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Research article

Non-specific protection against severe COVID-19 associated to typhoid fever and DTP vaccination

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A B S T R A C T

Trained immunity (TRAIM) or the enhanced non-specific immune response after primary stimulation by infection or vaccination is a recent but well-recognized concept. To verify its predictions, our objective was to determine the effects of two bacterial vaccines, typhoid fever (TFV) and diphtheria-tetanus-pertussis (DTP) on the infection, hospitalization and death frequencies associated to COVID-19 in a retrospective study on subjects vaccinated or not with TFV and DTP in the 4 years prior to the start of COVID-19 pandemia in the Basque Country (Spain). The studied outcome records were split into two periods according to COVID-19 vaccination, the pre-vaccination (ACV) from March to December 2020 and the post-vaccination (PCV) from September 2021 to June 2022). In total, 13,673 subjects were vaccinated against TFV and 42,997 against DTP.

A total of 2,005,084 individual records were studied in the ACV period and 1,436,693 in the PCV period. The proportion of infection, hospitalization and death associated to COVID-19 among controls in ACV was 4.97 %, 7.14 % and 3.54 %, respectively *vs.* 7.20 %, 2.24 % and 0.10 % among TFV subjects. Regarding DTP, the proportions were 4.97 %, 7.12 % and 3.58 % for controls and 5.79 %, 5.79 % and 0.80 % for vaccinees. In the PCV period, the proportion of infection, hospitalization and death among controls was 21.89 %, 2.62 % and 0.92 %, respectively *vs.* 31.19 %, 0.76 %, 0.00 % among TFV. For DTP, infection, hospitalization and death proportions were 21.89 %, 2.62 % and 0.92 %, respectively, among controls *vs.* 32.03 %, 1.85 % and 0.24 % among vaccinated subjects. The corresponding combined ACV and PCV odds ratios (OR) for SARS-CoV2 infection were 1.505 (95%CI 1.455–1.558; $p < 0.0001$; reduction −41.85 %) and 1.633 (95%CI 1.603–1.662; $p < 0.0001$; reduction −51.74 %), for TFV and DTP, respectively. Regarding COVID-19 associated hospitalization, the OR were 0.295 (95%CI 0.220–0.396; $p = 0.0001$; reduction 69.74 %) and 0.667 (95%CI 0.601–0.741; $p = 0.0001$; reduction 32.44 %), for TFV and DTP, respectively). COVID-19 associated death OR were 0.016 (95%CI 0.002–0.113, $p < 0.0001$; reduction 98.38 %) and 0.212 (95%CI 0.161–0.280; $p = 0.0001$; reduction 78.52 %), for TFV and DTP, respectively. We conclude that TRAIM effects by TFV and DTP vaccination in the four years prior to the pandemic SARS-CoV2 were supported by slightly increased infection rates, but strongly reduced COVID-19 associated hospitalization and death rates.

1. Introduction

The appearance of the COVID-19 pandemic has challenged the sanitary systems throughout the world and has caused millions of

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cases of disease and hundreds of thousands of deaths [1]. However, its impact shows substantial differences between countries [1,2]. The recent proposal of the trained immunity theory implies that exposure to pathogen-associated molecular patterns (PAMP) or, more generally, to microbe-associated molecular patterns, and its recognition by pattern recognition receptors, generates a non-specific memory that improves defense against different microbial agents [3]. Vaccination against tuberculosis has been frequently cited as a useful trigger of this type of immune response [4–15]. Although preliminary essentially ecological analyses indicated that such an effect could have moderated the impact of COVID-19 [[16–26], more recent studies have not confirmed this hypothesis [27–37]. The effects of other vaccines were recently examined in relationship with COVID-19 in two studies [38] [39]. In particular, in a UK study, the diphtheria-tetanus-pertussis (DTP) vaccine presented a lower odds ratio for developing severe COVID-19. However, this vaccine is universally applied since childhood following a lifelong protocol, thus making it difficult to be used for comparisons. What is more, if its non-specific effects (NSE) have a limited duration, they might have protected the young, but not the older adults where the disease took its heaviest toll. In that sense, in a more recent USA study considering only vaccines given 1–5 years before the COVID-19 outbreak, differences in severe disease rate were reported for some vaccines, but not for DTP [38]. Therefore, we found necessary to test NSE cross-protection on COVID-19 with a vaccine that is applied in adulthood and therefore closer to the SARS-CoV2 exposure. To cover a wide range of ages and to use a more distant antigen, we focused on the typhoid fever vaccine (TFV). *Salmonella enterica* infections by serovars Typhi and paraTyphi (typhoid and paratyphoid fever, respectively) are widespread life-threatening conditions affecting especially regions with poor water supply and sanitation infrastructures [39]. The vaccine against these diseases is commonly used in Spain on people traveling to high prevalence countries. We hypothesized that this could have played a role in shielding against COVID-19 during its protection period, between 3 and 5 years prior to the outbreak. The evidence from the UK study with the trivalent DTP showing a protective effect, led us to use it as a control. Therefore, we decided to test whether typhoid and DTP vaccination, according to the cross-protection predicted by the trained immunity theory (TRAIM), had the NSE of modifying COVID-19 outcomes in terms of infection, hospitalization and death frequencies compared to the non-vaccinated population.

2. Material & methods

2.1. Information source

The Basque Country public health system (Osakidetza) offers universal and free of charge assistance to the entire Basque population, i.e. around 2 million people. Each user counts with an electronic health record, where all their health-related information is stored [40]. The data used in this study was extracted from these health records, via the Osakidetza Business Intelligence tools, through a query crossing COVID-19 outcomes with TFV and DTP vaccination information. These records did not registered asymptomatic infection cases since laboratory diagnostic was only carried out by request upon appearance of suspect clinical signs.

