients of IHU-Méditerranée Infection was downloaded from a public depository site DRYAD [17]. A subset consisting of a very large number of patients (N=16063) with known vaccination status (vaccinated and unvaccinated) in the time period from 23 November 2020 until 21 December 2021 was extracted. Although this is not specified in the raw data supplied to the public, we assume that all patients for whom the last dose of vaccine was injected more than 4 months previously were considered as unvaccinated. Baseline characteristics, including all the variables (also indistinctly called covariates) at disposal, were established for the two subsets and Chi-square tests were calculated to evaluate the proportion imbalance in the percentage of occurrence between vaccinated and unvaccinated patients of every baseline demographic variable, treatment received: hydroxychloroquine (HCQ), ivermectin (IVM) and azithromycin (AZ)), disease severity and disease aggravating cofactors including risk factors (diabetes, high blood pressure and obesity) and other aggravating factors (asthma, chronic obstructive pulmonary disease - COPD -, immunodeficiency, auto-immune diseases and chronic cardiac diseases). A p-value < 0.05 means there are less than 5% chances to be wrong when asserting that the proportions differ between the vaccinated and unvaccinated subgroup for a given baseline characteristic. The “period” categorical variable was excluded from the covariates list (see result

section of Part 1 of our study for detailed analysis). Of note, the treatment variables HCQ, IVM and AZ overlap (meaning they are not independent) to some extent since HCQ was administered with or without AZ and sometimes interrupted to be followed by ivermectin. In our study we have created the independent variable “AZ_only” to specify when only AZ was administered to the patient.

Variables assessing event-free survival were constructed at 42, 56, 90 and 640 days following admission at the IHU-Méditerranée either as outpatient (ambulatory care) or as inpatient (hospitalized patient), the first day was the day of admission. These variables were set either to 0 by default or to 1 when death or transfer to the intensive care unit (ICU) occurred in the period of time considered. Multivariate analysis using logistic models regressed on the baseline covariates was performed with the software package R version 4.3.1 [18] to assess the effect of vaccination on event-free survival. Detail of the statistical calculations performed is described in Part 1 of our study [14].

Results

Baseline characteristics:

Baseline characteristics of the subset “Vaccination” are collected in Table 1 showing imbalances ($p < 0.001$) for most of the variables and risk factor covariates between the treatment and control groups.

Analysis of the Variables (covariates) Independence

Tables 2 presents the detailed analysis of the categorical variable “Variant” in the subset “Vaccination”. It shows that the number of events (death or transfer to ICU within 56 days from admission) is homogeneously distributed (ca. 1.4 %) in the unvaccinated patients across the different variants that have appeared between Nov. 23, 2020 and Dec. 21, 2021. Except for the “null” category (data missing or not determined) which was multicorrelated to other categories (see Part 1 of our study, [14]), the variant categories were independent from each other and thus the categorical variable “Variant” is well suited for logistic regression.

In Part 1 of our study [14] we noted that there was a large chunk of missing data for the covariates describing disease aggravating factors in the dataset of IHU-Méditerranée. In fact, for the “Period” category ≤ 3 , all these covariates had null values. We had used a statistical procedure to deal with the issue, possibly introducing bias in the results. However, in the present case, the Vaccination subset corresponds to the “Period” ≥ 4 where all risk factors and disease aggravating factors covariates are informed. Table 3 shows that these covariates were actually highly correlated among themselves. Patients at risk who experienced one event (ICU transfer or death within 56 days) presented on average a ratio of 1.92 (317/165) disease aggravating factors. 77.8% (168/216) of

the events were experienced by inpatients, 73.9% (216/287) of which presented at least one disease aggravating factors (comorbidities). 57.4% (74/129) of the inpatients at risk, who experienced an event, presented at least 2 disease aggravating factors.

Analysis of the events distribution across risk factors and aggravating factors

Tables 4a and 4b show the distribution of events across all covariates in the women and men subgroups, respectively. Covariates with zero event (highlighted in orange color) either in the vaccinated group or in the control group may have some impact on the accuracy of the logistic regression results because a null propensity (zero score) does not reflect reality, although calculation can still be performed.

Propensity score matching

The results of the propensity score matching (PSM) procedure using Optimal Full Matching (“full” option) to correct for imbalances between treatment and control subgroups in the number of patients in every subgroups of the Vaccination subset are assessed in Figure 1. Calculations were performed for the 3 different models (a), (b) and (c). In model (a) all covariates were included. In model (b) disease aggravating factors were removed except risk factors (diabetes, high blood pressure and obesity) and in model (c) both risk factors covariates and disease aggravating factor covariates were removed. Figures of merit of the PSM calculations are presented in the supplementary material section (appendices 1a, 1b and 1c). Each subset required several minutes of central processing unit time (ca. 5 minutes). The Love plots calculated for the 3 different models (a) (b) and (c) showed the absolute standardized mean differences (ASMD) between treatment and control subgroups, before and after matching for each covariate (Figure 1).

Ideally, ASMDs should approach 0.0 and be lower than the ASMDs for unmatched subgroups. For instance, when all covariates were included (model (a)) we noted that the procedure could not converge to improve balance for the covariates SEX and COPD that were slightly deteriorated. In model (b) it is the covariate “Inpatient” that is deteriorated instead of being improved. In fact, PSM allowed improvement in all covariate subgroups only when risk factors and disease aggravating were removed in model (c). The reason is the high level of correlation between all these covariates (see previous section). Overall, all ASMDs ≤ 0.1 are usually considered as acceptable matching [19,20]. Here we have this condition fulfilled, especially for model (a) with most values close to 0.05 insuring high reliability for this particular model which includes all confounding covariates. Density plots are shown to illustrate the efficacy of the PSM balancing procedure for the categorical covariates “Age” and “Variant” in model (c).

