TITLE: “Effects of BNT162b2 mRNA vaccination on COVID-19 disease, hospitalisation and mortality in nursing homes and healthcare workers: a prospective cohort study including 28,594 nursing home residents, 26,238 nursing home staff, and 61,951 healthcare workers in Catalonia”

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ABSTRACT [295w]

Background

Spain began vaccinating priority groups against COVID-19 with BNT162b2 in late December 2020. We report associations of vaccination with COVID-19 infection, hospitalisation, and mortality among nursing home residents, nursing home staff, and healthcare workers.

Methods

We analysed three cohorts of all nursing home residents, nursing home staff, and healthcare workers in Catalonia on 27 December 2020. Data were obtained from linked primary care, RT-PCR and lateral flow test, hospital, and mortality records. Those with a pre-study COVID-19 diagnosis or no linked electronic medical records were excluded. Two doses of BNT162b2 were administered 3 weeks apart. Participants were followed until the earliest of an outcome (confirmed COVID-19 infection, hospitalisation, and mortality) or 5 March 2021. Participants could contribute data to the unvaccinated, one-dose, and two-dose groups. Analyses were conducted using time-varying Cox regression. Multivariable adjustment for imbalances in socio-demographics, comorbidity, and polypharmacy.

Findings

We included 28,594 nursing home residents, 26,238 nursing home staff, and 61,951 healthcare workers, of whom 2,405, 1,584, and 2,672 received COVID-19 diagnoses; 383, 35 , and 76 were hospitalised; and 409, 0, and 1 died. The adjusted hazard ratio (HR) (95% confidence interval) for COVID-19 infection after two-dose vaccination was 0·08 (0·07-0·09) for nursing home residents, 0·12 (0·10-0·15) for nursing home staff, and 0·05 (0·04-0·07) for healthcare workers. The adjusted HRs for hospitalisation and mortality after two-dose vaccination were 0·03 (0·02-0·05) and 0·02 (0·01-0·03), respectively, for nursing home residents. Nursing home staff and healthcare workers recorded insufficient events for mortality analysis.

Interpretation
Vaccination was associated with 85%-96% reduction in SARS-CoV-2 infection in all three cohorts, and bigger reductions in hospitalisations and mortality amongst nursing home residents for up to two months. More data are needed on the long-term effects of COVID-19 vaccines.

Funding
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Key words: care home, COVID19 vaccine, effectiveness

RESEARCH IN CONTEXT

Evidence before this study

- Three COVID-19 vaccines have been approved for use in the UK and European Union to date.
- A large US-based trial found that the first vaccine to be approved, the BNT162b2 mRNA vaccine, had >90% efficacy against symptomatic COVID-19.
- Emerging evidence from observational studies have confirmed similar results in the UK and Israel.

Added value of this study

- Two-dose BNT162b2 vaccination was associated with 88% to 95% reductions in symptomatic and asymptomatic SARS-CoV-2 infections among nursing home residents, nursing home staff, and healthcare workers.
- Additionally, vaccination with two doses of BNT162b2 led to >95% reductions in COVID-19 hospitalisation and mortality among nursing home residents.
- This study outlines the effectiveness of the vaccine in the most vulnerable population to the complications of COVID: nursing home residents.
- This is the first study showing the effectiveness of the BNT162b2 vaccines in Spain.

Implications of all the available evidence

- The BNT162b2 vaccine is highly effective against SARS-CoV-2 infection in randomised controlled trials and observational cohort studies representative of actual practice settings and environments.
- BNT162b2 appears to effectively reduce infection, mild disease, and severe disease, including COVID-19 hospitalisation and mortality.
- The effects of two-dose vaccination with BNT162b2 in nursing home residents are equivalent to those demonstrated in randomised controlled trial participants.

INTRODUCTION

The global pandemic of coronavirus disease (COVID-19) has caused over 100 million confirmed cases and 2 million deaths to date.[1] Spain is one of the most affected countries in Europe, reporting over 3 million cases by February 2021, the second highest figure among the European Union (EU) and European Economic Area (EEA) member states.[2]

Three vaccines had been approved by the European Medicines Agency (EMA) at the time of writing, BNT162b2 mRNA, mRNA-1273, and ChAdOx1 nCoV-19.[3] All three have shown great efficacy in clinical trials, with 95% efficacy against symptomatic COVID-19 for BNT162b2 mRNA, 94·1% for mRNA-1273, and 70·4% for ChAdOx1 nCoV-19.[4–6] However, the trials have not included large enough sample sizes to provide reliable evidence of protection against severe diseases or mortality.

Certain population groups, such as nursing home residents, have been underrepresented in existing clinical trials of COVID-19 vaccination, despite evidence suggesting that nursing home residents and staff are disproportionately affected by COVD-19. Nursing homes accounted for a large proportion of deaths globally, and showed a disproportionately higher mortality than the general population of the same age.[7–9] Preventing outbreaks of infections and reducing related mortality in nursing home settings is crucial for minimising the impact of the pandemic. However, no trial has studied this population specifically. It is important to determine how effective COVID-19 vaccines are in these high-risk populations.

Little is known about the effectiveness of the approved vaccines in routine practice. Differences in compliance with vaccine doses and intervals, testing for SARS-CoV-2 infection, and management of COVID-19 in busy clinical settings may all affect the external validity of reported trial data.

Spain started its mass immunisation programme on 27 December 2020, soon after the first COVID-19 vaccine (BNT162b2 mRNA) was approved earlier that month. No data have been reported yet on vaccination compliance and its observable effects in the Spanish population. We aimed to characterise the first three cohorts of vaccinated individuals (nursing home residents, nursing home staff, and healthcare workers) and estimate the short-term effectiveness of the BNT162b2 mRNA vaccine in preventing infections, hospitalisation, and mortality.

METHODS

Study design and setting

We performed a prospective cohort study of three populations that were analysed separately: nursing home residents, nursing home staff, and healthcare workers. Vaccination status against SARS-CoV-2 infection was obtained from the Catalan Shared Clinical Records, a clinical database of electronic medical records that links primary care and hospital diagnoses and treatments for the whole universal Catalan health system. Data were further linked to the regional central database of reverse transcriptase polymerase chain reaction (RT-PCR) and lateral flow tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hospital admissions, mortality registries, and primary care electronic health records (EHR). Ninety percent of primary care practices in Catalonia, and 90% of the population, were included in the dataset. Data from these databases have been previously validated and used for epidemiological research,[10–12] including numerous COVID-19 studies.[7,13–15]

Participants and follow-up

We included all individuals alive at the beginning of the COVID-19 vaccination campaign with BNT162b2 mRNA in Catalonia on 27 December 2020 who were vaccine-eligible nursing home residents or staff or who were identified as a healthcare worker. We excluded those with a previous SARS-CoV-2 infection identified by a positive RT-PCR or lateral flow test and those who were not assigned to one of the primary care practices contributing to our database.