2.2. Vaccines and outcomes

Three COVID-19 related outcomes were considered: 1) infection confirmed by Polymerase Chain Reaction (PCR) in clinically suspect cases, 2) hospitalization attributed to COVID-19, and 3) death, both associated with COVID-19 and all-cause.

The TFV is recommended for travelers going to endemic regions [41]. Two types of TFV vaccine are available: a live oral vaccine (Vivotif) [42] and a capsular Vi polysaccharide extract parenteral one (Typhim Vi) [43–46], with the latter administered to >96 % of the cases. The DTP vaccination is currently part of the childhood vaccination calendar in Spain. In the Basque Country in particular, this vaccine is given at 2, 4, and 11 months and boosted at 6 years (Triaxis, Boostrix) [47,48]. An additional Diphtheria-Tetanus shot (Diftavax, Ditebooster) [47] is administered at the age of 16[42,50]. The antigens are polypeptides or proteins. All adults are recommended to receive a total of 5 Diphtheria-Tetanus doses, while one dose is recommended for women in each pregnancy [41,49,50].

2.3. Extraction periods and data type

Data were extracted from two periods of 10 months' time duration. The pre-vaccination (ACV) period covered between the beginning of the pandemic and the start of COVID-19 vaccination. This included from the March 1, 2020 until the December 31, 2020. As post-COVID-19 vaccination (PCV) period was considered the interval from the September 1, 2021 to the June 30, 2022; when over 70 % of the population had received at least one dose [51]. During the ACV period, SARS-CoV2 infection was confirmed only in clinical cases and contacts. In the PCV period, rapid and inexpensive antigen tests were readily available and COVID-19 vaccines were extensively administered. All Osakidetza records on persons aged ≥15 years of age were considered for crossing with TFV and DTP vaccination records. Group aggregated data according to TFV or DTP vaccination within the previous 4 years for six age groups (15–30, 31–40, 41–50, 51–60, 61–70, >70 years) divided by sex were drawn. For each one of these sub-groups, the frequency of each one of the three above-mentioned outcomes was extracted as a separate variable.

2.4. Overall mortality

Considering the reported non-specific effects of vaccination in young children [52,53] and animals [54] where decreases of overall mortality around 30 % have been observed, the query was extended to all-cause mortality. To avoid the bias caused by the low numbers of vaccinees in the highest age interval, where most deaths occur in the Basque population, but very little other vaccinations are administered due to their lower mobility and declining health, records were censored at 70 years for this variable.

2.5. Non-COVID-19 mortality

Subtraction of covid-associated deaths (defined as those occurring while SARS-CoV2 infected) from all-cause mortality in each basic category was calculated to make an estimate of TFV and DTP non-specific protection in a non-COVID-19 scenario.

2.6. Frequency analysis

All analyses were run with the jamovi statistical package [55,56]. The associations between categorical variables and vaccine status (vaccinated/non-vaccinated) for the TFV and DTP were tested using the frequency analysis module with weighted data corresponding to the size of each variable class crossing frequency. Associations were tested with the Fisher's exact test. Effect size estimations were derived in terms of odds ratio (OR) and their 95 % confidence intervals (95%CI). The more intuitive frequency reduction rates were also calculated as the percent difference of cases between principal and reference groups (i.e. vaccinated minus non-vaccinated proportions divided by non-vaccinated proportion). Statistical significance was accepted at the $p < 0.05$ level.

2.7. Linear model analysis

Aggregated data were expanded into individual records corresponding to the actual number of entries in each category and binomial quantitative values of 0 and 1 for the negative and positive clinical outcome, respectively. With these datasets a general linear model analysis was run with the jamovi Linear Model module Generalized Linear Model logistic option [57–59]. This compared the proportions of the different COVID-19 outcomes associated with TFV and DTP vaccination at each period compared to the TFV and DTP non-vaccinated (in the PCV period, they were COVID-19 vaccinated). The other groups represented the interaction of COVID-19 vaccination with either TFV or DTP vaccination. Since including the 5 data recovery levels left the outcome without replicates to calculate errors, the Lenth's pseudo standard error was used to represent significance in the full model (Fig. 2) [60]. Successive pooling of age and sex lead to the simplest model for overall vaccine effects analysis according to each COVID-19 outcome (Fig. 3). Group post-hoc paired comparisons were estimated with the Holm correction at $p < 0.05$ as the statistical significance threshold.

3. Results

3.1. COVID-19 general data

The data extracted in the two study periods are presented in Table 1. A total of 2,005,084 individual records were obtained in the ACV period and of 1,436,693 in the PCV. In the ACV period, 4.99 % of the population had at least one confirmed SARS-Cov2 infection. COVID-19 hospitalization and death occurred in 0.35 % and 0.18 % of the population, respectively. All-cause deaths occurred in 1.02 %. In the PCV period the SARS-CoV2 infections had more than a fourfold increase (22.16 %) over the ACV. However, hospitalization increased only less than twofold (0.57 %), while deaths (0.20 %) and all causes mortality (1.22 %) remained nearly unchanged.

There were 13673 (0.68 %) records of TFV and 42997 (2.14 %) of DTP vaccination in the ACV period and 9767 (0.68 %) and 38714 (2.69 %) in the PCV. In the ACV period, TFV vaccinees accounted for 0.98 % of the cases, while in the PCV, they represented 0.96 %. For DTP vaccinees, the figures were 2.49 % and 3.89 % out of the infected in each period, respectively.

Table 1
Summary of information extracted from the Osakidetza databases, for the general population and the TFV and DTP vaccinations in the two study periods.