Table 1: Baseline characteristics for the “Vaccination” subset covering the pandemic periods from Nov. 23, 2020 until Dec. 21, 2021

	All		Vaccinated		Not vaccinated		p-value*
	N	%	N	%	N	%	
N	16063		2124		13939		
Women	7532	46.9	991	46.7	6541	46.9	0.906
Men	8531	53.1	1133	53.3	7398	53.1	0.914
Age (yrs)							
< 50	8627	53.7	953	44.9	7674	55.1	< 0.001
50-69	5898	36.7	827	38.9	5071	36.4	0.13
70-89	1483	9.2	332	15.6	1151	8.3	< 0.001
> 89	55	3.4	12	0.6	43	0.3	0.093
SARS-CoV-2 variants							
Wuhan	0		0		0		
B.1.160 (Marseille 4)	1601	10	27	1.3	1574	11.3	< 0.001
B.1.7.7 (UK)	4764	29.7	333	15.7	4431	31.8	< 0.001
B.1.617.2 (Delta)	4973	31	1355	63.8	3618	26	< 0.001
Outpatients only	14868	92.6	1989	93.6	12879	92.4	0.701
Inpatients only	728	4.5	89	4.2	639	4.6	0.47
Out- and In-patients	467	2.9	46	2.2	421	3	0.04
Diabetes	1035	6.4	195	9.2	840	6	< 0.001
High blood pressure	2214	13.8	402	18.9	1812	13	< 0.001
Obesity	3272	20.4	417	19.6	2855	20.5	0.478
Patient with ≥ 2 of the 3 factors above	1284	8	228	10.7	1056	7.6	< 0.001
COPD	222	1.3	31	1.5	191	1.4	0.823
Cancer	698	4.3	145	6.8	553	4	< 0.001
Auto-immune diseases	870	5.41	154	7.3	716	5.1	< 0.001
Chronic cardiac diseases	428	2.7	95	4.5	333	2.4	< 0.001
ICU transfer	156	1	13	0.6	143	1	0.093
Death							
days							
42	73	0.5	6	0.3	67	0.5	0.277
56	77	0.5	7	0.3	70	0.5	0.368
90	80	0.5	8	0.3	72	0.5	0.494
640	110	0.7	12	0.6	98	0.7	0.566
Received HCQ	13258	82.5	1631	76.8	11627	83.4	0.003
Received HCQ-AZ	12948	80.6	1599	75.3	11349	81.4	0.028
Received HCQ only	296	1.8	31	1.5	265	1.9	0.194
Received AZ only	1025	6.4	114	5.4	911	6.5	0.036
Received ivermectin	1577	9.8	398	18.7	1179	8.5	< 0.001
Received HCQ and ivermectin	292	1.8	66	3.11	226	1.6	< 0.001

*Chi-square test for the equality of proportion: p < 0.05 indicates that the proportion statistically differ between the two groups for the considered baseline characteristic.

Table 2: “Variant” variable analysis: Vaccination subset at 56 days

Variant	Patients		Vaccinated		Events in vaccinated		Events in control group	
	N	(%)	N	(%)	N	(%)	N	(%)
Wuhan	0		0	(0.0)	0	(0.0)	0	(0.0)
Marseille 4	1601		27	(1.7)	0	(0.0)	24	(1.5)
UK	4764		333	(7.0)	8	(2.4)	71	(1.6)
Delta	4973		1355	(27.2)	11	(0.8)	51	(1.4)
others	1079		88	(8.2)	0	(0.0)	19	(1.9)
null	3646		321	(8.8)	0	(0.0)	30	(0.9)
total	16063		2124	(13.2)	19	(0.9)	195	(1.4)

Table 3: Events distribution at 56 days for Covid-19 disease Aggravating Covariates

	Vaccination subset reduced to “Period” ≥ 4							
	Vaccinated (N=2124)				Unvaccinated (N=13939)			
	N	%	Events	%	N	%	Events	%
Patients total	2124	-	19	0.9	13939	-	195	1.4
Inpatient	135	6.4	16	11.9	1060	7.6	151	14.3
Risk factors covariates								
Diabetes	195	9.2	5	2.6	840	6	45	5.4
Obesity	417	19.6	5	1.2	2855	20.5	91	3.2
High blood pressure	402	18.9	8	2	1812	13	79	4.4
Asthma	184	8.7	1	0.5	1022	7.3	12	1.2
COPD	31	1.5	2	6.5	191	1.4	11	5.8
Cancer	145	6.8	2	1.4	553	4	17	3.1
Immunodeficiency	62	2.9	4	6.5	249	17.9	6	2.4
Auto-immune diseases	154	7.3	1	0.6	716	5.1	6	0.8
Chronic cardiac diseases	95	4.5	1	1.1	333	2.4	19	5.7
Total redundant number of events¹			29				286	
Patient at risk²	1026	48.3	13	1.3	5858	42	153	2.6
Inpatient at risk³	95	4.5	10	10.5	729	5.2	121	16.6
Inpatient not at risk⁴	40	2.4	6	15	331	2.4	30	9.1
Inpatient with one aggravating cofactor	40	1.9	3	7.5	355	2.5	52	14.6
Inpatient with ≥ 2 aggravating cofactors	52	2.4	6	11.5	354	2.5	68	19.2

¹a number of patients that experienced a defined event (ICU transfer or death with 56 days) had more than 1 baseline disease aggravating factors.

²patients presenting at least one disease aggravating cofactor.

³inpatients with at least one disease aggravating cofactor.

⁴inpatients with no disease aggravating cofactor.

