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The impact of vaccination on transmission and death by COVID-19: an observational study in Portugal's biggest primary care cluster

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The impact of vaccination on transmission and death by COVID-19: an observational study in Portugal's biggest primary care cluster"

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Abstract:

Vaccines are a key tool to manage the COVID-19 pandemic by preventing infection, hospitalization, severe disease, or death. In Portugal, information on vaccine effectiveness in real-life settings is still limited. Therefore, the main goal of this study is to evaluate the association between vaccination against COVID-19 and mortality and transmissibility in the population of the biggest Primary Care Cluster in Portugal, ACES Baixo Vouga (ACES BV).

A retrospective, observational study including all reported cases of COVID-19 in ACES BV between December 2020 and September 2021 was conducted (N=18,415). Anonymized data on demographic, clinical, epidemiological characteristics and outcomes of interest of the COVID-19 confirmed cases were collected. To model vaccination's association with death, a logistic regression analysis was performed. To estimate the effect of vaccination on the number of secondary cases, a zero-inflated negative binomial model was used.

Of 18,415 confirmed cases included in this study, 1,981 (10.8%) were vaccinated. A complete vaccination scheme against COVID-19 (OR=0.22, CI95 0.09-0.47) and female sex (OR=0.42, CI95 0.30-0.57) protected against death, while age (OR=1.12, CI95 1.10-1.13), comorbidities (OR=4.14, CI95 2.27- 8.34) and the presence of symptoms (OR=1.72, CI95 2.27-8.34) increased the odds of death. A complete vaccination scheme (RR 0.63, CI95 0.49–0.81) decreased the risk for the number of secondary cases in the model without outliers.

It is vital to monitor the vaccination effects in the real world and to better understand the characteristics of COVID-19 vaccine-induced immunity.

Keywords:

COVID-19; Vaccination; Observational study; Mortality; Infectious Disease Transmission.

Introduction:

The coronavirus disease (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first reported in patients with atypical pneumonia, in December 2019, in China. These cases were epidemiologically linked with an animal market in Wuhan, Hubei province (1). On January 30, 2020, the outbreak was declared by the World Health Organization (WHO) a Public Health Emergency of International Concern (PHEIC) (2). Portugal has a population of 10,347,892 people (3) and had its first detected case reported on March 2, 2020, reaching 406,051 cases and 6,830 deaths by December 29, 2020, and 1,054,673 cases and 17,853 deaths by September 10, 2021(4,5). Baixo Vouga Primary Care Cluster (ACES BV) comprises 11 municipalities and is Portugal's biggest Primary Care Cluster, considering its registered users (assigned or not to a family medicine physician). According to the national official records (last updated on September 2021), ACES BV accounts for 390,144 users (6). The first confirmed case of COVID-19 in this ACES occurred on March 8, 2020.

The virulence of COVID-19 refers to the degree of the disease's pathogenicity, expressed as the ratio of severe disease cases over the total cases (case fatality ratio (CFR)). For this study, we only consider death as a criterion of severity. A recent meta-analysis, showed an overall pooled CFR of 10.0% (95% confidence interval, CI95 8.0-11.0) for COVID-19 (7). Hospitalized patients presented higher risk of death (13.0%, CI95 9.0-17.0) compared to non-hospitalized (1.0%, CI95 1.0-3.0), and being admitted in the Intensive Care Unit (ICU) presented a CFR of 37.0% (CI95 24.0-51.0). Older patients (over 50 years old) presented a CFR of 19.0% (CI95 13.0-24.0) (7).

Besides age and clinical status, other risk factors have been associated with higher risks of death. Some comorbidities presented high Hazard Ratio (HR) or Odds Ratio (OR) associated with fatal COVID-19, as diabetes (HR 1.2-2.0), obesity (OR 1.5-1.75), heart failure (HR 1.3-3.3), chronic obstructive pulmonary disease (HR 1.12-2.2), dementia (HR 1.4-7.7), liver cirrhosis (OR 3.2-5.9) and active cancer (OR 1.6-4.7) (8). Some studies have described older age groups, male sex, living in a more socio-economically deprived community as relevant risk factors for death by COVID-19 (9,10). A large study concluded that patients of female sex had significantly lower odds of in-hospital mortality than males, as well as fewer admissions to the ICU and less need for mechanical ventilation (11).

In Portugal, increasing age was, at the beginning of the pandemic, the most relevant risk factor for hospitalization, ICU admission and death (12). Hospitalization and ICU admissions had a relevant increase in risk in 60-69 and 70-79-year-old people (12). Comorbidities also have an impact on clinical outcomes, but this risk was smaller than age and varied for different outcomes. Still, cardiovascular disease and chronic kidney disease were also found to represent a higher risk for both ICU admission and death (12).