Period	General population			TFV		DTP	
	Information type	Population	%	n	%	n	%
Pre-COVID-19 vaccination	Total	2,005,084	100	13673	0.68	42997	2.14
	COVID-19 infection	99979	4.99	984	0.98	2488	2.49
	COVID-19 hospitalization	7089	0.35	22	0.31	144	2.03
	COVID-19 associated death	3510	0.18	1	0.03	20	0.57
	All-cause death	20519	1.02	5	0.02	109	0.53
	All-cause death <70	4353	0.26	5	0.04	38	0.10
	All-cause non-COVID-19 death <70	3845	0.23	4	0.03	35	0.09
Post-COVID-19 vaccination	Total	1,436,693	100	9767	0.68	38714	2.69
	COVID-19 infection	318374	22.16	3046	0.96	12400	3.89
	COVID-19 hospitalization	8245	0.57	23	0.28	229	2.78
	COVID-19 associated death	2847	0.20	0	0.00	30	1.05
	All causes death	17489	1.22	2	0.01	183	1.05
	All causes death <70	3194	0.29	2	0.02	63	0.18
	All causes non-COVID-19 death <70	2729	0.25	2	0.02	57	0.16

TFV: typhoid fever vaccination. DTP: diphtheria-tetanus-pertussis vaccination. Pre-COVID-19 vaccination corresponds to the years 2017–2020. Post-COVID-19 vaccination corresponds to the interval from September 1, 2021 to June 30, 2022 (Post-COVID-19). All-cause death includes COVID-19 death. The data are frequencies (n) and percentages (%). Percentages calculated based on the corresponding population (n).

3.2. Frequency analysis

Overall, typhoid fever vaccinated individuals appeared to have higher COVID-19 infection odds than non-vaccinated ones. That was consistent for both periods, ACV and PCV (Table 2, Fig. 1A). On the contrary, among the infected, hospitalization odds of vaccinated individuals were much lower than for non-vaccinated, and remarkably similar for both periods (Table 2, Fig. 1C). In the infected group, the odds of COVID-19 associated deaths were very low during both periods (Table 2, Fig. 1D). All-cause mortality in the entire population showed similar lower odds for TFV treated persons, again with similar figures for ACV and PCV (Table 2, Fig. 1B).

DTP vaccination showed similar trends, but at lower levels. Overall SARS-CoV2 infection odds were higher for vaccinated individuals, both in ACV and PCV (Table 2, Fig. 1A). Hospitalization odds were lower for those infected and vaccinated in both study periods considered together and, also, separating ACV and PCV (Table 2, Fig. 1C). COVID-19 associated death odds were lower for vaccinated infected in the whole study, and for ACV and PCV periods (Table 2, Fig. 1D). All-cause mortality odds were lower for DTP treated population, with odds in the ACV period being nearly half those in the PCV (Table 2, Fig. 1B).

Non-COVID-19 mortality OR were 0.126 and 0.085 for TFV vaccinated in the ACV and PCV periods, respectively, and 0.370 and 0.646 for DTP vaccinated in ACV and PCV periods (Table 2).

Overall, for TFV and DTP together, the SARS-CoV19 infection OR was 1.599, hospitalization over infection OR was 0.588 and death OR was 0.172.

The better odds for severity (hospitalization and death) were those of the TFV vaccinated, with a maximum effect on death and all-cause mortality during the PCV period for TFV.

3.3. Age and sex effects

Age and sex were the only individual characteristics retrieved from the database. Both had a significant association with all clinical outcomes (Table 3). Globally, age infection rates in both periods ranged between 6.38 % in the 61–70 years old group to 14.91 % in the 31–40 ($p < 0.0001$). Although the infection rates strongly varied from the first to the second period, the ranking of age frequency was similar. The minimum for both periods was observed in the 61–70 age interval. The maximum for the ACV and PCV periods was seen in the 15–30 and 31–40 age intervals, respectively. Female infection prevalence significantly differed from male prevalence, both considering the two periods together, and each one of them separately.

TFV vaccinees presented a higher infection rate at all age intervals in both periods, except for the >70 class during the ACV period and 41–50 class during the PCV. All vaccinated group rates showed higher frequencies than non-vaccinated for DTP. But only for the two first age intervals during the ACV and all during the PCV, differences were statistically significant.

Age and sex interaction with vaccine effects generally maintained the same trends although there was more variability, and significant p values were obtained only for specific age and sex combinations. Such was the case for infection in the younger groups for TFV and females for DTP at all ages. No significant differences were seen in hospitalization rates for TFV within age and sex basic groups, but strikingly, there was an important negative effect in females in the younger age groups (15–41 years) in both periods, and then only in the PCV group between 51 and 70 years old for DTP. Regarding COVID-19 associated deaths, the only significant positive reduction occurred in the over 70 years old during the ACV period.

Table 2
Frequency, odds ratio, and reduction of the COVID-19 outcome according to vaccination status and period for each denominator population. Notice that infection OR are higher for vaccinees for both vaccines and periods. However, severe forms OR are lower for all comparisons except for hospitalization in DTP vaccinees. TFV: Typhoid fever vaccine. DTP: Diphtheria-Tetanus-Pertussis vaccine. All-cause mortality: Mortality by all causes in younger than 70 years of age. ACM<70: All-cause mortality in population younger than 70 years. C19: COVID-19.