Table 4a: Analysis of events at 56 days in women subgroup (N=8531)

	Vaccination Status					
	Vaccinated			Unvaccinated		
	N	Event	%	N	Event	%
Women	1133	7	0.6	7398	61	0.8
Age (yrs)						
< 50	548	1	0.2	4110	4	0.1
50-69	427	3	0.7	2637	32	1.2
70-89	151	1	0.7	629	22	3.5
> 89	7	2	28.6	22	3	13.6
SARS-CoV-2 variants						
Wuhan	0	0		0	0	0
B.1.160 (Marseille 4)	22	0		836	8	
B.1.1.7.7 (UK)	165	2		2295	27	
B.1.617.2 (Delta)	716	5		1908	19	
Others	44	0		504	3	
Null	186	0		1855	4	
Inpatients	53	6	11.3	452	47	10.4
Treatments						
HCQ	883	2	0.2	6098	28	0.5
AZ only	55	2	3.6	519	14	2.7
Ivermectin	213	3	1.4	664	19	2.9
Risk factors						
Diabetes	74	1	1.4	404	16	4
High blood pressure	186	3	0.5	881	27	3.1
Obesity	202	2	1	1401	28	2
Comorbidities						
COPD	16	0	NA	95	2	2.1
Cancer	82	1	1.2	373	5	1.3
Asthma	114	1	0.9	633	5	0.8
Immunodeficiency	30	1	3.3	143	2	1.4
Auto-immune diseases	119	1	0.8	546	3	5.5
Chronic cardiac diseases	17	0	NA	84	2	2.4
Events summary		7	0.6		61	0.8
ICU transfer		4	0.4		41	0.6
Death	days					
	42	3	0.3		25	0.3
	56	3	0.3		25	0.3
	90	4	0.4		27	0.4
	640	5	0.5		38	0.5

Table 4b: Analysis of events at 56 days in men subgroup (N=7532)

	Vaccinated			Unvaccinated		
	N	Event	%	N	Event	%
Men	991	12	1.2	6541	136	2.1
Age (yrs)						
< 50	405	1	0.2	3564	23	0.6
50-69	400	5	1.3	2434	66	2.7
70-89	181	6	3.3	522	40	7.7
> 89	5	0	NA	21	5	23.8
SARS-CoV-2 variants						
Wuhan	0			0		
B.1.160 (Marseille 4)	2	0		738	16	2.2
B.1.7.7 (UK)	168	6		2136	44	2.1
B.1.617.2 (Delta)	639	6	3.6	1710	32	1.9
Others	44	0	0.9	487	16	3.3
Null	135	0		1470	26	1.8
Inpatients	82	10	12.2	608	104	17.1
Treatments						
HCQ with or without AZ	748	6	0.8	5529	89	1.6
AZ only	59	2	3.4	392	22	5.6
Ivermectin	185	5	2.7	515	29	5.6
Risk factors						
Diabetes	121	4	3.3	436	29	6.7
High blood pressure	216	5	2.3	931	52	5.6
Obesity	215	3	1.4	1454	63	4.3
Comorbidities						
COPD	5	2	40	96	9	9.4
Cancer	63	1	1.6	180	12	6.7
Asthma	70	0	NA	389	7	1.8
Immunodeficiency	106	3	2.83	32	4	12.5
Auto-immune diseases	35	0	NA	170	3	NA
Chronic cardiac diseases	78	1	1.2	249	17	6.8
Events summary		12	1.2		134	2
ICU transfer		9	0.9		100	1.5
Death	days					
	42	3	0.3	42	0.6	
	56	4	0.4	45	0.7	
	90	4	0.4	45	0.7	
	640	7	0.7	60	0.9	