SARS-CoV-2 prevention and control measures depend on controlling person-to-person viral transmission. The number of secondary cases that arise from an index case is a commonly used indicator. To allow the determination of risk, secondary attack rates are more useful, but they are sometimes hard to estimate since their denominator refers to all the exposed people. Certain settings of enclosed spaces and overcrowding present with high frequencies of contacts between individuals. A meta-analysis showed a pooled secondary attack rate of 0.7% (CI95 0.4%-1.0%) for healthcare settings and 18.1% (CI95 15.7%-20.6%) for households. Symptomatic index cases presented higher secondary attack rates than asymptomatic cases (RR 3.23, CI95 1.46, 7.14) (13).

Vaccines are a key tool to manage the COVID-19 pandemic. They aim to prevent COVID-19 infection, hospitalization, severe disease, or death, by triggering an immune response. Thanks to an unprecedented effort, information sharing, and bureaucracy reduction, it was possible to

produce several vaccines against COVID-19 in a record timespan. In Portugal, vaccination started on December 27, 2020 (14).

As of September 2021, Portugal has 4 available vaccines: SPIKEVAX® (15), VAXZEVRIA® (16), Janssen® (17), and COMIRNATY® (18). A meta-analysis that assessed the vaccine effectiveness, for all the four previously mentioned vaccines, found that they prevented any infection 66.9% of the times (CI95 58.4–73.6) (19). When the outcome was symptomatic infection, the pooled vaccine effectiveness was 75.7% (CI95 69.3–80.8), as for prevention of severe disease and hospitalization was 93.8% (CI95 83–98) (19).

Guidelines for operating the community vaccination centers and administration of different vaccines have been released by the Directorate-General of Health (DGS) (15–18,20,21). The prioritization started by the following groups, in three arms: (1) healthcare workers (HCW), (2) people living or working at nursing homes (NH), and (3) general population aged 50 or more, with comorbidities (heart failure, cardiovascular disease cardiac disease, kidney failure, chronic obstructive pulmonary disease), starting by the older ones. At NH, people were vaccinated against COVID-19 even if they have had a recent infection (less than six months). By September 12, 2021, Portugal had 8,983,915 people (85% of the population) with at least one dose of the vaccine and 8,273,795 people (80% of the population) fully vaccinated against COVID-19 (22). In ACES BV, 75.6% of its population was vaccinated with at least one dose and 59.9% was fully vaccinated (23). By that time, in the whole country, people aged 65 or older were approximately 100% fully vaccinated (22).

There is a lack of information on vaccine efficacy in real-life settings in Portugal. Only one multicentric study (24), that included Portugal, has assessed vaccine effectiveness so far, through a convenience sample gathered from a sentinel network of physicians. We aim to evaluate the effectiveness of COVID-19 vaccination on mortality and transmissibility of the SARS-CoV-2 in the population of ACES BV. As far as we know, this is the first observational study providing such data in this country.

Methods:

Study design and data sources

An observational study including all confirmed cases of COVID-19 in ACES BV reported to the Public Health Unit (PHU) between 29 December 2020 and 10 September 2021 was conducted (N = 18,415). Note that we did not consider reinfection cases. The main outcomes were the number of secondary cases and death. Secondary anonymized data was extracted from the local database of the Public Health Unit of ACES BV on September 10, 2021, including all COVID-19 confirmed cases whose information was gathered during the epidemiological investigation.

Case definitions

A confirmed case of COVID-19 was defined as anyone with: (1) a positive result for SARS-CoV-2 RNA (by Reverse transcription polymerase chain reaction RT-PCR) in nasopharyngeal and/or oropharyngeal specimens; or (2) a positive result in a SARS-CoV-2 antigen test, performed under the DGS Standard number 019/2020 (25).

A vaccinated person was defined as someone who got administered one or two doses of the available vaccines in Portugal, while a non-vaccinated did not receive any dose. A complete scheme was considered when a person got: (1) two doses of COMIRNATY®, SPIKEVAX® or VAXZEVRIA®; or (2) one dose of Janssen®. An incomplete scheme refers to a single dose of COMIRNATY®, SPIKEVAX® or VAXZEVRIA®.

The number of secondary cases is the number of COVID-19 confirmed cases generated by a unique infector (a previously confirmed case), according to the epidemiological investigation undertaken by the PHU.

Risk factors

The following variables were included: vaccination status, age, sex, comorbidities, symptoms, healthcare worker (HCW), institution (NH or school).