Population	Outcome	Vaccine	Period	+ (%)	Control (%)	p	OR	95 LCI	95 UCI	reduction
All	Infection	TFV	ACV	7.20	4.97	<0.0001	1.482	1.389	1.582	−44.77
			PCV	31.19	22.10	<0.0001	1.598	1.530	1.668	−41.13
		DTP	ACV	5.79	4.97	<0.0001	1.175	1.128	1.224	−16.46
			PCV	32.03	21.89	<0.0001	1.682	1.646	1.719	−46.34
All	ACM <70	TFV	ACV	0.04	0.27	<0.0001	0.139	0.058	0.334	86.08
			PCV	0.02	0.29	<0.0001	0.072	0.018	0.289	92.75
		DTP	ACV	0.10	0.27	<0.0001	0.355	0.258	0.488	64.47
			PCV	0.18	0.29	<0.0001	0.610	0.475	0.782	38.98
All	ACM<70 no covid	TFV	ACV	0.03	0.24	<0.0001	0.126	0.047	0.335	87.50
			PCV	0.02	0.25	<0.0001	0.085	0.021	0.339	91.52
		DTP	ACV	0.09	0.24	<0.0001	0.370	0.265	0.516	62.95
			PCV	0.16	0.25	0.0006	0.646	0.497	0.840	35.92
Infection	Hospitalization	TFV	ACV	2.24	7.14	<0.0001	0.298	0.195	0.454	68.68
			PCV	0.76	2.61	<0.0001	0.284	0.188	0.429	71.04
		DTP	ACV	5.79	7.12	0.0101	0.801	0.676	0.949	18.75
			PCV	1.85	2.62	<0.0001	0.699	0.613	0.799	29.51
Infection	C19 associated death	TFV	ACV	0.10	3.54	<0.0001	0.028	0.004	0.197	97.13
			PCV	0.00	0.90	<0.0001	0.018	0.001	0.288	100.00
		DTP	ACV	0.80	3.58	<0.0001	0.218	0.140	0.339	77.54
			PCV	0.24	0.92	<0.0001	0.261	0.182	0.374	73.72

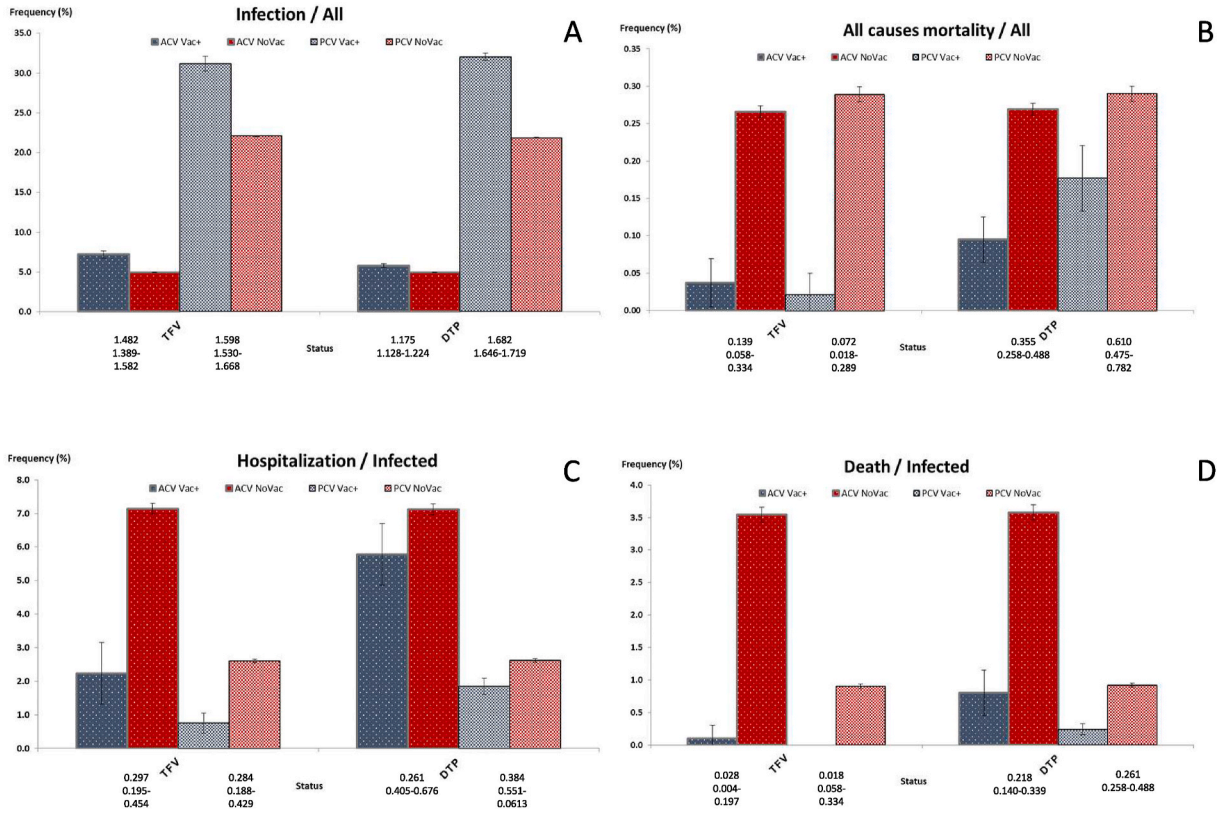


Fig. 1. Frequency of each outcome for typhoid fever (TFV) and Diphtheria-tetanus-pertussis (DTP) vaccination in the pre-COVID-19 (ACV) and in the post-COVID-19 vaccination period (PCV). A) SARS-CoV2 infection out of the whole population. B) All-cause mortality out of the whole population. C) Hospitalization out of the infected population. D) Death out of the infected population. Notice that PCV SARS-Cov2 infection frequency is much higher than ACV infection frequency. For the rest of the outcomes, frequencies are much smaller for vaccinated than for non-vaccinated people. All the comparisons between vaccinated and non-vaccinated people show a highly significant difference ($p < 0.0001$) in the Fisher exact test, except for DTP vaccination hospitalization ($p = 0.0101$). Numbers below x-axis are OR and its 95 % CI for vaccinated versus non-vaccinated. Vac+: Vaccinated; NoVac: Not vaccinated.