Non-vaccinated participants were followed from the beginning of the vaccination campaign until the earliest of: first dose of vaccine (they then switched to the 'single-dose vaccinated' arm), outcome (positive RT-PCR or lateral flow test, hospital admission, ICU admission, or death) or the end of study (5 March 2021). Single-dose vaccinated participants were followed from the day they received the first dose of the vaccine until the earliest of: a second dose of vaccine (they then switched to the 'two-dose vaccinated' arm), an outcome, or the end of the study. Two-dose vaccinated participants were followed from the day they received their second dose until an outcome or the end of the study. Exposure was treated as time-varying, with an individual able to contribute person-years of follow-up to all three arms.

Outcomes

We studied SARS-CoV-2 infection, COVID-19 hospital admission, and COVID-19-cause of death. COVID-19 infection was defined by the date of the earliest of a positive RT-PCR or lateral flow test, regardless of symptoms. Screening to all nursing home staff and residents using RT-PCR was conducted after any one case was identified. In addition, RT-PCR and lateral flow tests were done amongst healthcare workers on a fortnightly basis, and after 3 or more weeks of absence (eg after a holiday or leave). Hospital admission was considered as the date of hospitalisation for COVID-19 as reported in a bespoke official COVID-19 inpatient registry. Death due to COVID-19 was based on the reported diagnosis in the mortality registry.

Additional variables and potential confounders

Individual-level socio-demographics and clinical features were assessed at the time of inclusion as collected from primary care EHRs: age (in years), sex, residence status (nursing home resident or staff) or profession (healthcare worker), pre-existing comorbidities, and use of long-term medicines based on primary care prescriptions active at the time of the study. Lists of ICD-10-CM codes for comorbidities and lists of medicines identified using Anatomical Therapeutic Chemical Classification System codes are provided in Supplementary Table 1.

Statistical analysis

For descriptive analysis, continuous variables were expressed as mean (standard deviation) or median (interquartile range) and categorical variables were summarised as number (percentage). We analysed the existence of confounding by indication by comparing vaccinated and unvaccinated groups using the standardised mean difference (SMD) of all confounders listed above. An SMD >0·1 was considered equivalent to a relevant imbalance and was adjusted for in multivariable analyses.[16] Additionally, an analysis of effects in the first 12 days after first dose was conducted to assess the likely presence of residual confounding due to participant (unrecorded) variables, cluster effects at nursing home level, or changes in epidemiological parameters related to the COVID-19 pandemic at the community level. Any departure from the expected null effect (HR=1) in these first 12 days after first dose vaccination can be interpreted as a measure of residual confounding.

We analysed vaccination as a time-varying exposure with three follow-up intervals:

1) No vaccination: from 27th December 2020 until first dose vaccination, outcome, or end of study
2) One dose vaccination: from date of first dose administration to date of second dose, outcome, or end of study
3) Two dose vaccination: from date of second dose administration to outcome or end of study

For each of these periods, we calculated the rate of outcomes per 10,000 person-days by dividing the number of observed events within a period by the number of exposure days, multiplied by 10,000. We calculated relative risk reduction (RRR) for each outcome and study period based on the incidence rate ratio using the formula described by Rothman et al.[17]

Kaplan-Meier estimates for each study outcome stratified by vaccination status were plotted for visualisation and are provided in full in Appendix 2. Proportional hazard time-varying Cox models were fitted to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for each study outcome according to vaccination status. All Cox models were adjusted for age, sex, and any confounders with an SMD >0·1 and were conducted separately for each of the three cohorts (nursing home residents, nursing home staff, and healthcare workers). Proportionality of hazards in the Cox models was assessed by visual inspection of scaled Schoenfeld residuals.

All analyses were conducted using R version 3·5·1.[18]

Ethics

The use of pseudonymised routinely collected data described above for this project is allowed under disposition 17.2b of local data protection law. The study was approved by the Clinical Research Ethics Committee of the IDIAP Jordi Gol with reference number 21/045-PCV. The study authors did not access identified patient-level data for these analyses. All result sets represent aggregated, de-identified data that are reported at a minimum cell size of >5 to reduce potential for re-identification.

RESULTS

Before exclusions, data for 42,747 nursing home residents, 32,474 nursing home staff, and 83,344 healthcare workers were available for the study. We excluded 10,420 (24·4%) nursing home residents, 3,991 (12·3%) nursing home staff, and 12,919 (15·5%) healthcare workers as they had previously been infected with COVID-19. We also excluded 3,733 (11·5%) nursing home residents, 2,245 (7·9%) nursing home staff, and 8,474 (12·0%) healthcare workers due to a lack of linked primary care records data. We therefore analysed data from 28,594 nursing home residents, 26,238 nursing home staff, and 61,951 healthcare workers. Supplementary Table 2 shows socio-demographics for the excluded compared to the analysed populations.

By the end of the study period, 26,436 (92.74%) nursing home residents,19,898 (75.84%) nursing home staff, and 52,160 (84.2%) healthcare workers had been vaccinated with at least one dose. Figure 1 shows vaccine uptake in the three cohorts over the study period. Second doses were administered within a median 21 (interquartile range 0) days after the first dose.

Table 1 and Supplementary Figure 1 compare the vaccinated and unvaccinated groups of the three cohorts. There were no major differences (defined as SMD>0·1) between vaccinated and unvaccinated nursing home residents· Vaccinated residents had a mean age of 85.52 years old and were 73·35% female, while unvaccinated residents had a mean age of 84·78 years and were 70·89% female. They had otherwise similar prevalence of comorbidities and use of medicines. All covariates were sufficiently balanced without adjustment (SMD≤0·1). Vaccinated and unvaccinated nursing home staff were also similar in terms of age and sex: vaccinated staff had an average age of 45·1 years and 86.74% were female, while unvaccinated staff had an average age of 41·2 and were 88.28% female, with all SMD≤0.1. Vaccinated healthcare workers differed from unvaccinated ones in terms of age (43·5 vs 40.9 years, SMD=0.2), and sex (74.98% vs 79.25% female, SMD=0.102). No other relevant differences were detected.