Vaccination subset

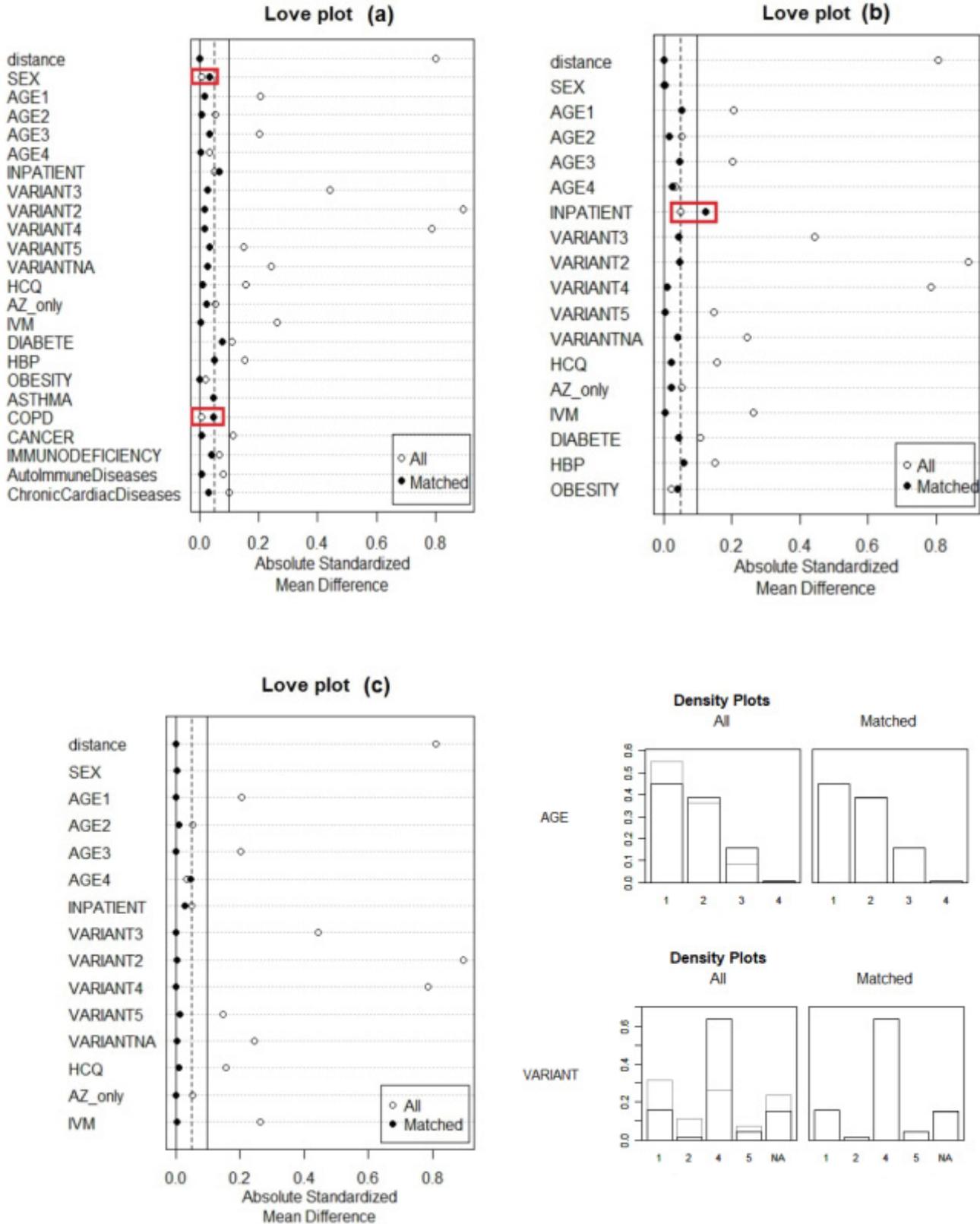


Figure 1: Propensity Score Optimal Full Matching

Logistic regression model - multivariate analysis

The logistic models regressed on all the IHU-Méditerranée baseline predefined covariates (except for the “Period” covariate that was excluded) converged. Results at 56 days cutoffs are presented for models (a), (b) and (c) in Table 5. Results for model (a) with PSM at 42, 56, 90 and 640 days cutoffs using full optimal matching are presented in Table 5b. One can notice a regular decrease of vaccination efficacy with the cutoff time increasing. There is an absolute 6-7% decrease in the reduction of the risk of events between 42 days and 640 days cutoffs indicating that after Covid-19 remission, vaccinated patients survive less well over the next two years than unvaccinated patients.

Multivariate logistic regressions with adjusted ORs at 56 days cutoff using Optimal Full Matching are presented with all covariates (model (a)), with only risk factors covariates (model (b)) and without risk factors and comorbidities covariates (model (c)) for the “Vaccination” subset (Table 6a, Table 6b and Table 6c). The reference for the “Variant” categorical variable was set to B.1.1.7 (UK) instead of B.1.160 (Marseille 4) because of too few vaccinated individuals and an absence of event in the vaccinated group for the variant Marseille 4 category (see Table 2) leading to strong model bias.

In all models the calculated OR evaluating the average treatment effect in the treated patients (ATT) was statistically significant indicating the overall efficacy of vaccination. Adjusted treatment ORs were comprised between 0.28 and 0.46 with respect to no vaccination, that is to say a reduction of the risk of being transferred to ICU or dying reduced by 54% (model (a)) to 72% (model (c)). We see the calculated

treatment OR is quite sensitive to the inclusion of risk factors and comorbidities in the model because many covariates are partial confounders. Thus, the effect of vaccination must be carefully appraised taking into account all covariates. A too simplistic approach (model(c)) may actually lead to an overestimate of the vaccination benefit. The inclusion of risk factors and comorbidities covariates in the models largely suppressed this apparent global effect of vaccination (model (c)). In this respect, according to model (a) with risk factors and comorbidities covariates included the general trend of the vaccination effect is around an absolute risk reduction of 54% only. The problem with vaccination is that it interacts negatively with certain categories of patients as we show in the next section (Interaction analysis).

Analysis of the covariates ORs (that assess their separate effects independently of other covariates by setting all their values to 0) showed that the variables “sex”, “age” and “inpatient”, describing the patient demographic characteristics and disease severity, all had a statistically significant impact ($p < 0.001$) with comparable OR values trends between model (a), (b) and (c). The odds ratio was very favorable for women whereas it became very unfavorable as age increases and with disease severity. The trends are consistently the same indicating model robustness in this respect. For age categories ≥ 50 years, a statistically significant increase in the risk of event ($OR \gg 1$) was observed for each age subgroup with respect to patients of age < 50 years.

$OR = 13.9$ for the covariate “inpatient” (model(a)) means that hospitalized patients had overall 14 times more chances to be transferred to ICU or to die than ambulatory (day hospital) patients.

Table 5a: Treatment ORs for the different logistic regression models calculated at 56 days cutoff using PSM with Optimal Full Matching

Model	“Vaccination” subset					
	OR	95%CI	p-value	OR	95%CI	p-value
	unadjusted after PSM			adjusted after PSM		
a	0.498	[0.313 ; 0.794]	0.003	0.462	[0.307 ; 0.670]	< 0.001
b	0.393	[0.222 ; 0.698]	0.001	0.336	[0.209 ; 0.516]	< 0.001
c	0.353	[0.186 ; 0.669]	0.001	0.278	[0.162 ; 0.450]	< 0.001

Table 5b: Logistic regression models treatment adjusted ORs calculated at different time cutoffs for model (a) (PSM with Optimal Full Matching)

Cutoff (days)	Vaccination subset			Vaccination subset		
	unadjusted ORs after PSM			adjusted ORs after PSM		
	OR	95%CI	p-value	OR	95%CI	p-value
42	0.475	[0.298 ; 0.757]	0.002	0.438	[0.288 ; 0.640]	< 0.001
56	0.498	[0.313 ; 0.794]	0.003	0.462	[0.307 ; 0.670]	< 0.001
90	0.521	[0.329 ; 0.826]	0.006	0.486	[0.326 ; 0.700]	< 0.001
640	0.542	[0.355 ; 0.827]	0.005	0.508	[0.357 ; 0.704]	< 0.001

As for the “Variant” categorical variable, results were very unstable across model (a), (b) and (c) depending strongly on whether or not risk factors and other comorbidities covariates are included in the model, reflecting intrication between the “Variant” variable and comorbidities. There was no statistically significant impact ($p > 0.05$) for the Marseille 4, UK and Delta main variants with respect to the risk of event in the complete model (model (a)) nor for the categories “other” variant and “null” variant. Regarding the effect of other treatments, hydroxychloroquine (HCQ) (with or without azithromycin and sometimes with ivermectin subsequently) was significantly associated with a risk reduction in both models (a) and (b) whereas ivermectin (IVM) was significantly associated with an increase of the risk of event in the 3 models (a), (b) and model (c). The meaning of these ORs must not be mistaken with a measured average treatment effect. However, they indicate the relative risk of event in the overall vaccination subset with respect to the covariate HCQ, AZ and Ivermectin, respectively. OR < 1 for HCQ must be interpreted as patients having less risk of experiencing event when having received HCQ and OR > 1 for ivermectin as patients having a higher risk of event when having received ivermectin. Indeed ivermectin could have been prescribed to patients with a more severe illness. Azithromycin alone was not associated with any significant effect on the risk of event in any of the 3 models.