3.4. General linear model analysis

Fig. 2 summarizes information for the full 5 factors logistic model and the 4 main outcomes (infection, non-COVID-19 all-cause mortality, hospitalization and COVID-19 associated deaths. Age and sex showed strong interaction effects in opposite senses according to factor combinations (Fig. 2). Regarding infection (Fig. 2A), the strong effect of the selected period influences all the other effects, with older ages involved in all the relevant interactions in both senses and males generally having higher rates than females but also with some combinations where the rates were smaller. Hospitalization (Fig. 2B) was analyzed compared to infection instead of to the entire population to reduce background noise. Only six effects surpassed Lenth's critical value, half related to increases and half to decreased rates explaining 30 % of variability. COVID-19 associated death rates (Fig. 2C) were reduced in all vaccine types and status, sex, and age groups. The strongest effect on non-COVID-19 all-cause mortality rate was an increase. However, it might be heavily influenced by the natural effect of age on mortality compared to the reference 15–30 years level. This would be shown by the reduction associated with type of vaccine, vaccination treatment and their interaction as can be seen in Fig. 2D.

Fig. 3 summarizes the main effects probabilities of the different outcomes in the three factors models. Each graph shows an outcome hypothesis. Overall, vaccinated population showed a negative reduction (increase) of the rate of infection compared to the non-vaccinated controls (Fig. 3A). This effect held for both vaccines and periods. Infection increased more than three times from the first to the second period. No significant differences were observed according to the type of vaccine in general, although the proportion of infection among TFV vaccinated individuals was higher than that among DTP vaccinated during the first period. During the PCV period, DTP vaccination was associated with a very small but significant difference in the same direction.

Overall effect of vaccination (Fig. 3B) was reduction of cases requiring hospitalization (40.27 %). Reduction was even larger in the PCV with respect to the ACV and smaller for the type of vaccine taking as the reference the DTP rate. This was due to the larger and more significant effect of TFV in relationship with DTP in both periods. Hospitalization was 63.48 % ($p < 0.0001$) lower during PCV than during ACV.

COVID-19 associated deaths were reduced by 82.59 % (Fig. 3C) according to vaccination status with both vaccines and in both