Statistical analysis

A descriptive analysis was performed to characterize the study sample of the confirmed COVID-19 cases and the distribution of the outcomes. Qualitative variables were reported as counts and

percentages. Quantitative variables were reported as means and standard deviations (sd). To test the different allocations between the two groups (vaccinated and non-vaccinated) chi-square was used for qualitative variables and Wilcox Mann-Whitney for quantitative variables. Lilliefors test was used to assess normality.

Death was modelled using a logistic regression model. First, univariate models were calculated using each co-variable (risk factor) as predictor. Considering the risk factors identified in previous literature, stepwise selection based on AIC (Akaike information criterion) was applied to obtain the final multivariate model. Only main effects (main associations) were considered. The same process was used for the number of secondary cases using a zero-inflated negative binomial model. Unknown classifications were removed from the models, resulting in different N depending on the model.

Regression models were compared using the Likelihood-ratio test. To determine models´ robustness, outliers in the models were identified based on standardized Pearson Residual and removed if the absolute value was higher than three.

Observations were assumed to be independent despite possible clustering within the municipalities. Statistical analysis was performed using R version 4.0.5. All analyses are presented with 95% confidence intervals (CI95). In statistical hypothesis, a p-value <0.05 is considered as statistically significant.

Results:

Descriptive

Descriptive statistics comparing the vaccinated and non-vaccinated populations of infected individuals (N = 18,415) are presented in Table 1. Considering the population of infected individuals in ACES BV, the proportion of death in non-vaccinated individuals was 1.66% compared to 0.86% in individuals with some sort of vaccination. Comorbidities were statistically different in the non-vaccinated (29.4%) and vaccinated (35.0%). A similar result was observed for

sex, where females correspond to 58.3% of vaccinated compared to 53.4% of non-vaccinated. Accordingly, the mean age is different in non-vaccinated (41.2 years) and vaccinated populations (51.2 years). Individuals who died from COVID-19 have a mean age of 82.4 years (sd 11.8) compared to 41.6 years (sd 21.9) of the remaining infected. The distribution for the number of secondary cases (Figure 1) reached higher values for the non-vaccinated with symptoms (range 0 to 31). In the groups referring to the individuals without vaccination (range 0 to 31) and an incomplete scheme (range 0 to 19), having symptoms appeared to be associated with a higher number of secondary cases, when compared to not having symptoms (range 0 to 8 and 0 to 4 respectively). This was no longer visible in the complete scheme group, where the maximum number of secondary cases is very close for both the symptomatic (7) and non-symptomatic group (5).

Mortality

Results for the univariate model considering death as the outcome (Table 2) showed that having started vaccination (OR 0.51, CI95 0.30-0.81) and being female (OR 0.64, CI95 0.51-0.81) both protected from death, while having associated comorbidities (OR 38.6, CI95 22.0-75.5) and working or living in an NH institution (OR 6.17, CI95 4.76-7.94) were risk factors. Age (OR 1.12, CI95 1.11-1.13) also presented as a risk factor, while presenting symptoms is a protective factor (OR 0.63, CI95 0.50-0.81). In the multivariate analysis, of the initially considered variables, HCW and institution were not selected for the optimized model. Considering the remaining variables, the behavior (the tendency of the effect size) was consistent except for the presence of symptoms, which changed from protective to a risk factor (OR 1.69, CI95 1.17-2.49). Also, the effect of comorbidities decreased in the multivariate model (OR 4.15, CI95 2.27-8.35).

An alternative model tested vaccination as a three-class variable (complete, incomplete and non-vaccinated) and the fit was similar to the two-class model (AIC of 1,266.8). All OR had the same order of magnitude and tendency. Having a complete (OR 0.55, CI95 0.27-0.99) or incomplete (OR 0.41, CI95 0.16-0.84) scheme showed to be a protective factor against death when com-pared to

non-vaccinated. However, only a complete scheme was statistically significant. A sensitivity analysis to the exclusion of outliers showed both models are robust to outliers´ exclusion.

Discussion:

As expected, according to previous literature, our results showed that older people, male sex, and people with comorbidities had a higher risk of mortality [5], with risk of death increasing 6% for each year of life. Additionally, belonging to an institution, when adjusted for confounders, did not appear to play an important role in mortality.

These results have some limitations that should be considered. The analysis was made using the cumulative COVID-19 confirmed cases in ACES Baixo Vouga and did not consider the timely variation of the epidemic's characteristics in that area – e.g. incidence, transmissibility, prevalence of variants with different virulence, and the characteristics of the affected population in each phase (age, comorbidities).