Supplementary Figure 2 depicts the number of participants tested over time. By the end of the study period, a total of 26,974 (94.63%) nursing home residents, 24,186 (92.17%) nursing home staff, and 35,480 (57.27%) had been tested a median (inter-quartile range) of 3(4), 9(8), and 2(3) times respectively. There were 1,339 COVID-19 infections among unvaccinated nursing home residents and 1,066 among vaccinated residents. Most post-vaccination infections were after the first vaccine dose (876), with few after the second dose (180). The incidence rates of infection were 26.62/10,000 person-days for unvaccinated residents, 8·1/10,000 for all vaccinated residents, 15·9/10,000 for residents with one dose, and 2·4/10,000 for residents with two doses. Any vaccination led to an RRR for COVID-19 infection of 69.54 [95% CI: 69.49-69.59]. A single vaccine dose led to an RRR of 40.28 [95% CI: 40.17-40.39] and a second dose 90·89 [90.84-90.95] (Table 2). The resulting adjusted HRs were 0·53 [0·49-0·58] after the first dose and 0·08 [0·07-0·09] after the second. Figure 2a shows Kaplan Meier plots stratified by vaccination status, where a modest but noticeable reduction in infections was apparent earlier than expected, already in the first 12 days amongst the vaccinated vs unvaccinated. The resulting adjusted HR of 0·77 [0·69-0·86] is a measure of residual confounding due to individual,

nursing home factors, or community changes in COVID-19 transmission. Full Kaplan-Meier estimates are reported in Appendix 2.

Similar results were observed for nursing home staff, with 1,055 infections among unvaccinated staff and 525 among vaccinated. Most infections among vaccinated staff were after the first vaccine dose (413), not the second (105). The incidence rates of infection were 13·86/10,000 person-days for unvaccinated staff, 5·58 for all vaccinated staff, 10·19 for staff with one dose, and 2·08 for staff with two doses. Any vaccination led to an RRR for infection of 59.76 [95% CI: 59·64-59·87]. A single vaccine dose led to an RRR of 26·49 [95% CI: 26·25-26·74], while a second dose led to 85·02 [95% CI: 84·86-85·17]. The resulting adjusted HRs were 0·60 [0·53-0·67] after one dose and 0·12 [0·10-0·15] after two doses (Table 2, Figure 2). Kaplan-Meier estimates are detailed in Appendix 2. The adjusted HR associated with 1-dose vaccination during the first 12 days was 0·80 [0·68-0·93], suggesting the presence of moderate unresolved confounding at the individual, nursing home, and/or community level/s.

Finally, in the cohort of healthcare workers, 1,844 unvaccinated and 815 vaccinated staff tested positive for SARS-CoV-2 (743 after one dose, 69 after the second). The incidence rates of infection were 10·32/10,000 person-days among unvaccinated healthcare workers and 3·65 /10,000 among all vaccinated healthcare workers (6·83/10,000 after one dose and 0·62/10,000 after two doses). Any vaccination led to an RRR of 64·63 [95% CI: 64·57-64·70]. A single dose led to an RRR of 33·80 [95% CI: 33·66-33·92], while a second dose led to 94·01 [95% CI: 93·92-94·10]. The resulting adjusted HRs were 0·57 [0·53-0·63] after one dose and 0·05 [0·04-0·07] after two doses (Table 2, Figure 2). Kaplan-Meier aggregated data are fully reported in Appendix 2. The adjusted HR for the first 12 days after first dose vaccination was 0·85 [0·77-0·95], suggesting the presence of some residual confounding.

Hospitalisations were recorded for 383 nursing home residents. The incidence rates of COVID-19 hospitalisation were 4·28/10,000 person-days for unvaccinated residents and 1·11/10,000 for all vaccinated residents (2·30/10,000 after one dose and 0·21/10,000 after two doses). Any vaccination led to an RRR for hospitalisation of 74.06 [95% CI: 73·78-74.34]. One vaccine dose led to an RRR of 46.24 [95% CI: 45·62-46·86], while a second dose led to 95·06 [94·73-95·38]. Multivariable Cox regression models resulted in adjusted HRs of 0·45 [0·36-0·56] after the first dose and 0·03 [0·02-0·05] after the second (Table 3). Figure 3 shows Kaplan-Meier plots for hospitalisations in nursing home residents by vaccination status, with full aggregated data available in Appendix 2.

We observed 409 deaths among nursing home residents. Incidence rates of COVID-19 mortality were 4·82 /10,000 person-days in unvaccinated residents and 1·08/10,000 in all vaccinated residents (2·33/10,000 after one dose and 0·24/10,000 after two doses). Any vaccination led to an RRR for death of 77·51 [95% CI: 77·28-75·75]. One vaccine dose led to an RRR of 51·71 [95% CI: 51·17-52·23], while two doses led to 96·73 [96·43-96·99]. Cox regression models gave adjusted HRs of 0·50 [0·40-0·63] after the first dose and 0·02 [0·01-0·03] after the second (Table 3). Figure 3 shows Kaplan-Meier plots for mortality in nursing home residents by vaccination status (full aggregated figures in Appendix 2).

We recorded hospitalisations for 35 nursing home staff and 76 healthcare workers and no deaths in either cohort. We did not model these outcomes in these two cohorts, as the few small numbers of events gave limited statistical power.

DISCUSSION

This is the first report of the clinical effectiveness of a COVID-19 vaccine in nursing homes globally to our knowledge, and the first set of results on the effect of vaccination to prevent COVID-19 in Spain. Using a comprehensive linked database that combined primary care, screening and diagnostic RT-PCR and lateral flow tests, hospital, and mortality data, we studied the effects of the BNT162b2 mRNA vaccine in the three populations prioritised for vaccination nationally. Partial (single-dose) vaccination resulted in 40%-50% reductions in COVID-19 infections in all three cohorts, while full (two-dose) vaccination led to 88%-95% protection. The observed effects were slightly stronger in healthcare workers (95%) than in nursing home staff (92%) and nursing home residents (88%). We identified mild-moderate reductions in COVID-19 infections during the first 12 days after the first dose, suggesting that 15% to 20% of the observed reductions are not attributable to vaccination but to unobserved confounders, nursing home cluster effects, or changes in the background community transmission measures.

We also found significant, clinically relevant reductions in the risks of severe COVID-19 amongst nursing home residents, amounting to a striking 97% and 98% reduction in hospitalization and mortality risks respectively, after two doses of BNT162b2.