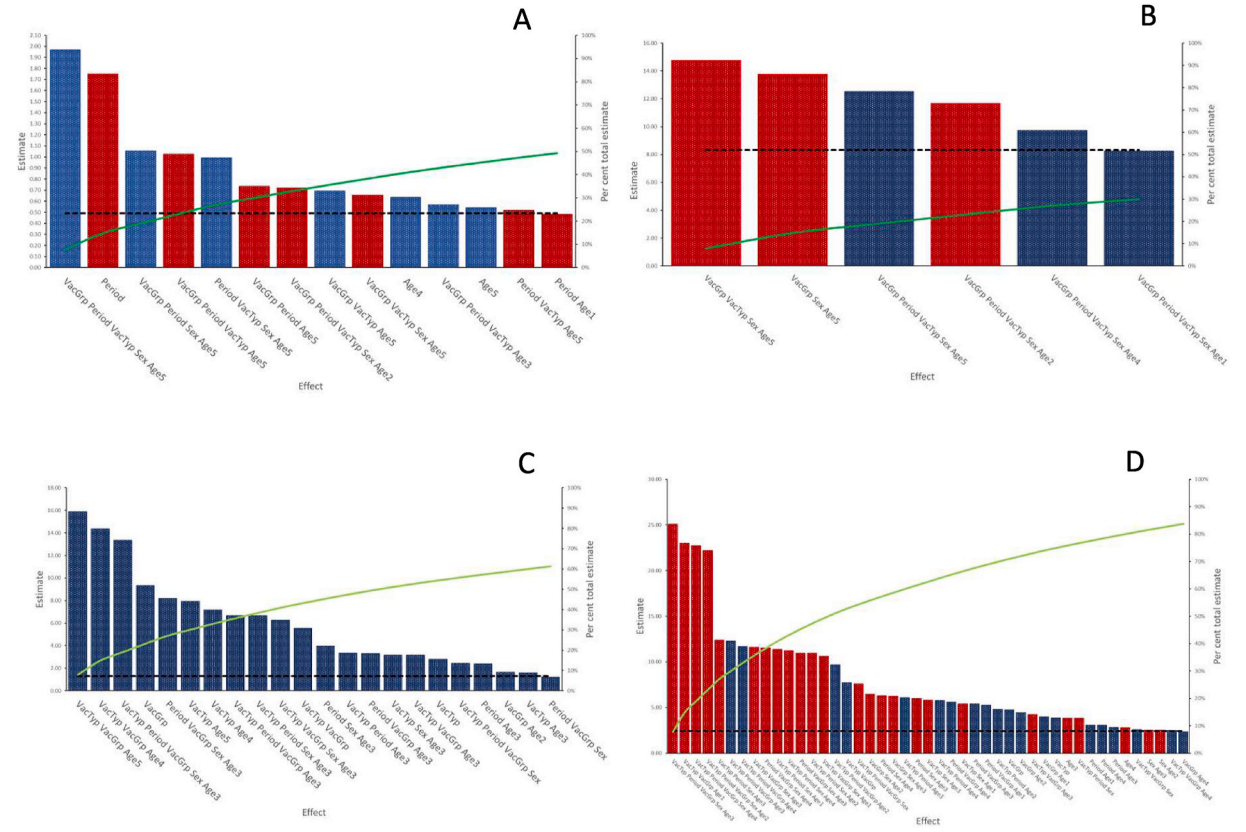


Fig. 2. Full model (Period, Vaccine type, Vaccine group, Sex, Age) results represented as a Pareto's chart of main effects and interaction estimates in the logistic general linear model for binomial outcomes. A) SARS-CoV2 infection out of the whole population. B) Non-COVID-19 all-cause mortality out of the whole population. C) COVID-19 associated hospitalization out of the infected population. D) COVID-19 associated deaths out of the infected population. Blue bars represent lower than zero OR (reduction) and red bars represent higher than zero OR (increase) compared to the reference level. VacTyp: Vaccine type (TFV *versus* reference DTP). Period: Period of study relative to COVID-19 specific vaccination (Pre-vaccination [ACV] *versus* reference post-vaccination [PCV]). VacGrp: Vaccination status group (Vac + *versus* reference NoVac). Sex: Sex (Male *versus* reference Female). Age 1: First age effect (31–40 years *versus* reference 15–30 years). Age 2: Second age effect (41–50 years *versus* reference 15–30 years). Age 3: Third age effect (51–60 years *versus* reference 15–30 years). Age 4: Fourth age effect (61–70 years *versus* reference 15–30 years). Age 5: Fifth age effect (>70 years *versus* reference 15–30 years). Black dashed horizontal line represents the Lenth's Pseudo-Standard Error (PSE) critical value. Green line represents the percent of the total model effects at each effect. Only effects above the Lenth's PSE critical value except the first below it are represented. Notice the complex interactions between effects. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

periods. There was a reduction of 74.28 % from the ACV to the PCV in the non-vaccinated groups and the DTP vaccinated one but not in TFV. Type of vaccine had no effect ($p = 1.000$) on COVID-19 associated deaths.

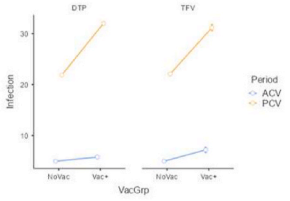
Joint DTP and TFV showed a 58.62 % non-COVID-19 associated mortality reduction (Fig. 3D). A slight overall increase of all-cause mortality (−4.58 %) occurred despite specific COVID-19 vaccination. Overall non-COVID-19 mortality was identical for both vaccine types and vaccination status.

4. Discussion

Overall, the results of this study support the hypothesis that non-specific vaccination within the 5 years before COVID-19 outbreak may modify this infection outcomes. This is broadly in agreement with the conclusions of previous studies in relationship with other vaccines [19,61,38,62–66]. However, our work reveals some new insights. In the first place, to the best of our knowledge, this is the first observation of an association of TFV with COVID-19 severe clinical outcome. Secondly, we get a lower hospitalization and COVID-19 associated death OR than in any previous study with non-specific vaccines. Thirdly, we report an opposite effect of vaccination on COVID-19 outcome depending on whether it is just infection or severe disease and death. Finally, we found a significant effect on all-cause non-COVID-19 mortality (meaning either more COVID-19 undetected mortality or a general NSE). This association was found both for TFV and for DTP, albeit at different degrees. Both results strongly reinforce the hypothesis of lack of specificity of the mechanisms involved and point out to an interaction of standing vaccination schedules on results of the new SARS-CoV2 vaccine.

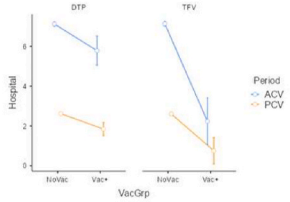
This study reach is limited by its observational and aggregated nature that hinders discarding confounding effects related to

A



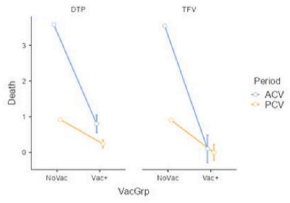
Hypothesis	Infection	OR	Reduction	Overall p	Factor 1	Factor 2 OR (TFV)	p (TFV)	OR (DTP)	p (DTP)
Vac+	15.15%	1.471	-39.89%	< .0001	ACV	1.482	< .0001	1.175	< .0001
NoVac	10.83%				PCV	1.598	< .0001	1.682	< .0001
						NoVac		Vac+	
PCV	26.52%	6.010	-367.72%	< .0001	DTP	5.359	< .0001	7.675	< .0001
ACV	5.67%				TFV	5.423	< .0001	5.845	< .0001
						PCV		ACV	
TFV	13.13%	1.053	-8.02%	< .0001	NoVac	1.012	< .0001	1.001	0.9141
DTP	12.16%				Vac+	0.962	0.2201	1.263	< .0001

B



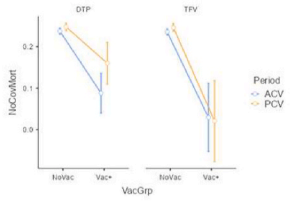
Hypothesis	Hospital	OR	Reduction	Overall p	Factor 1	Factor 2 OR (TFV)	p (TFV)	OR (DTP)	p (DTP)
Vac+	2.07%	0.466	52.30%	< .0001	ACV	0.297	< .0001	0.801	0.068
NoVac	4.34%				PCV	0.284	< .0001	0.699	< .0001
						NoVac		Vac+	
PCV	1.76%	0.334	65.42%	< .0001	DTP	0.351	< .0001	0.306	< .0001
ACV	5.09%				TFV	0.306	< .0001	0.333	0.002
						PCV		ACV	
TFV	2.39%	0.622	34.79%	< .0001	NoVac	0.995	1	1.002	1
DTP	3.67%				Vac+	0.404	0.0003	0.372	0.0002