Number of secondary cases

The first approach used to model the number of secondary cases was a Poisson model. However, it was not adequate due to overdispersion. Furthermore, the distribution for the number of secondary cases is negatively skewed presenting a large incidence of zero (Figure 2). In these cases, zero-inflated models are more adequate, as they provide a better fit (26,27). Zero-inflated negative binomial was considered better when compared to the Zero-inflated Poisson, as proven by the result of the likelihood ratio test comparing both models ($\chi2(1)=720.89$, $p< 0.001$) (28). Uni-variate analysis (Table 3) showed that the relative risk (RR) for the number of secondary cases was lower in vaccinated individuals when compared to non-vaccinated (RR 0.83, CI95 0.70–0.99). Age had a RR close to 1 (RR 0.99, CI95 0.99–0.99), despite being statistically significant its effect has no practical meaning. Having symptoms presented as a risk factor for the number of secondary cases (RR 1.35, CI95 1.16–1.58) while the relative risk is lower for individuals who have comorbidities (RR 0.87, CI95 0.78-0.98). Being an HCW was not associated with the outcome in a

statistically significant way (RR 0.82, CI95 0.64–1.04), as well as being part of an NH (RR 1.21, CI95 0.96–1.52) or a school (RR 1.05, CI95 0.91–1.21).

In the multivariable model (M1), vaccination, comorbidities, symptoms, HCW and institution were selected to predict the number of secondary cases deriving from a unique infector. Having symptoms increased the risk of the outcome (RR 1.44, CI95 1.21–1.71), corresponding to a small increase in the risk when compared to the univariate analysis. In this model, the protective effect of comorbidities is no longer statistically significant (RR 0.94, CI95 0.85-1.03). Despite the results in the univariate analysis (p-value> 0.05), HCW and institution were selected to the adjusted model, using AIC to select variables. HCW (RR 0.77, CI95 0.62–0.95) and school (RR 0.97, CI95 0.84–1.12) were protective factors for the outcome. The latter showed an opposite tendency to the one on the univariate analysis, however, it was not statistically significant. Institutionalization in an NH (RR 1.46, CI95 1.17–1.81) increased the risk of the outcome, which is consistent with the univariate model. In M1, vaccination decreased the risk of the outcome (RR 0.89, CI95 0.78–1.04), but was no longer statistically significant.

As before, a similar model (M2) was calculated using vaccination as a three-class variable (Table 4). The models were very similar in what comes to fitness. All co-variables presented the same behavior. Presenting symptoms was a risk factor (RR 1.44, CI95 1.21-1.71) as well as being part of an NH (RR 1.48, CI95 1.18–1.86). Being an HCW decreased the risk of the outcome (RR 0.76, CI95 0.61–0.95). Being associated with a school was not statistically significant (RR 0.97, CI95 0.83–1.12), as well as having comorbidities (RR 0.93, CI95 0.85-1.03). Both complete (RR 0.81, CI95 0.67–1.01) and incomplete (RR 0.97, CI95 0.79–1.19) vaccination schemes were protective when compared with non-vaccinated individuals. Models' sensitivity to outliers was tested, resulting in model M3 (two-class vaccination) and M4 (three-class vaccination). In both cases, the results agreed with univariate analysis. Any vaccination (RR 0.72, CI95 0.61–0.84), or a complete scheme (RR 0.63, CI95 0.49–0.81) or incomplete scheme (RR 0.73, CI95 0.59-0.90), were statistically significant when compared with non-vaccination. Other covariables had very similar behavior in both models. Symptoms in M3 (RR 2.69, CI95 2.14–3.38) and M4 (RR 2.20, CI95 1.80–2.68), and

comorbidities in M3 (RR 0.75, CI95 0.68-0.83) and in M4 (RR 0.75, CI95 0.68-0.82) were statistically significant, while HCW, NH and school were not.

Discussion:

This study was performed in the early phases of vaccination against COVID-19 in Portugal and used data from 18,415 confirmed cases, from which 1,981 were vaccinated. In the infected population, HCWs, as well as members of an NH, have a higher proportion of vaccinated individuals whereas in schools most infected individuals are not vaccinated, which is concordant with the Portuguese vaccination plan phases (21). The mean age and the proportion of comorbidities of the infected are higher in the vaccinated than that of the non-vaccinated individuals. These results might be a reflex of the vaccination phases where older people with comorbidities were prioritized (15). The proportion of deaths is lower in the vaccinated group, as well as the mean number of secondary cases generated.