The percentage of events in the subgroups of patients having received HCQ and ivermectin is 5.82% (17/292) and ivermectin only was 3.11% (40/1285). However, in the “Vaccination” subset the overall percentage of events dropped to hardly 1.34%. Without additional information on the patients disease condition, these results do not necessarily mean a deleterious effect of ivermectin, but could be due to the fact that ivermectin was administered in first intention or second intention in patients with aggravated disease conditions with a markedly higher risk of event. Moreover, it is worth noting that the proportion of patients having received ivermectin in the vaccinated subgroup is 18.7% that is twice as much as in the unvaccinated subgroup (8.5%) (Table 1).

Interactions analysis

All the detected interactions for the models are listed in Table 7. The complete model (a) detected statistically significant interactions of some covariates with the treatment in the “Vaccination” subset : favorable with variant Delta (VARIANT4) and unfavorable with “Age > 89 years”, “Inpatient” and “Immunodeficiency”. We report also a possible interaction with COPD (this interaction has a p-value < 0.05 when the covariate “AZ_only” is excluded from the model (a)). In model (b) favorable interactions between vaccination and “ $69 < \text{Age} \leq 89$ ” and with the variant Delta

Table 6a: Multivariate logistic regression model (a) for the “Vaccination” subset at 56 days cutoff (PSM with Optimal Full Matching)

	“Vaccination” subset (N= 16063)		
Treatment actor	OR*	95%CI	p-value
Vaccination	0.462	[0.307 ; 0.670]	< 0.001
Demography			
Sex (female/male)	0.533	[0.431 ; 0.657]	< 0.001
Age < 50 yrs (reference)			
Age 50-69 (vs ref.)	2.023	[1.457 ; 2.852]	< 0.001
Age 70-89 (vs ref.)	2.876	[2.021 ; 4.144]	< 0.001
Age > 89 (vs ref.)	3.865	[1.830 ; 7.751]	< 0.001
Disease severity			
Inpatient (vs ref.)	13.96	[11.242 ; 17.384]	< 0.001
Variant			
B.1.7.7 (UK) (reference)			
B.1.160 (Marseille 4)	1.127	[0.517 ; 2.217]	0.744
B.1.617.2 (Delta)	1.006	[0.777 ; 1.304]	0.966
Others	0.902	[0.568 ; 1.398]	0.653
Null	0.8085	[0.562 ; 1.152]	0.38
Other treatments			
HCQ	0.726	[0.530 ; 1.000]	0.05
Ivermectin	1.74	[1.270 ; 2.379]	< 0.001
AZ only	0.813	[0.510 ; 1.287]	0.38
Comorbidities			
Diabetes	1.151	[0.904 ; 1.460]	0.25
Obesity	2.507	[2.023 ; 3.101]	< 0.001
High blood pressure	1.041	[0.830 ; 1.304]	0.728
Asthma	0.325	[0.189 ; 0.524]	< 0.001
COPD	4.554	[3.245 ; 6.316]	< 0.001
Cancer	1.003	[0.722 ; 1.369]	0.985
Immunodeficiency	1.71	[1.131 ; 2.516]	0.008
Auto-immune diseases	0.592	[0.345 ; 0.954]	0.04
Chronic cardiac diseases	1.05	[0.778 ; 1.403]	0.745

*if not indicated otherwise ORs are with respect to covariates values set to zeros

Table 6b: Multivariate logistic regression model (b) for the “Vaccination” subset at 56 days cutoff (PSM with Optimal Full Matching)

	“Vaccination” subset (N= 16063)		
Treatment actor	OR*	95%CI	p-value
Vaccination	0.336	[0.209 ; 0.516]	< 0.001
Demography			
Sex (female/male)	0.416	[0.331 ; 0.519]	< 0.001
Age < 50 yrs (reference)			
Age 50-69 (vs ref.)	2.919	[1.976 ; 4.406]	< 0.001
Age 70-89 (vs ref.)	7.13	[4.817 ; 10.850]	< 0.001
Age > 89 (vs ref.)	8.436	[4.255 ; 16.483]	< 0.001
Disease severity			
Inpatient (vs ref.)	14.119	[11.331 ; 17.650]	< 0.001
Variant			
B.1.7.7 (UK) (reference)			
B.1.160 (Marseille 4)	0.347	[0.111 ; 0.842]	0.036
B.1.617.2 (Delta)	0.813	[0.634 ; 1.046]	0.104
Others	0.54	[0.298 ; 0.917]	0.03
Null	0.31	[0.206 ; 0.451]	< 0.001
Other treatments			
HCQ	0.454	[0.325 ; 0.634]	< 0.001
AZ only	0.655	[0.407 ; 1.047]	0.079
Ivermectin	1.587	[1.135 ; 2.213]	0.007
Risk factors			
Diabetes	0.946	[0.721 ; 1.234]	0.685
Obesity	1.732	[1.378 ; 2.171]	< 0.001
High blood pressure	0.8	[0.629 ; 1.014]	0.066

*if not indicated otherwise ORs are with respect to covariates values set to zeros

Table 6c: Multivariate logistic regression model (c) for Vaccination subset at 56 days cutoff (PSM with Optimal Full Matching) without risk factors and aggravating factors (comorbidities)