C



Hypothesis	CA death	OR	Reduction	Overall p	Factor 1	Factor 2 OR (TFV)	p (TFV)	OR (DTP)	p (DTP)
Vac+	0.16%	0.358	91.16%	0.0042	ACV	0.028	0.0003	0.218	< .0001
NoVac	1.81%				PCV	0.036	0.0008	0.261	< .0001
						NoVac		Vac+	
PCV	0.29%	0.278	71.57%	0.0004	DTP	0.250	< .0001	0.299	< .0001
ACV	1.02%				TFV	0.248	< .0001	0.323	0.4211
						PCV		ACV	
TFV	0.32%	0.087	64.44%	< .0001	NoVac	0.980	0.4606	0.990	0.6739
DTP	0.90%				Vac+	0.135	0.0463	0.126	0.043

D



Hypothesis	NC19 death	OR	Reduction	Overall p	Factor 1	Factor 2 OR (TFV)	p (TFV)	OR (DTP)	p (DTP)
Vac+	0.05%	0.225	79.17%	< .0001	ACV	0.126	0.0007	0.370	< .0001
NoVac	0.24%				PCV	0.085	0.0092	0.646	0.0177
						NoVac		Vac+	
PCV	0.12%	1.088	-9.09%	0.7057	DTP	1.043	0.4763	1.822	0.0524
ACV	0.11%				TFV	1.822	0.0524	0.705	1
						PCV		ACV	
TFV	0.12%	0.456	49.60%	0.0004	NoVac	0.994	1	0.992	1
DTP	0.24%				Vac+	0.130	0.0503	0.337	0.3546

Fig. 3. Graphic representation and odds ratio, reduction and p-value of the comparisons from the three-effects simplified model according to outcome and effect hypothesis (**vaccine group** [Vac + *versus* reference NoVac], overall and interacting with period [PCV *versus* reference ACV] and vaccine type [TFV *versus* reference DTP]; **period** [PCV versus reference ACV], overall and interacting with vaccine type [TFV *versus* reference DTP] and vaccine group [Vac + *versus* reference NoVac]; **vaccine type** [TFV *versus* reference DTP], overall and interacting with vaccine group [Vac + versus NoVac], and period [PCV versus reference ACV]). A) Infection. B) Hospitalization. C) COVID-19 associated death. D) Non-COVID-19 associated death. ACV: Pre-COVID-19 vaccination period, PCV: post-COVID-19 vaccination period; DTP: Diphtheria-tetanus-pertussis vaccination, TFV: Typhoid fever vaccination. Detailed outcome rates and OR are displayed in Table 2.

lifestyle (social and cultural level, income, traveling, etc.) or physiological condition (pregnancy, co-morbidities, etc.). However, the study of two different vaccines, as well as the large numbers of individual records analyzed allows to assume that uncontrolled factors were randomly distributed in all groups. Another weakness of this study is that period and vaccine type were recorded from the same population and therefore the results in each set are not independent and represent an amplification of the real number of individuals studied.

The frequency of SARS-CoV2 infection hugely increased from the ACV to the PCV period (Fig. 1A). Changes in the diagnostic protocols and virus genetic shifts could have caused the paradoxical infection rate increase after extensive population specific vaccination. Studies on the effects of several non-COVID-19 vaccines on COVID-19 have yielded contradictory results [61]. While some studies report significant reductions, other did not find any difference. A recent analysis [38] demonstrated the beneficial effects of several vaccines on COVID-19 infection rate, but also the negative effects of others including TFV. This could be due to non-specific effects being different according to the type of vaccine and the treated population [67–69].

Regarding severe disease, vaccined individuals had much smaller odds of needing hospitalization or of dying either by COVID-19 or by any other causes. This is in line with other studies and would add a new vaccine to the list of vaccines with such an effect on COVID-19[38,39,63,67] In this study TFV and, to a lesser extent, DTP appeared to be associated to a higher protection against hospitalization than other non-specific vaccines. These protection rates against severe COVID-19 were even stronger for both COVID-19 associated and all-cause death rates in comparison with those found in previous studies [70–74].

The contradictory observation that vaccination favors infection but reduces severe outcomes is consistent with its targeting the host response efficiency instead of the virus entrance targeted by the COVID-19 specific vaccines [75–77], and therefore its pathological

Table 3
Overall COVID-19 outcome and all-cause mortality frequencies out of the whole population at each period. ACV: Pre-COVID-19 vaccination period. PCV: Post-COVID-19 vaccination period. ACM: All-cause mortality.