Associations between the vaccination status and the two main outcomes (death and number of secondary cases) were identified. For death, complete vaccination showed a protective association after adjustment for confounding factors, with an OR of 0.22 (CI95 0.09-0.47), which is in line with previous literature (19). For the number of secondary cases, complete vaccination presented a nearly statistically significant protective effect with an RR of 0.81 (CI95 0.65–1.01). This association presented as significant when removing outliers (RR 0.63, CI95 0.49–0.81). These results are coherent with other studies that analyzed the same association (19).

When analyzing death as an outcome, age, comorbidities, and the presence of symptoms presented as risk factors, while being of the female sex was protective. Vaccination in general was protective against death which is consistent with the results found in the literature (29). Analyzing particularly the vaccination scheme, only complete vaccination is statistically significant. These results are consistent in all models proposed. The only variable for which the behavior (direction of the effect size) differentiates from the univariate (protective factor) to the multivariate model (risk factor) is the presence of symptoms. This happens in both models: for two and three-class status

of vaccination, indicating that other variables are confounding factors regarding the presence of symptoms. However, it is important to highlight that this variable includes a great variety of symptoms ranging from anosmia to dyspnea and is not consistently filled by PHU staff and may be associated with a memory bias due to retrospective report from patients. The analysis could have been performed considering a category for each symptom, but data was not robust enough and misclassification would be very probable. Future research should analyze confounding associations between symptoms and death.

In M1 and M2 models, used to describe the number of secondary cases, vaccination status, as a two or three-class variable, was selected. In all models under analysis, vaccination decreases the risk of the outcome. Having symptoms was always a significant risk factor. Being an HCW was a protective factor for the outcome number of secondary cases deriving from a unique infector in all models. Being part of an NH institution was a risk factor in all analyses except for the model considering the three-class vaccination without outliers. Being part of a school presented an RR around 1 and was never statistically significant. These covariables were not statistically significant in the univariate analysis as well as in both models without outliers (M3 and M4). Having comorbidities was in all models a protective factor, however, it was only significant in the univariate analysis and the models without outliers. Further research is needed for the effect of these covariables on the number of secondary cases deriving from one infector, especially to understand its effect on individuals' behavior to comprehend transmission patterns.

Generally, the results when using a three-class variable for vaccination (complete, incomplete or non-vaccinated) were consistent with the classification as a two-class variable. Using a three-class variable allows for a more detailed explanation of the effect of vaccines on the outcomes.

A major strength of our study is that it assessed the COVID-19 vaccination effectiveness in a real setting, estimating its effect on SARS-CoV-2 death and transmissibility (number of secondary cases). As far as we know, this is the first study in Portugal aiming to evaluate the impact of the COVID-19 vaccination on mortality and transmissibility of the SARS-CoV-2 at a local level (ACES), in this case in Baixo Vouga, the biggest primary Care Cluster in Portugal. However, some

limitations can be raised. Data collection was conditioned to the available human resources thus local or general peaks of incidence, where a massive number of cases had to be registered simultaneously, led to inconsistent data collection and consequent decrease of its quality. For example, the type of comorbidities was under registered in situations related to outbreaks in NH. The same happened during periods of high incidence for the description of symptoms. This conditioned the use of the data related to the type of symptoms and type of comorbidities in the analysis. Further studies are needed to explore the mechanisms involved in the confounding effect of symptoms and comorbidities in the main associations. To do so, reliable data should be available, which derives from reinforcement or reorganization of the resources that perform the epidemiological investigation. Contact tracing was also affected in situations where a lot of cases had to be registered simultaneously. Most cases in our dataset did not generate any secondary infections (N=13 968) and our data had a high frequency of zeros, which could underestimate our main association. Zero-inflated models were used to try to overcome this limitation /adapt to this situation and obtain a more precise estimate. These models accommodate the existence of false zeros resulting from observational errors (27).

Data robustness and reliability depends on trustful notification systems and in-depth epidemiological investigation. Future studies must consider the importance of having reliable databases that consistently report epidemiological links to assess transmissibility. Additionally, upcoming research should consider different pandemic phases, circulating viral variants, and the heterologous schedules with different vaccines, as well as the recent homologous or heterologous booster which is being administered in many European countries. Some herd immunity might already exist in some areas, but efforts should be done to keep stable settings and avoid future lockdowns.

Ethics committee and informed consent:

This study used a secondary data source, containing anonymous information. It was conducted in accordance with the Declaration of Helsinki.

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Tables:

Table 1: Descriptive statistics considering the infected population, n= 18,415.