	“Vaccination” subset		
Treatment factor	OR*	95%CI	p-value
Vaccination	0.278	[0.162 ; 0.450]	< 0.001
Demography			
Sex (female/male)	0.248	[0.186 ; 0.326]	< 0.001
Age < 50 yrs (reference)			
Age 50-69 (vs ref.)	2.878	[1.866 ; 4.576]	< 0.001
Age 70-89 (vs ref.)	12.41	[8.218 ; 19.430]	< 0.001
Age > 89 (vs ref.)	82.807	[45.843 ; 151.433]	< 0.001
Disease severity			
Inpatient	5.839	[4.513 ; 7.548]	< 0.001
Variant			
B.1.7.7 (UK) (reference)			
B.1.160 (Marseille 4)	1.905	[0.718 ; 4.526]	0.168
B.1.617.2 (Delta)	2.451	[1.760 ; 3.474]	< 0.001
Others	1.544	[0.790 ; 2.876]	0.186
Null	0.514	[0.281 ; 0.902]	0.025
Other treatments			
HCQ	0.808	[0.531 ; 1.226]	0.319
AZ only	1.238	[0.677 ; 2.224]	0.485
Ivermectin	5.1	[3.327 ; 7.814]	< 0.001

*if not indicated otherwise ORs are with respect to covariates values set to zeros

are also found. The favorable interaction with the variant Delta and the unfavorable interaction between vaccination and “Inpatient” was consistently found in the 3 models indicating the robustness of these two findings, especially of the latter.

It must be pointed out that the OR of an interaction is the risk of event calculated for a product covariate (eg. Vaccination*Inpatient) taking the value 1 relative to the situation of the three other possibilities where this product is 0 after propensity score matching to correct for imbalances between covariate distribution between vaccinated and unvaccinated patients. For instance, unfavorable interaction of vaccination with the inpatient status means that the risk of event is higher in the group of vaccinated inpatients than in the group constituted of unvaccinated inpatients, vaccinated outpatients and unvaccinated outpatients. In fact, one can see easily that there were 65% more events in the group of vaccinated inpatients not at risk compared with the unvaccinated inpatients not at risk (see Table 3).

Table 7: Treatment: covariate interactions detected in the logistic regression models (PSM with Optimal Full Matching) at 56 days cutoff.

Interaction	OR	95%CI	p-value
“Vaccination” subset			
Model (a)			
VACCINATION:AGE4	15.149	[1.460 ; 164.864]	0.022
VACCINATION:INPATIENT	8.071	[2.479 ; 34.612]	0.002
VACCINATION:VARIANT4	0.201	[0.075 ; 0.531]	0.001
VACCINATION:OBESITY	0.409	[0.142 ; 1.098]	0.084
VACCINATION:COPD	4.773	[0.781 ; 25.577]	0.072
VACCINATION:IMMUNODEFICIENCY	10.958	[2.702 ; 44.150]	< 0.001
VACCINATION:ChronicCardiacDiseases	0.168	[0.014 ; 1.028]	0.09
Model (b)			
VACCINATION:AGE3	0.124	[0.020 ; 0.991]	0.031
VACCINATION:INPATIENT	5.017	[1.468 ; 22.664]	0.018
VACCINATION:VARIANT4	0.324	[0.108 ; 0.973]	0.042
Model (c)			
VACCINATION:AGE3	0.078	[0.011 ; 0.805]	0.015
VACCINATION:INPATIENT	12.536	[3.181 ; 70.686]	< 0.001
VACCINATION:VARIANT4	0.091	[0.026 ; 0.319]	< 0.001

Sensitivity analysis

To assess the relative efficacy of vaccination with respect to age and sex we performed additional sensitivity calculations. Due to a reduced number of patients compared with the complete “Vaccination” subset the models could not converge (spurious ORs and confidence intervals) when all covariates were included in the logistic regression. However, removing the “AZ only” covariate from the models fairly allowed their convergence (see Appendix 2 for complete calculation results).

Vaccination subset with age < 50 years (N=8627): when we reduced the Vaccination subset to age ≤ 50 years 50 years (“Age” = 1) vaccination had no efficacy: unadjusted OR = 1.32; 95%CI = [0.48; 3.66], $p = 0.588$ and adjusted OR = 1.35 ; 95%CI = [0.09 ; 8.84], $p = 0.781$.

Vaccination subset with age ≥ 50 years (N=7436): when we reduced the Vaccination subset to age ≥ 50 years (“Age” ≥ 2) vaccination efficacy was: unadjusted OR = 0.406 ; 95%CI = [0.251 ; 0.657], $p < 0.001$ and adjusted OR = 0.335; 95%CI = [0.183 ; 0.572], $p < 0.001$ (see complete result in Appendix 2a in supplementary material).

Vaccination subset reduced to women (N = 8531): vaccination unadjusted OR = 0.518, 95%CI = [0.259 ; 1.040] $p = 0.0629$ and adjusted OR = 0.472; 95%CI = [0.238 ; 0.855] $p = 0.0203$ (see Appendix 2b for complete data). A weakly significant unfavorable interaction was found with immunodeficiency OR = 2.447, 95%CI = [1.319 ; 1.855] $p = 0.0636$ (see complete data in Appendix 2b).

Vaccination subset reduced to men (N = 7532): vaccination unadjusted OR = 0.311, 95%CI = [0.164 ; 0.588] $p < 0.001$ and adjusted OR = 0.222, 95%CI = [0.107 ; 0.418] $p < 0.001$. Statistically significant unfavorable interactions were found between vaccination and immunodeficiency: OR = 6.027, 95%CI = [1.958 ; 3.078] $p = 0.0021$; and vaccination and COPD: OR = 4.1000 95%CI = [1.660 ; 2.470] $p = 0.0135$ (see complete data in Appendix 2c).

Discussion

The main concern in Part 2 of our study was the evaluation of the Covid-19 vaccination efficacy based on a large corpus of real life data provided by a very large single institution cohort treated for Covid-19 on both an outpatient and inpatient basis. Our aim was to establish a result on vaccination efficacy that allows side by side comparison with Part 1 of our study where we evaluated the efficacy of the hydroxychloroquine-azithromycin (HCQ-AZ) combination treatment deployed at the IHU Méditerranée [14]. Since the same single institution cohort was rigorously analyzed and the same statistical methods were used to assess the HCQ-AZ and the vaccination average effects on the treated patients, it is expected that the results convey meaningful information on the respective merit of the two approaches, within the limitations of the statistical method used (see article Part 1 of our study for the detailed description of the limitations) [14].