While ambitious COVID-19 vaccination campaigns are ongoing around the world, knowledge is still scarce on the real-world effectiveness of COVID-19 vaccines, especially in high-risk populations such as nursing home residents and healthcare workers. Although vaccines have shown high efficacy in clinical trials, real-world evidence on effectiveness is needed to confirm their effects in routine practice settings and among populations under-represented in pivotal trials. A recent study with national population-level Scottish data showed that by the fourth week after the first dose, the BNT162b2 and ChadOx1 vaccines reduced the risk of hospitalisation by 85% (95% CI: 76-91%) and 94% (95% CI: 73-99%), respectively. It also showed that two doses of the BNT162b2 mRNA vaccine offered more than 85% protection against symptomatic infection among those aged over 80.[19] A prospective cohort study of hospital staff in England reported vaccine effectiveness of 72% (95% CI: 58-86%) in the 21 days after the first dose of the BNT162b2 mRNA vaccine.[20] A cohort study in Israel of healthcare workers reported a 75% reduction in SARS-CoV-2 infection and 85% (95% CI: 71-92%) reduction in symptomatic COVID-19 during the 15-28 days after the first dose of BNT162b2.[21] A recent study including over half a million people in Israel estimated the effectiveness of the BNT162b2 vaccine against infection at 46% (95% CI: 40-51%) 14 to 20 days after the first dose and 92% (95% CI: 88-95%) 1 week after the second dose.[22]

We found that one dose of the BNT162b2 vaccine reduced the risk of infection by 42% in nursing home residents, 35% in nursing home staff, and 32% in healthcare workers. These results are equivalent to the reported vaccine efficacy of 52·4% between the first and second dose in the BNT162b2 mRNA phase 3 trial.[5] In line with phase 3 trial findings, our results

highlight that vaccine recipients should be told about the modest protection seen between the first and second dose and encouraged to continue shielding, physical distancing, and other protective measures, especially during the first two weeks after the initial dose.

Our study differs from the trial in setting, participants, and outcome ascertainment. Although the trial only included symptomatic COVID-19, we included any RT-PCR- or lateral-flow-tested positive infection, including regular screening testing. The three populations included were screened periodically during the study period to minimise potential outbreaks: whilst nursing homes conducted universal RT-PCR amongst staff and residents every time a case was identified, healthcare workers were tested (with RT-PCR or lateral flow test) every fortnight and after a leave of absence >3 weeks. The observed reduction in infection rates including screening tests is of high relevance, and supports recent data suggesting that vaccination could reduce overall transmission of the virus.[20]

Our study has several limitations. The observational nature of our data may have led to confounding by indication. Comprehensive linkage to primary care and hospital records allowed us to measure differences in socio-demographics, comorbidity, and medication usage. We examined the distribution of the individual characteristics collected in our linked databases. The only measured confounder with identified imbalance was age, which we adjusted for in multivariable models. We quantified that a moderate 15% to 25% of the observed reductions in COVID-19 risk were attributable to factors other than vaccination. Unobserved participant covariates, nursing home cluster effects, and changes in community transmission likely account for these. In addition to these, increased personal protection during the first two weeks after vaccination could also contribute to this. Such measures were not recommended in pivotal trials as participants were blinded to vaccine exposure and neither participants or investigators had knowledge of the lack of effect during the first 12 days post vaccination. Our database also had a relatively short follow-up, with a maximum of 2 months. The studied cohorts will continue to be followed-up over time, allowing us to report on longer-term outcomes in future analyses.

This study also has strengths. The comprehensive linkage and coverage in our database is unique, including primary care, hospital, RT-PCR and lateral flow test results, and mortality data for over 90% of the regional population. The Catalan health system is universal, minimising dropouts and maximising the completeness of outcome ascertainment. Access to basic socio-demographics and events for people excluded from the analysis allowed us to measure potential selection bias. Our included study population allowed us to study the effects of vaccination against hospitalisation and death in nursing home residents, a population subgroup extremely vulnerable to severe and lethal forms of COVID-19,[7] and under-represented in previous studies.[22] The pivotal trial was underpowered to analyse these outcomes.[5]

In conclusion, our data confirmed that the BNT162b2 vaccination strongly reduced the risk of SARS-CoV-2 infection in nursing homes and in health care workers with comparable results to those observed in US-based phase 3 trials and other international observational studies. Hospitalisation and death with COVID-19 were similarly reduced among nursing home residents, who accounted for a large proportion of COVID-19 deaths in 2020. Although further data and studies are needed to assess the long-term effectiveness and safety of this and other

COVID-19 vaccines, these findings should reassure the population of the major benefits associated with the ongoing vaccination campaign in Spain and elsewhere.

Data sharing: No patient level data can be shared due to local information governance and data protection regulations. Aggregated data are available and reported in the supplement.

Conflict of interest statement: DPA's research group have received grants and advisory or speaker fees from Amgen and UCB, unrelated to the current work. None of the other co-authors have relevant conflicts of interest to report. Individual conflict of interest disclosures have been uploaded separately with this manuscript.

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Author contributions: Authorship forms have been uploaded separately. CC, DPA, EC and NCF were responsible for study design. EC and NCF data analyses DPA, EC and XL drafted the manuscript, and all co-authors reviewed and approved for submission.

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TABLES AND FIGURES

Table 1. Baseline characteristics stratified by vaccination status (none vs any)

Table 1. Baseline characteristics stratified by vaccination (none vs any) status

	Nursing home residents		Nursing home staff		Healthcare workers	
	Vaccinated N = 26,436	Unvaccinated N = 2,068	Vaccinated N = 19,898	Unvaccinated N =6,340	Vaccinated N =52,160	Unvaccinated N = 9,791
Age	85.52 (9.05)	84.78 (11.09)	45.05 (12.44)	41.21 (13.41)	43.54 (12.22)	40.92 (12.86)
Gender (Female)	19,391 (73.35%)	1,466 (70.89%)	17,260 (86.74%)	5,597 (88.28%)	39,108 (74.98%)	7,759 (79.25%)
Number of patients with test performed (%)	25,287 (95.65%)	1,687 (81.57%)	19,207 (96.52%)	4,979 (78.53%)	29,780 (57.09%)	5,700 (58.21%)
Number of test per patient	3 [1-5]	3 [2-5]	9 [7 -13]	8 [4-11]	2 [1-4]	2 [1-4]
Analgesics	13,705 (51.84%)	1,074 (51.93%)	1,470 (7.39%)	506 (7.98%)	2,758 (5.29%)	664 (6.78%)
Sedatives/hypnotics	10,431 (39.46%)	735 (35.54%)	1,914 (9.62%)	616 (9.72%)	4,177 (8.01%)	844 (8.62%)
Anticoagulants	11,260 (42.59%)	880 (42.55%)	347 (1.74%)	121 (1.91%)	904 (1.73%)	287 (2.93%)
Antidepressants	12,732 (48.16%)	900 (43.52%)	1,943 (9.76%)	657 (10.36%)	4,334 (8.31%)	883 (9.02%)
Antiepileptics	4,528 (17.13%)	338 (16.34%)	581 (2.92%)	185 (2.92%)	1,276 (2.45%)	262 (2.68%)