		ACV				PCV			
Sex	**Age**	**Infection**	**Hospitalization**	**Death**	**ACM**	**Infection**	**Hospitalization**	**Death**	**ACM**
Female	***15–30***	6.38 %	0.83 %	0.02 %	0.01 %	29.31 %	0.36 %	0.01 %	0.01 %
	31–40	5.59 %	2.65 %	0.10 %	0.03 %	34.64 %	0.59 %	0.02 %	0.03 %
	41–50	5.40 %	2.61 %	0.16 %	0.09 %	31.12 %	0.47 %	0.04 %	0.07 %
	51–60	5.53 %	4.43 %	0.51 %	0.22 %	21.44 %	1.00 %	0.17 %	0.23 %
	61–70	3.73 %	8.07 %	1.44 %	0.46 %	15.42 %	2.14 %	0.48 %	0.44 %
	>70	4.97 %	16.54 %	15.72 %	3.40 %	15.72 %	8.57 %	4.11 %	3.47 %
Male	***15–30***	5.67 %	0.83 %	0.03 %	0.03 %	23.51 %	0.22 %	0.02 %	0.02 %
	31–40	4.40 %	2.79 %	0.14 %	0.06 %	28.46 %	0.31 %	0.04 %	0.03 %
	41–50	4.31 %	5.02 %	0.24 %	0.14 %	26.78 %	0.69 %	0.07 %	0.12 %
	51–60	4.71 %	8.74 %	1.00 %	0.43 %	18.73 %	1.91 %	0.31 %	0.40 %
	61–70	4.14 %	14.77 %	4.34 %	1.06 %	14.24 %	5.11 %	1.13 %	0.88 %
	>70	4.72 %	24.30 %	19.42 %	4.14 %	17.04 %	12.82 %	5.17 %	4.13 %
Both	***15–30***	6.02 %	0.83 %	0.02 %	0.02 %	26.46 %	0.30 %	0.02 %	0.01 %
	31–40	4.99 %	2.71 %	0.11 %	0.04 %	31.60 %	0.46 %	0.03 %	0.03 %
	41–50	4.84 %	3.70 %	0.20 %	0.12 %	28.98 %	0.57 %	0.05 %	0.10 %
	51–60	5.12 %	6.41 %	0.73 %	0.33 %	20.12 %	1.41 %	0.23 %	0.31 %
	61–70	3.93 %	11.47 %	2.92 %	0.75 %	14.85 %	3.50 %	0.78 %	0.65 %
	>70	4.87 %	19.62 %	17.19 %	3.70 %	16.26 %	10.39 %	4.57 %	3.74 %

consequences [78–80]. Actually, this might constitute a powerful driver of natural immunization since it favors population exposure to the infection at a lower cost of disease damage.

The better odds for severity were those of the TFV vaccinated population, with a maximum effect on COVID-19 associated death and all-cause mortality during the PCV period. This would indicate a synergy between TFV and COVID-19 vaccination.

Although the general results are coherent and consistent with a vaccination induced non-specific effect, age and sex seem to strongly influence the infection evolution. This can be due to the correspondingly diminishing numbers of records in the considered sub-categories and the selective prescription of both vaccines. Since TFV is only prescribed to travelers to TF endemic countries [49], their likely higher economic level and health might have biased the COVID-19 outcomes. Additionally, their exposure to *Salmonella* and other pathogens in those regions might have boosted of the TRAIM mechanisms according to the environmental effects suggested by the negative correlation observed in ecological studies on territorial association of TF and COVID-19 incidence [81] On the other hand, the DTP vaccination that appears to have a similar protective effect but at a lower scale is consistent with other vaccines having such a similar effect [19,61,38,62–66]. The comparatively smaller effect of DTP could be caused by the control population having received DTP earlier in their life according to the Spanish protocol, with serial repetitions since the first year of age [82,49]. But also by the different nature of each active component: proteinic in the DTP vaccine [48] and polysaccharidic in the TF vaccine [44]. In this sense, one additional interesting point that comes out from this study is that the TRAIM NSE observed would have been induced by non-live components: a polysaccharide for TFV [38,83] and polypeptidic/proteinic toxoids for diphtheria, tetanus and pertussis [47, 48]. This is in opposition to previous observations that only live vaccines can induce TRAIM NSE [84–88]. This observation further supports attributing effects to vaccination treatment rather than to other causes and would suggest a stronger TRAIM induction associated to polysaccharides than to proteins.

This study draws the attention to non-specific mechanisms that might have reduced the impact of a new highly transmissible viral infectious agent. This points out the interaction of standing vaccination programs with new vaccines. It also supports the view that TRAIM mechanisms play a critical role in both the phylogenetic and ontogenetic lines of human immune fitness [89]. That means that these mechanisms could potentially be advantageously applied to strengthen undeveloped or weakened individual immune responses to protect against both old and new generic and specific morbidities.

An important caveat, however, is that sex and age might negatively influence the vaccination clinical course of the infection [67,69, 90]. Being mostly related to DTP vaccination at female reproductive ages, it is possible that an excess sensitization might induce some kind of permissiveness to viral replication.

In summary, the results of this field observational study, strongly support the beneficial effect of current vaccination protocols on the clinical outcome of SARS-CoV2 infection in terms of hospitalization and death, both COVID-19 associated and by all causes. These conclusions lend further support to the predictions of the trained immunity theory and show that there might be an additive effect of TFV and COVID-19 vaccination that would improve the effects of each one separately. More generally speaking, this work supports the immense value of vaccination programs promoting immune fitness in large populations [84,85]. It should not overlooked that when assessing vaccine efficacy, clinical trials should take into account interactions with previous vaccination programs and even natural exposure to TRAIM driving agents. TFV could be a good candidate for a universal emergency vaccine [88], but the reference of DTP results according to sex [67,69] and other experiences in animals with mycobacterial vaccines [91,92] indicates that such a goal faces many complexities that are not yet well understood and need more research for practical application.

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Ethics committee approval

CEI Euskadi PI2020087.

CRediT authorship contribution statement

Ramon A. Juste: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Kalliopi Vrotsou:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Maider Mateo-Abad:** Writing – original draft, Resources, Data curation, Conceptualization. **Maria A. Gutiérrez-Stampa:** Writing – review & editing, Resources, Data curation. **Rafael Rotaeche:** Writing – review & editing, Resources, Data curation. **Itziar Vergara:** Writing – review & editing, Resources, Data curation. **Luis Bujanda:** Writing – review & editing, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The first author, Ramon A. Juste is a Heliyon Associated Editor for Veterinary Sciences. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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