Importantly, no statistical significant interaction was detected between vaccination and the variable HCQ in all models constructed for the “Vaccination” subset. The 3 models

constructed consistently assess an efficacy of vaccination with an absolute risk reduction of events (ICU transfer or death) comprised between 54% and 72% in the vaccinated subgroup with respect to the unvaccinated subgroup. It must be pointed out that model (a) with 54% absolute risk reduction is the most accurate model because it includes all covariates that are partial confounders (multi-correlated among themselves). Despite the number of covariates and their intrication, the PSM procedure converged for this model insuring its reliability. Similarly, in Part 1 of our study, the efficacy of the HCQ-AZ combination treatment was consistently established around 54-58% with no statistically significant interaction detected with the covariate vaccination.

Although tempting, a like for like comparison of these two numbers would be misleading as a vaccination intervention entails several issues, that are preventing it from being considered as a treatment. Firstly, the approval of vaccination presumed the absence of efficacy of treatments, which is not the case. Secondly, vaccination posed an ethical problem since it presents an irreversible modification of the immune system of healthy individuals, with the risk of inducing potentially severe unwanted or unknown side effects due to the experimental nature of the genetic therapies. Third, it was previously known that vaccination against SARS coronavirus could induce an aggravated disease state in some healthy individuals (see further sections in the discussion). And fourth, peaks of contamination were observed within 2-3 weeks subsequent to mass vaccination episodes. Therefore, vaccination efficacy ought to be measured in a different manner, as a contingent efficacy, via more advanced probabilistic methods including a context wider than the IHU dataset.

Additionally, the respective merits of these approaches for combined HCQ-AZ therapy or vaccination must be assessed also taking into account their economical costs, their easiness to administrate and rapidity of access, as well as their short term and long term side effects (benefit/risk ratio). Sensitivity assessment conducted in the "Vaccination" subset reduced to age < 50 years shows that no statistical efficacy of vaccination could be detected in terms of risk of ICU transfer or death for this category of age. Indeed, in this category the percentage of events was very low, $\leq 0.2\%$ in women and $\leq 0.6\%$ in men, with in fact proportionally more events in vaccinated women than in unvaccinated women. This clearly raises the question of the relevance of vaccination for age < 50 years, especially if we consider that vaccination failed to diminish transmission and contamination [1-5].

Another point of potential concern was the difference in vaccination efficacy with respect to sex. We find that vaccination is more effective in reducing the risk of event in men than in women with adjusted OR of 0.222 and 0.472,

respectively. In Part 1 of our study [14], we found the same trend for the efficacy of the combined treatment HCQ-AZ between men and women. We ascribed the difference to the propensity of women to respond to an infection and look for treatment faster than men, thus reducing the relative effectiveness of vaccination. The non-negligible absolute 7% decay over 640 days (21 months) of the measured vaccination efficacy, calculated at various event-free survival cutoffs (Table 5b), should be regarded cautiously. It could be ascribed to either a deleterious long-term effect of vaccination on event-free survival (EFS), regardless of the fact that patients have maintained or not their vaccination status after Covid-19 remission, or that there was a bias between vaccinated and unvaccinated patients, with a weaker general health condition in vaccinated patients, or conversely that healthier patients were less prone to accept vaccination, a possible bias that could not be reflected by the disease aggravating covariates included in the model. However, a long-term deleterious effect of vaccination cannot be excluded as well.

Finally, although results of interactions detected between treatment and covariates are often considered with caution because they are very sensitive to the inclusion confounder covariates, they are perhaps the most important considerations when debating the benefit of vaccination. Indeed the situation is complex since vaccination was officially initially supposed to stop the chain of transmission by preventing the development of the Covid-19 disease in individuals, and shortly after, only supposed to prevent severe forms in infected patients. However, a statistically significant unfavorable interaction was detected, consistently in the 3 different models, between vaccination and the "inpatient" status that reflects the severity of the disease. Despite the claim of the vaccine makers and proponents that Covid-19 vaccine reduced the occurrence of severe forms of Covid-19, this negative interaction detected by the 3 models indicates that, statistically, it was not always the case in the IHU Méditerranée cohort. Otherwise the interaction with the inpatient status would have been favorable with a decreased risk of ICU transfer or death. In fact, Table 3 shows clearly that for inpatients not at risk, the number of events was 65% higher in the vaccinated patients compared with the unvaccinated patients. Moreover, in complete contradiction with the official narrative, this finding is in line with what was demonstrated on laboratory animal tests showing that vaccines against SARS coronavirus may induce a worsening of the pneumonia and increase the risk of death [21-23].

Statistically significant favorable interactions of vaccination were detected with variant Delta (in the three models) and with age categories ≥ 50 years and ≤ 89 years (model (b) and model (c) less accurate) but not for age > 89 (model (a) more accurate) for which the interaction is unfavorable, coherently with a number of events elevated but

roughly the same in vaccinated (16.3%) and unvaccinated (18.6) patients for this latter category. Other statistically significant interactions were detected in model (a) ; unfavorable between vaccination and immunodeficiency and between vaccination and chronic obstructive pulmonary disease (COPD), confirming the suspected capacity of vaccination to worsen the underlying illness, particularly severe chronic illnesses. A reference to this problem is made by an author heavily sponsored by Pfizer (institutional funding, see the conflict of interest statement [5]) and affiliates in an admirable semantic squirming published in Nature Reviews Immunology : “Estimating the protective effect of vaccination against severe illness from descriptive population-level statistics is non-trivial. For instance, in a population with lower average vaccine uptake but very high uptake among the key risk groups — namely the elderly and chronically ill — severe cases might still be expected to occur disproportionately among those vaccinated even if vaccine effectiveness is very high.” [5]