Variable	Vaccinated				p-value
	No N=16,434		Yes N=1,981		
Scheme					
Complete	0	0.00%	1078	55.10%	
Incomplete	0	0.00%	880	44.90%	-
Non-vaccinated	16,434	100%	0	0.00%	
Number secondary cases	0.45	1.05	0.36	0.94	<0.001
Death:					0.009
No	16,161	98.30%	1,964	99.10%	
Yes by COVID-19	273	1.66%	17	0.86%	
Age:	41.2	22.4	51.2	19.9	<0.001
Gender:					<0.001
Female	8,780	53.40%	1,154	58.30%	
Male	7,654	46.60%	827	41.70%	
Comorbidities:					<0.001
No	10,004	70.60%	1,172	65.00%	
Yes	4,172	29.40%	632	35.00%	
Symptoms:					0.882

No	4,027	24.50%	489	24.70%	
Yes	12,407	75.50%	1,492	75.30%	
HCW:					<0.001
No	15,875	96.60%	1,831	92.40%	
Yes	559	3.40%	150	7.57%	
Institution:					<0.001
NH	872	5.31%	298	15.00%	
School	2,623	16.00%	107	5.40%	
No	12,939	78.70%	1,576	79.60%	

Qualitative variables as counts and percentages and quantitative variables as means and standard deviations. To test the homogeneity of the two groups chi-square was used for qualitative variables and Wilcox Mann-Whitney test for quantitative variables. Lilliefors test was used to assess normality.
*unknown/NA individuals classified as vaccinated but without information on vaccination scheme.
NH-nursing homes; HCW- healthcare workers

Table 2: Results for logistic regression models proposed to describe death (N= 18,415). Reference levels for categorical co-variables are male, no comorbidities, no symptoms, not an HCW and not institutionalized. The selection of the multivariate model was based on the best AIC.

a) Two-class vaccination classified model. n= 18,407.

	Univariate			Multivariate		
Variable	OR	CI95	p-value	OR	CI95	p-value
Vaccinated (Yes)	0.51	0.30, 0.81	**0.008**	0.3	0.15-0.53	**<0.001**
Age	1.12	1.11, 1.13	**<0.001**	1.12	1.10-1.13	**<0.001**
Sex (Female)	0.64	0.51, 0.81	**<0.001**	0.42	0.30-0.57	**<0.001**
Comorbidities (Yes)	38.6	22.0, 75.5	**<0.001**	4.15	2.27-8.35	**<0.001**
Symptoms (yes)	0.63	0.50, 0.81	**<0.001**	1.69	1.17-2.49	**0.006**
HCW (yes)	0	0.00, 0.00	0.953			
Institution (NH)	6.17	4.76, 7.94	**<0.001**			
Institution (School)	0	0.00, 0.00	0.962			

NH-nursing homes; HCW- healthcare workers.

b) Three-class vaccination model, n= 18,384.

	Univariate			Multivariate		
Variable	OR	CI95	p-value	OR	CI95	p-value
Scheme (Complete)*	0.55	0.27- 0.99	0.068	0.22	0.09- 0.47	**<0.001**
Scheme (Incomplete)*	0.41	0.16- 0.84	**0.03**	0.46	0.17- 1.00	0.075
Age	1.12	1.11- 1.13	**<0.001**	1.12	1.10- 1.13	**<0.001**
Sex (Female)	0.64	0.51- 0.81	**<0.001**	0.42	0.30- 0.57	**<0.001**
Comorbidities (Yes)	38.6	22.0- 75.5	**<0.001**	4.14	2.27- 8.34	**<0.001**
Symptoms (Yes)	0.63	0.50- 0.81	**<0.001**	1.72	1.19- 2.53	**0.005**
HCW (Yes)	0	0.00- 0.00	0.953			

Institution (NH)	6.17	4.76- 7.94	**<0.001**
Institution (School)	0	0.00- 0.00	0.962

*Vaccination classified as complete scheme, incomplete scheme or non-vaccinated (reference level).

NH-nursing homes; HCW- healthcare workers.

Table 3: Zero-inflated negative binomial model for the number of secondary cases, considering vaccination yes and non-vaccinated. Univariate and multivariate model (M1) n= 15,975.

	Univariable			**Multivariate (M1)**		
Variable	RR	CI95	p-value	RR	CI95	p-value
Count Model						
Vaccinated (Yes)	0.83	(0.70 – 0.99)	**0.036**	0.88	(0.76 – 1.03)	0.119
Age	0.99	(0.99 – 0.99)	**<0.001**			
Sex (Female)	1.05	(0.95 - 1.15)	**0.372**			
Comorbidities	0.87	(0.78 – 0.98)	**<0.001**	0.94	(0.85 – 1.03)	0.189
Symptoms (Yes)	1.35	(1.16 – 1.58)	**<0.001**	1.44	(1.21 – 1.71)	**<0.001**
HCW (Yes)	0.82	(0.64 – 1.04)	0.097	0.77	(0.62 – 0.95)	**0.015**
Institution (NH)	1.21	(0.96 – 1.52)	0.1	1.49	(1.18 – 1.87)	**0.001**
Institution (School)	1.05	(0.91 – 1.21)	0.5	0.97	(0.84 – 1.12)	0.673
				AIC	27435.9	

NH-nursing homes; HCW- healthcare workers.