Antipsychotics	11,460 (43.35%)	806 (38.97%)	197 (0.99%)	74 (1.17%)	368 (0.71%)	100 (1.02%)
Antacids	13,670 (51.71%)	1,054 (50.97%)	1,318 (6.62%)	396 (6.25%)	3,171 (6.08%)	582 (5.94%)
Systemic corticoids	932 (3.53%)	100 (4.84%)	145 (0.73%)	66 (1.04%)	383 (0.73%)	116 (1.18%)
Oral antidiabetics	3,921 (14.83%)	298 (14.41%)	508 (2.55%)	116 (1.83%)	873 (1.67%)	131 (1.34%)
Insulin	2,206 (8.34%)	203 (9.82%)	171 (0.86%)	50 (0.79%)	364 (0.70%)	64 (0.65%)
Lipid modifying agents	5,368 (20.31%)	384 (18.57%)	1,003 (5.04%)	241 (3.80%)	2,405 (4.61%)	333 (3.40%)
Alpha blockers	301 (1.14%)	22 (1.06%)	15 (0.08%)	6 (0.09%)	44 (0.08%)	11 (0.11%)
Other antihypertensives	112 (0.42%)	10 (0.48%)	4 (0.02%)	1 (0.02%)	18 (0.03%)	3 (0.03%)
Beta blockers	4,850 (18.35%)	416 (20.12%)	440 (2.21%)	112 (1.77%)	1,277 (2.45%)	182 (1.86%)
Calcium channel blockers	3,855 (14.58%)	298 (14.41%)	295 (1.48%)	88 (1.39%)	648 (1.24%)	96 (0.98%)
Combination antihypertensives	2,352 (8.90%)	153 (7.40%)	553 (2.78%)	159 (2.51%)	1,001 (1.92%)	166 (1.70%)
Diuretics	8,541 (32.31%)	685 (33.12%)	368 (1.85%)	90 (1.42%)	716 (1.37%)	129 (1.32%)
ACEi/ARBs	7,689 (29.09%)	595 (28.77%)	1,016 (5.11%)	239 (3.77%)	2,225 (4.27%)	333 (3.40%)
Chronic obstructive pulmonary disease/asthma inhalers	3,383 (12.80%)	287 (13.88%)	753 (3.78%)	260 (4.10%)	2,055 (3.94%)	460 (4.70%)
Atrial fibrillation	4,401 (16.65%)	384 (18.57%)	45 (0.23%)	19 (0.30%)	207 (0.40%)	31 (0.32%)

Osteoarthritis	11,390 (43.09%)	851 (41.15%)	1,645 (8.27%)	446 (7.03%)	2,250 (4.31%)	435 (4.44%)
Asthma	1,190 (4.50%)	103 (4.98%)	1,043 (5.24%)	374 (5.90%)	3,200 (6.13%)	643 (6.57%)
Ischaemic heart disease	2,261 (8.55%)	171 (8.27%)	82 (0.41%)	21 (0.33%)	239 (0.46%)	40 (0.41%)
Dementia	11,010 (41.65%)	803 (38.83%)	7 (0.04%)	2 (0.03%)	3 (0.01%)	0
Diabetes mellitus	6,909 (26.13%)	552 (26.69%)	646 (3.25%)	159 (2.51%)	1,104 (2.12%)	197 (2.01%)
Liver disease	985 (3.73%)	76 (3.68%)	603 (3.03%)	159 (2.51%)	968 (1.86%)	173 (1.77%)
Hypertension	18,092 (68.44%)	1,399 (67.65%)	2,184 (10.98%)	519 (8.19%)	4,062 (7.79%)	640 (6.54%)
Heart Failure	3,079 (11.65%)	250 (12.09%)	19 (0.10%)	3 (0.05%)	31 (0.06%)	8 (0.08%)
Cerebrovascular disease	2,857 (10.81%)	249 (12.04%)	79 (0.40%)	29 (0.46%)	159 (0.30%)	30 (0.31%)
Chronic obstructive pulmonary disease	2,208 (8.35%)	168 (8.12%)	149 (0.75%)	50 (0.79%)	241 (0.46%)	55 (0.56%)
Chronic kidney disease	6,746 (25.52%)	567 (27.42%)	118 (0.59%)	19 (0.30%)	257 (0.49%)	43 (0.44%)
Cancer (all except non-melanoma skin cancer)	4,762 (18.01%)	387 (18.71%)	527 (2.65%)	176 (2.78%)	1,888 (3.62%)	385 (3.93%)
Obesity	5,372 (20.32%)	384 (18.57%)	3,555 (17.87%)	947 (14.94%)	4,643 (8.90%)	859 (8.77%)
AIDS	14 (0.05%)	2 (0.10%)	31 (0.16%)	7 (0.11%)	24 (0.05%)	6 (0.06%)
Valvular disease	1,619 (6.12%)	137 (6.62%)	124 (0.62%)	28 (0.44%)	355 (0.68%)	68 (0.69%)

Hepatitis B	79 (0.30%)	9 (0.44%)	47 (0.24%)	28 (0.44%)	54 (0.10%)	12 (0.12%)
Hepatitis C	298 (1.13%)	27 (1.31%)	76 (0.38%)	21 (0.33%)	84 (0.16%)	26 (0.27%)
HIV infection	14 (0.05%)	1 (0.05%)	66 (0.33%)	13 (0.21%)	62 (0.12%)	14 (0.14%)

Table 2. Number, incidence rates, relative risk reductions, and age-sex adjusted hazard ratios (HR) for COVID-19 according to vaccination status in nursing home residents, nursing home staff, and healthcare workers.