The negative interactions can be explained by combining the following insights: (a) the spike glycoprotein from both the SARS-CoV-2 virus and from COVID-19 vaccines has many known mechanisms of toxicity [25,26] and it is responsible for the formation of microscopic blood clots in the lung capillaries and alveoli [27-29] that result in the oxygen desaturation responsible for most hospitalizations and deaths; (b) the spike protein is known to persist in the human body for at least 15 months, if not longer [30], and experimental treatment protocols for removing it from the body have only just started being explored [31,32]. Because the spike protein has also been used as the antigen for the genetic COVID-19 vaccines, vaccination followed with a breakthrough infection, within close temporal proximity of a few months, could result in excess bio-accumulation of spike protein. Thus, although the vaccine appears have some positive efficacy towards the reduction of ICU admissions or deaths, via some non-sterilizing antiviral effect of vaccine induced antibodies averaged over the entire cohort, for those patients where this antiviral response fails to mitigate an infection, the greater cumulative load of spike protein from both infection and prior vaccination, can explain the unfavorable interaction between vaccination and severity of the disease. It can also explain why the vaccine has similar negative interactions for fragile patients with age > 89 years and patients with immunodeficiency, where the elicited antibody response may be insufficient, resulting in no antiviral protection but some harm due to excess accumulation of the spike protein.

Appendix 3, in supplementary material, includes the complete set of instructions needed to reproduce the calculations for model (a) using R. The design of our statistical analysis is retrospective and based on the same methodological approach used in Part 1, thus the same

remarks apply regarding the retrospective observational design vs prospective randomized controlled trial designs [14]. All things being considered, the ORs we have calculated are reliably evidencing of a true treatment effect in both cases of HCQ-AZ treatment and vaccination (within the limitations evoked at the second paragraph of the Discussion section). Many will argue that the level of confidence of our analysis cannot be considered at the same value of proof as for results from randomized clinical trials. But randomized trials have many pitfalls and cannot be conducted to completion in times of urgency for the reasons presented in the Introduction section of the Part 1 of our study [14]. All things being considered, the ORs we have calculated are reliably evidencing of a true treatment effect in both cases HCQ-AZ and vaccination.

It is indisputable that both HCQ-AZ and vaccination exhibit efficacy independently in multivariate analysis with a sufficiently improved survival benefit for the category of age ≥ 50 years to preclude doubts on the reality of the measurement, especially for HCQ-AZ that has been severely criticized and denied. Somehow ironically, HCQ-AZ and vaccination shared a similar fate in the analysis of the IHU-Méditerranée cohort. Because their ORs were close and the calculation data suffered from the same imperfection for both of them (see results for HCQ-AZ in article Part 1 of our study, [14]), if the analysis was deemed not valid for HCQ-AZ it should be deemed not valid as well for vaccination and vice versa.

This is quite embarrassing for the proponents of vaccination as being the only valid response to the pandemic. The approval conditions for a vaccine candidate under FDA rule is that no alternative treatment exists for emergency use authorisation (EUA). However the potential efficacy of HCQ-AZ in Covid-19 was known to Glaxo and Pfizer as early as March-May 2020 [33-35]. Furthermore, the Indian Council of Medical Research (ICMR) had proposed, as early as March 23, 2020, the prophylactic use of weekly low-dose hydroxychloroquine as pre-exposure prophylaxis for health-care workers [36], based on the biological plausibility of its antiviral action against COVID-19. A meta-analysis [37] of 11 Indian studies that followed the ICMR protocol found an infection ratio risk reduction with $RR=0.56$ ($p=0.004$), and for the five studies that included only patients that followed the ICMR protocol for at least 6 weeks, allowing for an optimal buildup of hydroxychloroquine in the lungs, the infection ratio risk reduction was $RR=0.25$ ($p<0.001$), which is comparable with the infection ratio risk reduction efficacy claimed by several COVID-19 vaccines on the market. The toxicity of this experimental vaccination should be emphasized as well as its association with a very large number of severe side-effects and even deaths, worldwide, at least in countries with a high vaccination coverage. Irreversible or long lasting debilitations of all sorts are reported in a non-negligible

fraction of the population, still to be evaluated thoroughly [38-40]. People with chronic symptoms may include patients who did not receive an early efficient treatment of their acute episode of Covid-19, such as HCQ-AZ, and developed a long Covid, but also persons suffering for long term vaccine side-effects. Moreover, the tens of billions US dollars benefit for the manufacturers and the too short delay to produce an effective and safe vaccine raise serious questions. Usually, it takes 10 years to develop a new vaccine. It should also be emphasized that the vaccination mandates, enforced in many countries on a large proportion of the population, were in total disagreement with the international conventions. Indeed, it is not allowed to administrate an experimental product without a free informed consent.

An additional disturbing reality with vaccination was the dramatic peak of Covid-19 infections observed about 2 to 3 weeks after the massive campaign of injections had started [41]. Antibody-dependent enhancement (ADE) may explain this phenomenon (due to facilitating antibody, initially neutralizing at low concentration and immune complexes). It is known that infection facilitating antibodies can appear two to three weeks after one dose of vaccine [41-43]. For instance, the vaccine against the dengue fever sensitized some of the dengue-naïve recipients leading to severe dengue fever [43]. Indeed, the IHU Méditerranée cohort does not show any improvement with vaccination for the risk of aggravated disease state in fragile patients (age > 89 years). In addition there is a significant unfavorable interaction of vaccination with the severity of the disease at patient admission. In view of such data, we must remember the outrageous cost for countries of this global human experiment.

Conclusion

External and independent state-of-the-art statistical analysis of the IHU-Mediterranée data demonstrated that the potential efficacy of vaccination was not substantially better than the empirical treatment using a combination of hydroxychloroquine and azithromycin, given as an early treatment. Vaccination had no measured efficacy for age < 50 years and, to the contrary of what was officially claimed, a negative (unfavorable) interaction was evidenced between vaccination and Covid-19 disease severity. These results indicated a disease worsening effect of previous vaccination in many cases, raising the question of the relevance and legitimacy of mass vaccination. The very large size of the observational single-institution cohort of patients coherently treated, together with the quality of the statistical approach we used, made these results very challenging for those who have continuously denied the potential efficacy of hydroxychloroquine-based treatment of Covid-19 patients during the pandemic and advocated systematic vaccination for all age categories.

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