Table4: Zero-inflated negative binomial model for the number of secondary cases, considering 3 levels for vaccination. n= 15,956 (M2).

	Multivariate (M2)			**Without outliers**		
Variable	RR	95% CI1	p-value	RR	95% CI1	p-value
Scheme (Complete)	0.81	(0.65 – 1.01)	0.062	0.63	(0.49 – 0.81)	**<0.001**
Scheme (Incomplete)	0.97	(0.79 – 1.19)	0.746	0.73	(0.59 – 0.90)	**<0.001**
Comorbidities (Yes)	0.93	(0.85 – 1.03)	0.19	0.75	(0.68 – 0.82)	**0.004**
Symptoms (Yes)	1.44	(1.21 – 1.71)	**<0.001**	2.2	(1.80 – 2.68)	**<0.001**
HCW (Yes)	0.76	(0.61 – 0.95)	**0.015**	0.84	(0.66 – 1.07)	0.151
Institution (NH)	1.48	(1.18 – 1.86)	**<0.001**	0.89	(0.71 – 1.12)	0.319
Institution (School)	0.97	(0.83 – 1.12)	0.662	0.92	(0.81 – 1.04)	0.167
	AIC	27418.26		AIC	23726.63	

NH-nursing homes; HCW- healthcare workers.

Figures:

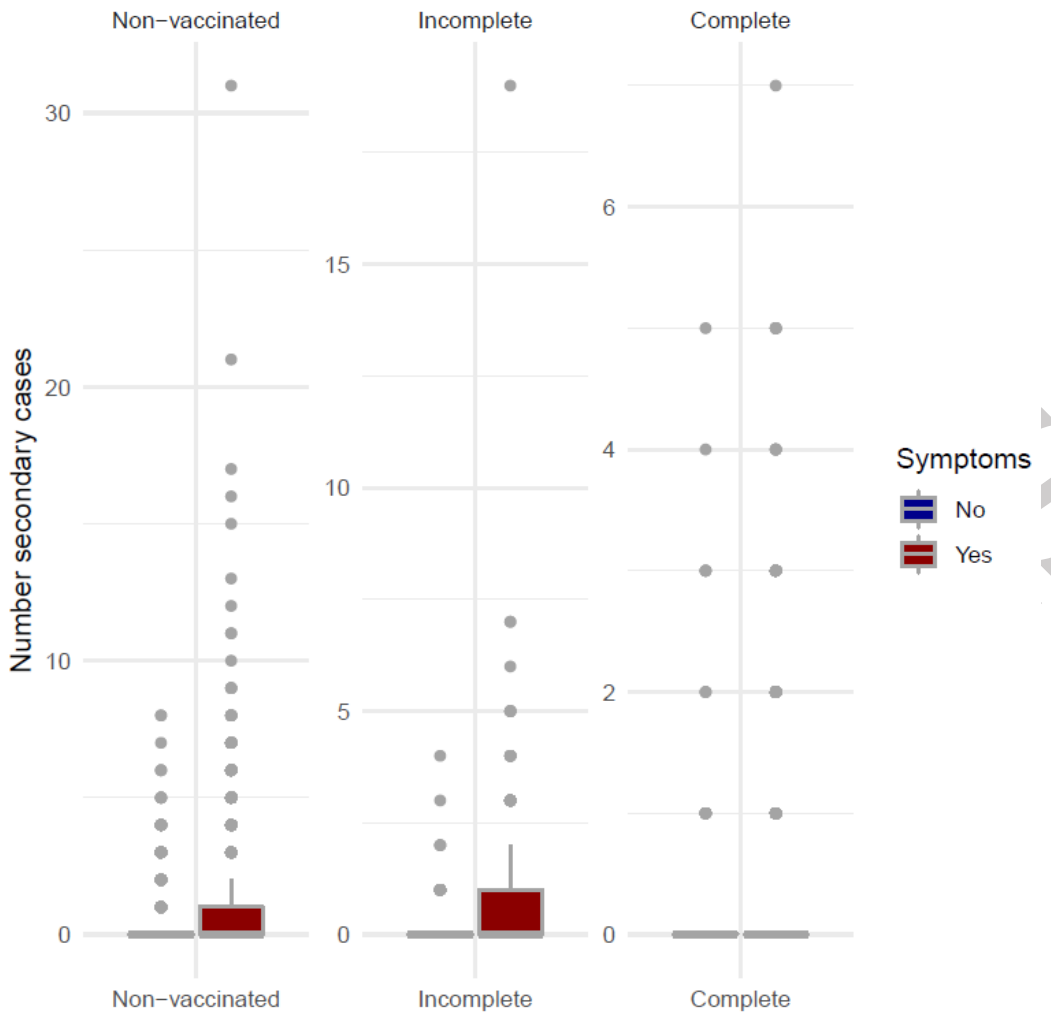

Figure 1: Box plot for the number of secondary cases in the non-vaccinated group and the incomplete and complete group scheme, categorized by the variable symptoms, n= 18,392 (for 23 individuals the vaccination scheme was unknown).

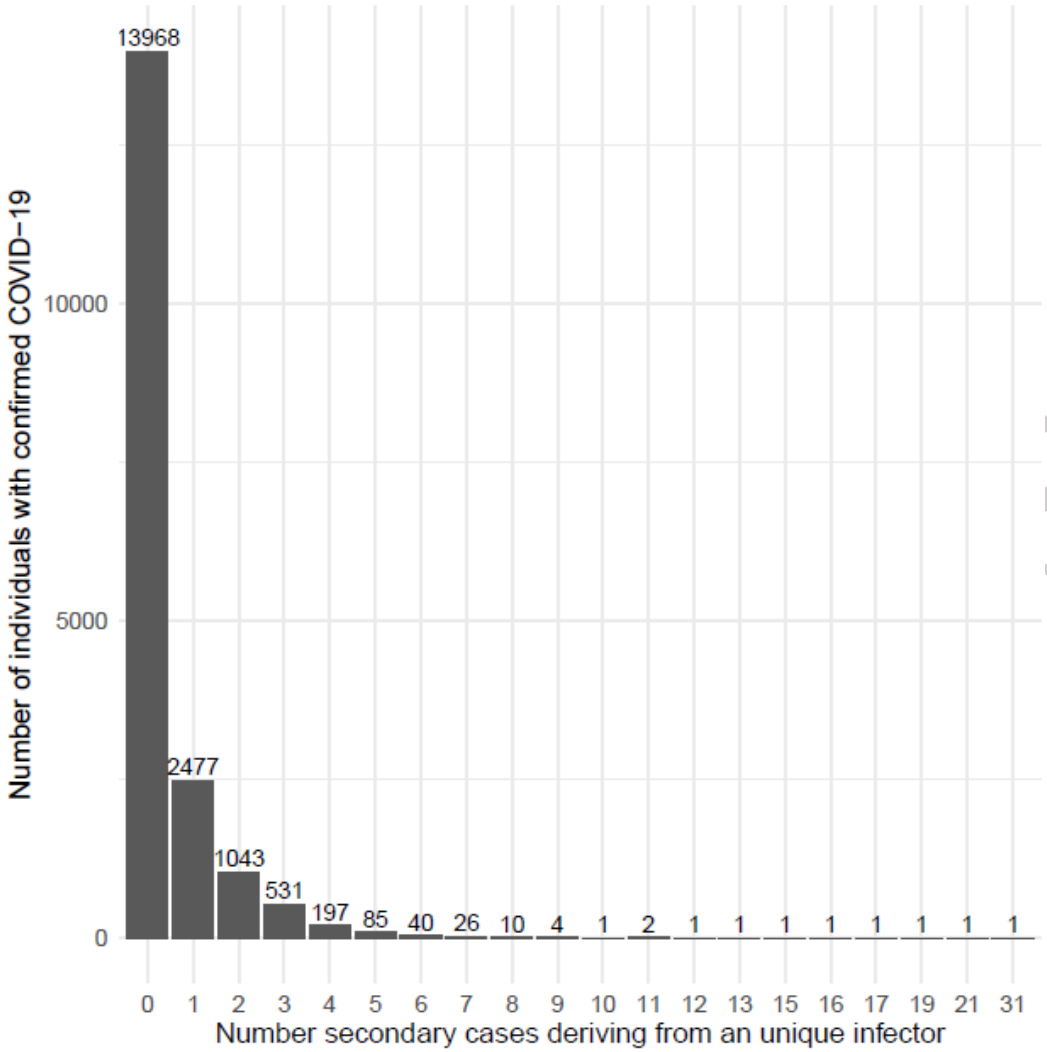

Figure 2: Distribution for the number of secondary cases, n=18,415.