Cohort	Periode	Population	Cases	Exposure person-days (N)	Exposure days (mean)	Rate per 10 000 pers-days	Risk reduction compared to unvaccinated [95% CI]	Age and sex-adjusted HR (95% CI)
Residents	Unvaccinated	28,191	1,339	503,074	17.85	26.62	REF	REF
Residents	Total follow-up	24,993	1,066	1,314,887	52.61	8.11	69.54 [69.49 - 69.59]	0.38 [0.35 - 0.42]
Residents	12 days after 1st dose	24,993	523	297,572	11.90	17.58	20.03 [19.76 - 20.30]	0.77 [0.69 - 0.86]
Residents	Vaccinated (1 dose)	24,993	876	551,132	22.051	15.89	40.28 [40.17 - 40.39]	0.53 [0.49 - 0.58]
Residents	Vaccinated (2 doses)	21,710	180	742,733	34.21	2.42	90.89 [90.84 - 90.95]	0.08 [0.07 - 0.09]
Staff	Unvaccinated	26,075	1,055	760,997	29.18	13.86	REF	REF
Staff	Total follow-up	18,561	525	940,990	50.7	5.58	59.76 [59.64 - 59.87]	0.43 [0.39 - 0.49]
Staff	12 days after 1st dose	18,561	268	221,219	11.92	12.11	20.27 [19.8 - 20.73]	0.8 [0.68 - 0.93]
Staff	Vaccinated (1 dose)	18,561	413	405,280	21.84	10.19	26.49 [26,25 - 26.74]	0.60 [0.53 - 0.67]
Staff	Vaccinated (2 doses)	15,295	105	505,426	33.05	2.08	85.015 [84.86 - 85.17]	0.12 [0.10 - 0.15]
Healthcare workers	Unvaccinated	61,938	1,844	1,788,049	28.87	10.32	REF	REF

Healthcare workers	Total follow-up	47,106	815	2,234,553	47.44	3.65	64.63 [64.57 - 64.7]	0.41 [0.38 - 0.45]
Healthcare workers	12 days after 1st dose	47,106	556	562,075	11.93	9.89	15.44 [15.19 - 15.68]	0.85 [0.77 - 0.95]
Healthcare workers	Vaccinated (1 dose)	47,106	743	1,088,264	23.10	6.83	33.8 [33.66 - 33.92]	0.57 [0.53 - 0.63]
Healthcare workers	Vaccinated (2 doses)	37,403	69	1,117,482	29.88	0.62	94.01 [93.92 - 94.1]	0.05 [0.04 - 0.07]

Table 3. Number of hospital admissions and deaths amongst nursing home residents, incidence rates, relative risk reductions, and age-sex adjusted hazard ratios (HR) according to vaccination

Outcome	Periode	Population	Cases	Exposure person-days (N)	Exposure days (mean)	Rate per 10 000 pers-days	Risk reduction compared to unvaccinated [95% CI]	Age and sex-adjusted HR (95% CI)
Hospital admissions	Unvaccinated	28,118	231	539,452	19.19	4.28	REF	REF
Hospital admissions	Total follow-up	25,487	152	1,368,470	53.69	1.11	74.06 [73.78 - 74.34]	0.22 [0.18 - 0.27]
Hospital admissions	12 days after 1st dose	25,487	19	305,784	11.99	0,62	67.59 [65.29 - 69.75]	0.30 [0.18 - 0.51]
Hospital admissions	Vaccinated (1 dose)	25,487	134	582,106	22.84	2.3	46.24 [45.62 - 46.86]	0.45 [0.36 - 0.56]

Hospital admissions	Vaccinated (2 doses)	22,071	16	757,019	34.29	0.21	95.06 [94.73 - 95.38]	0.03 [0.02 - 0.05]
Deaths	Unvaccinated	28,191	260	538,874	19.12	4.82	REF	REF
Deaths	Total follow-up	25,587	149	1,373,409	53.68	1.08	77.51 [77.28 - 77.75]	0.15 [0.12 - 0.18]
Deaths	12 days after 1st dose	25,587	15	306,992	11.99	0.49	43.95 [37.87 - 49.44]	0.47 [0.25 - 0.89]
Deaths	Vaccinated (1 dose)	25,587	136	583,665	22.81	2.33	51.71 [51.17 - 52.23]	0.50 [0.40 - 0.63]
Deaths	Vaccinated (2 doses)	22,149	12	759,531	34.29	0.16	96.73 [96,43 - 96,99]	0.02 [0.01 - 0.03]

Figure 1. Vaccine uptake by nursing home residents, nursing home staff, and healthcare workers in Spain, depicted as percentage who had received at least one dose over time from the first vaccination in Spain on 27 December 2020.

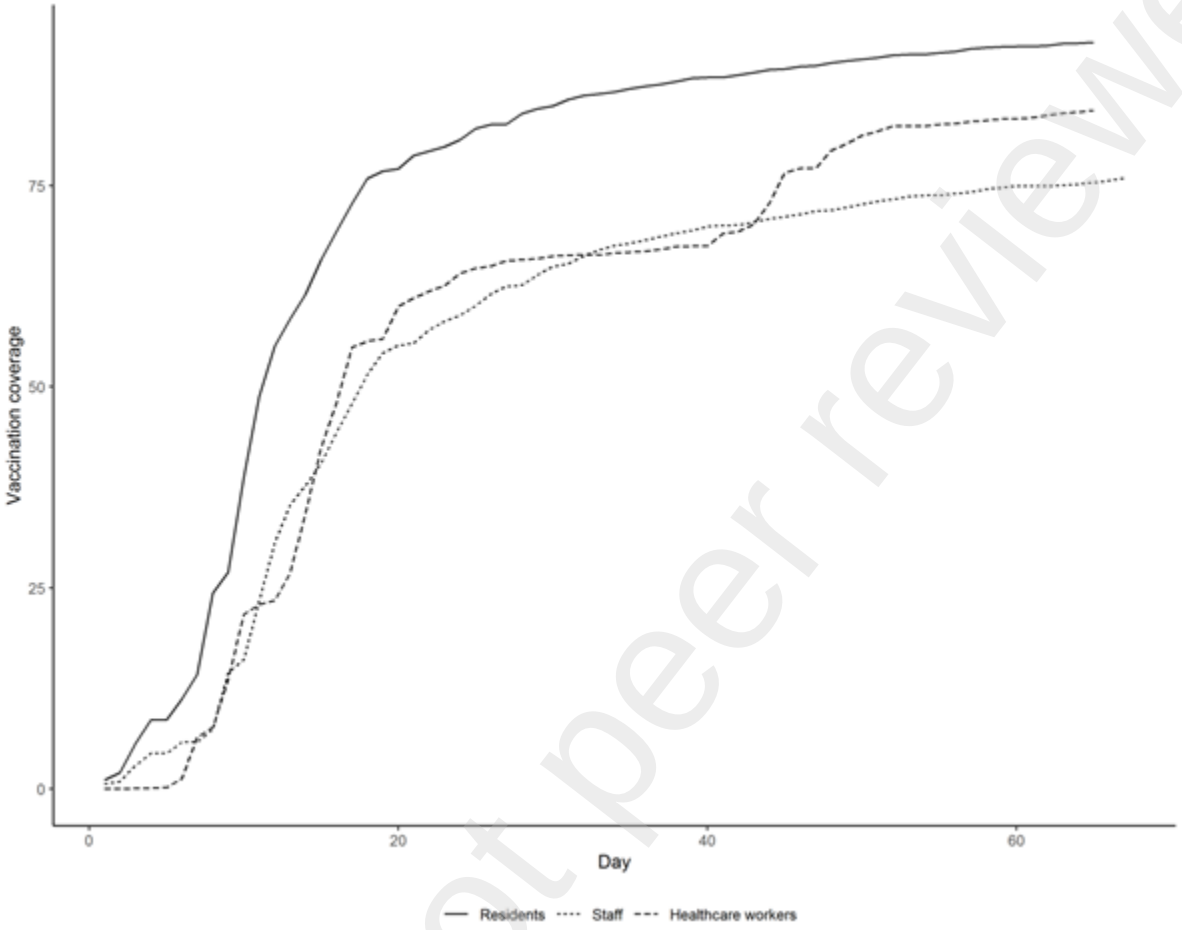


Figure 2. Kaplan-Meier estimates of COVID-19 infection according to vaccination status in nursing home residents (top left), nursing home staff (top right), and healthcare workers (bottom).

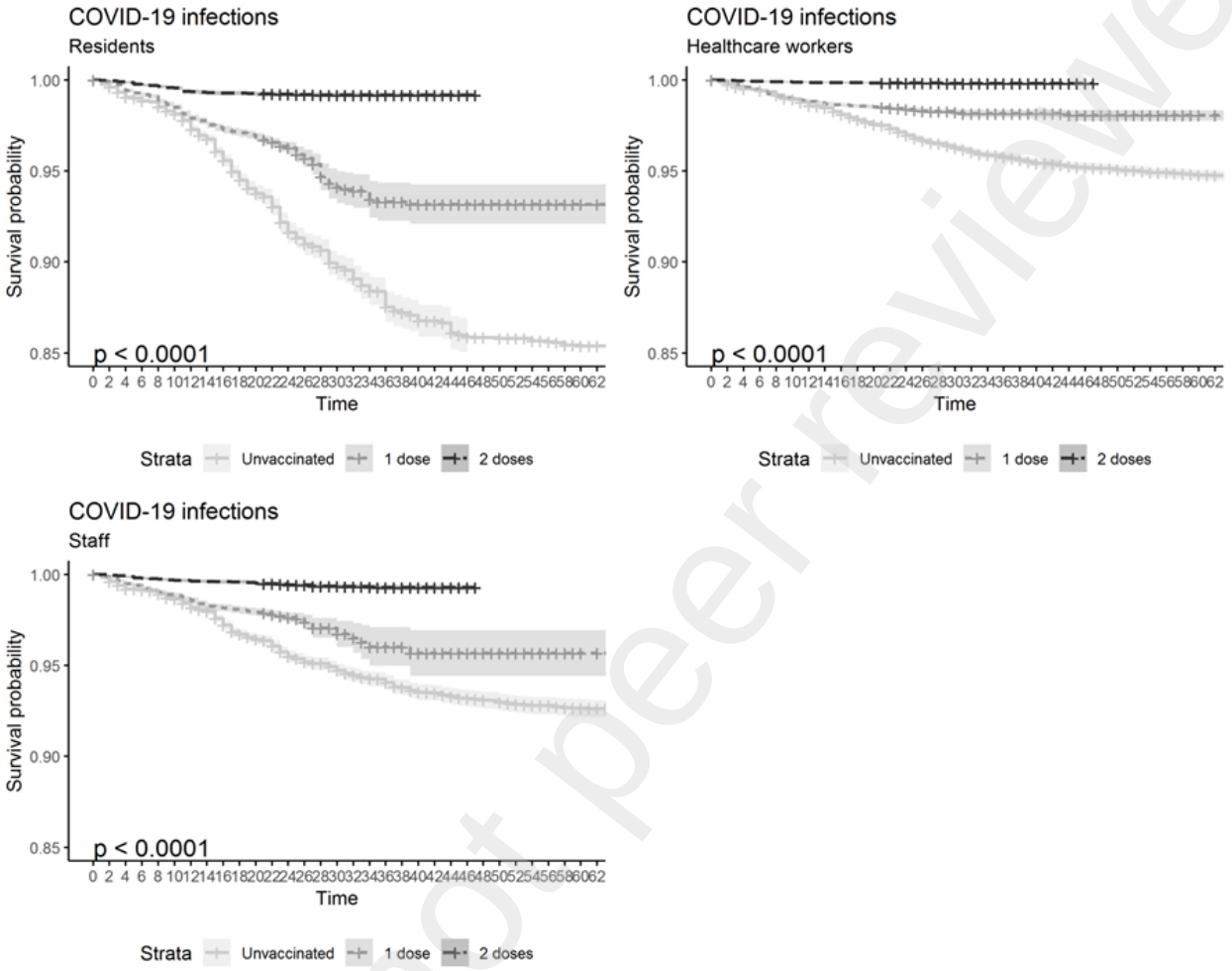
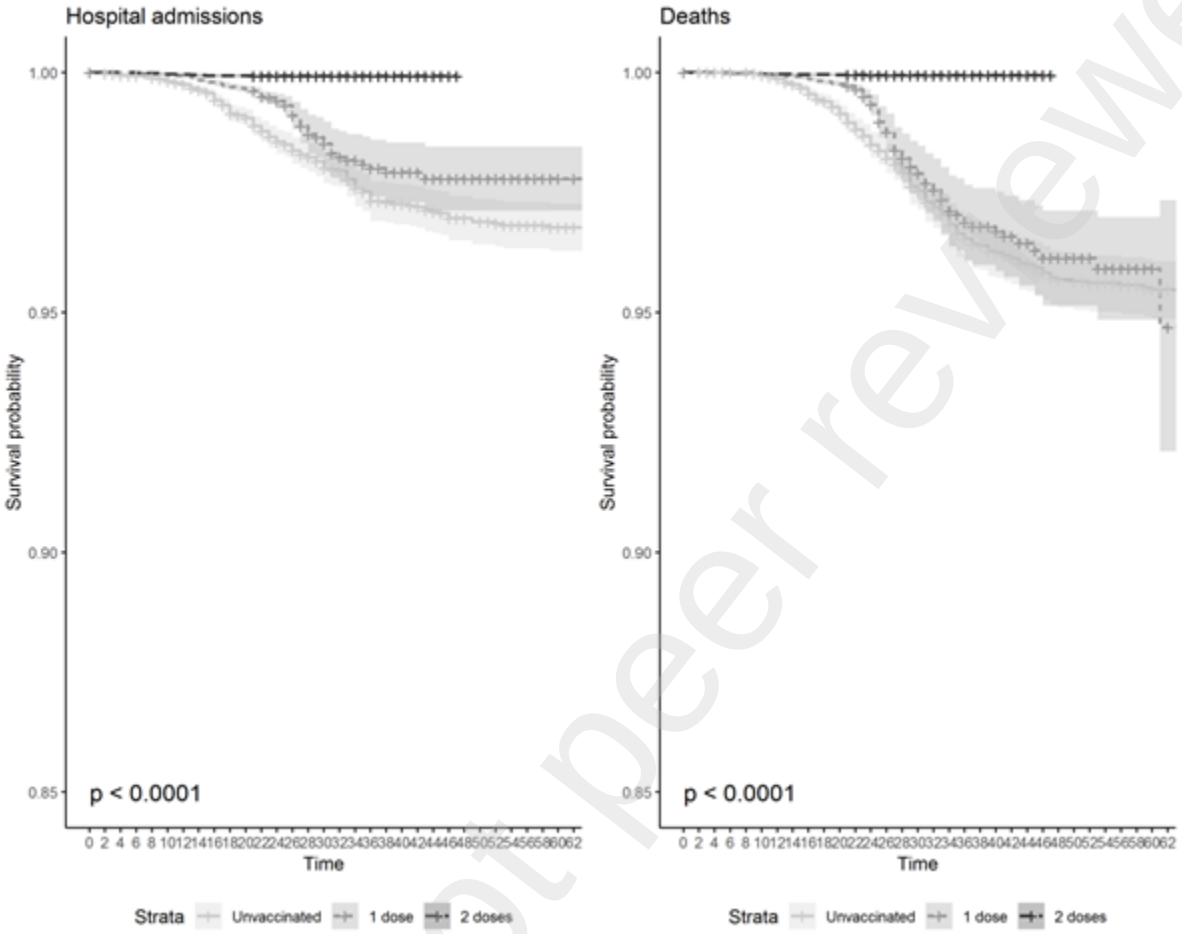


Figure 3. Kaplan-Meier estimates of COVID-19-related hospital admissions (left) and deaths (right) according to vaccination status in nursing home residents.



APPENDIX 1 – Supplementary Tables and Figures

Supplementary Table 1. Co-morbidities and long-term medications included in the analysis.

Supplementary Figure 1 Standardised mean differences (SMD) of comorbidities and long-term medicine uses between vaccinated and unvaccinated nursing home residents, nursing home staff, and healthcare workers.

Supplementary Table 2. Differences in socio-demographics and vaccination status between included and excluded study participants

Supplementary Figure 2. Number of RT-PCR or lateral flow tests performed during the study period.

APPENDIX 2 – Full Kaplan-Meier aggregated data

REFERENCES

1 WHO Coronavirus disease (COVID-19) dashboard. *COVID 19 Special Issue* 2020; **10**. DOI:10.46945/bpj.10.1.03.01.

2 COVID-19 situation update for the EU/EEA, as of week 6, updated 18 February 2021. https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea (accessed Feb 25, 2021).

3 Glanville D. Treatments and Vaccines for COVID-19: Authorised Medicines. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-vaccines-covid-19-authorised-medicines.

4 Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; **384**: 403–16.

5 Polack FP, Thomas SJ, Kitchin N, *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**: 2603–15.

6 Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397**: 99–111.

7 Prieto-Alhambra D, Balló E, Coma E, *et al.* Filling the gaps in the characterization of the clinical management of COVID-19: 30-day hospital admission and fatality rates in a cohort of 118 150 cases diagnosed in outpatient settings in Spain. *Int J Epidemiol* 2021; **49**: 1930–9.

8 Rada AG. Covid-19: the precarious position of Spain's nursing homes. *BMJ* 2020; **369**: m1554.

9 Morciano M, Stokes JM, Kontopantelis E, Hall I, Turner AJ. Excess mortality for care home residents during the first 23 weeks of the COVID-19 pandemic in England: a national cohort study. bioRxiv. 2020; published online Nov 13. DOI:10.1101/2020.11.11.20229815.

10 Baena-Díez JM, Garcia-Gil M, Comas-Cufí M, *et al.* Association between chronic immune-mediated inflammatory diseases and cardiovascular risk. *Heart* 2018; **104**: 119–26.

11 Garcia-Gil M, Elorza J-M, Banque M, *et al.* Linking of primary care records to census data to study the association between socioeconomic status and cancer incidence in Southern Europe: a nation-wide ecological study. *PLoS One* 2014; **9**: e109706.

12 García-Gil MDM, Hermosilla E, Prieto-Alhambra D, *et al.* Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). *Inform Prim Care* 2011; **19**: 135–45.

13 Burn E, Tebé C, Fernandez-Bertolin S, *et al.* The natural history of symptomatic COVID-19 during the first wave in Catalonia. *Nat Commun* 2021; **12**: 777.

14 Morales DR, Conover MM, You SC, *et al.* Renin-angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis. Lancet Digit

Health. 2021; **3**: e98–114.

15 Duarte-Salles T, Vizcaya D, Pistillo A, *et al.* Baseline characteristics, management, and outcomes of 55,270 children and adolescents diagnosed with COVID-19 and 1,952,693 with influenza in France, Germany, Spain, South Korea and the United States: an international network cohort study. *medRxiv* 2020; published online Oct 30. DOI:10.1101/2020.10.29.20222083.

16 Nguyen T-L, Collins GS, Spence J, *et al.* Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Med Res Methodol* 2017; **17**: 78.

17 Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Lippincott Williams & Wilkins, 2008.

18 R Core Team. R software: Version 3.5.1. R Found Stat Comput Published Online First: 2018. DOI:10.1007/978-3-540-74686-7.

19 Vasileiou E, Simpson CR, Robertson C, *et al.* Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People. 2021; published online Feb 19. DOI:10.2139/ssrn.3789264.

20 Hall VJ, Foulkes S, Saei A, *et al.* Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study). 2021; published online Feb 22. DOI:10.2139/ssrn.3790399.

21 Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *Lancet* 2021; published online Feb 18. DOI:10.1016/S0140-6736(21)00448-7.

22 Dagan N, Barda N, Kepten E, *et al.* BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med* 2021; published online Feb 24. DOI:10.1056/NEJMoa2101765.