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SARS-CoV-2 seroreversion and all-cause mortality in nursing home residents and staff post-primary course vaccination in Belgium between February and December 2021

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ABSTRACT

Background: During COVID-19 vaccine implementation, information on the persistence of antibody response and impact on mortality in nursing home residents was limited, as they were underrepresented in vaccine clinical trials and real-world data was lacking.
Objectives: (1) Measure the persistence of the SARS-CoV-2 antibody response and predictors for seroreversion after primary course COVID-19 vaccination in nursing home residents compared to staff and (2) assess all-cause mortality and predictors in nursing home residents after primary COVID-19 vaccination.
Methods: Seroprevalence and mortality data were collected within a national serosurveillance study in 1640 residents and 1368 staff from 69 nursing homes proportionally spread across Belgium between February and December 2021. To assess the persistence of the antibody response, parametric exponential survival models with interval censoring were fitted, reported with the percentage of seroreverters 120 and 140 days post-primary course vaccination. Furthermore, all-cause mortality rate was calculated and COVID-19 mortality was descriptively reported. Predictors of seroreversion and all-cause mortality were estimated using Cox proportional hazards model.
Results: Nursing home residents were 47 % more likely to serorevert in the 10 months after COVID-19 vaccination than staff. Infection naïvety, older age and high resident care dependency level were found as predictors for seroreversion. The all-cause mortality rate in vaccinated residents over 10 months was 14 % (95 % CI 13–16 %) ($n = 229$). In 2 % of cases, COVID-19 infection was the reported cause of death. Older age, being male, having severe renal, lung, or cardiac disease, or active cancer, and high care dependency level were identified as predictors for all-cause mortality, irrespective of history of SARS-CoV-2 or breakthrough infection.
Conclusion/practical implication: Future COVID-19 vaccination strategies should prioritize (infection naïve) nursing home residents, as they fail to mount a durable antibody response after primary course vaccination. Nevertheless, COVID-19 mortality remained low, representing only 2 % of the all-cause mortality rate.
This study was registered on ClinicalTrials.gov (NCT04738695).

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1. Background

During the first year of the SARS-CoV-2 pandemic, nursing homes (NH) in Belgium experienced severe COVID-19 attack rates and burden [1,2]. For this reason, when COVID-19 vaccines were implemented, nursing home residents (NHR) and nursing home staff (NHS) were prioritized in the vaccination campaign. Between January and March 2021, the majority of NHR and NHS in Belgium got vaccinated with a two-dose regimen of the BNT162b2 (Pfizer-BioNTech) vaccine, administered with a 3-week interval schedule [3]. A minority of NHR/NHS received two doses of mRNA-1273 (Moderna) or ChAdOx1-S (AstraZeneca-Oxford), or one dose of the Ad26.COV2-S vaccine (Johnson & Johnson). During vaccine implementation, it was unclear whether this population would mount sufficient antibody responses and whether they would persist over time. Specifically for NHR, who are generally frail, at high risk for developing severe COVID-19 and often have decreased immunity, questions were raised regarding the immune response in real-world settings [4]. Indeed, studies previously showed that older adults, like NHR, have compromised antibody responses against other vaccines, like influenza vaccines [5,6]. Furthermore, during the first year of the pandemic, mortality in NHR in Belgium was high [1]. Different predictors were identified for COVID-19-related mortality in NHR, such as being male and high age [7]. Yet again, during COVID-19 vaccine implementation, it was unknown whether COVID-19 vaccination would provide sufficient protection against outcomes such as hospitalization and mortality, as real-world data was lacking and NHR were underrepresented in COVID-19 vaccine clinical trials [8,9].

Therefore, the aim of this study was [1] to measure the persistence of the SARS-CoV-2 antibody response and predictors for seroreversion after primary course COVID-19 vaccination in NHR and NHS, and [2] to assess all-cause mortality and associated predictors in fully vaccinated NHR, using longitudinal data collected over a period of 10 months.

2. Methods

2.1. Study design and sample size

In this study, we report longitudinal data collected within the SCOPE study (Sars-COv-2 seroPrEvalence study), a national sero-epidemiological surveillance study that has been described previously [10,11]. The SCOPE study assessed the prevalence of SARS-CoV-2 antibodies in Belgian NHR and NHS bimonthly between February and December 2021. A sample of NH, evenly spread across Belgium, was recruited within strata defined by regions and provinces, proportionally to the population and the number of NH beds, respectively (Supplementary Fig. 1). The sample size calculation was previously described [10]. In brief, the sample size was calculated assuming a seroprevalence rate of 0.5 at the start of the study with a half-width of 5 %, using a 95 % Wilson score interval, an intraclass correlation coefficient of 0.12 and a drop-out rate over ten months of 0.2 and 0.4 for NHS and NHR, respectively.

2.2. Study population and recruitment

Out of a total of 1521 NH in Belgium, 69 NH were randomly recruited. Within every participating NH, 24 NHR and 20 NHS were randomly selected and invited to participate. The detailed recruitment strategy was previously described [10]. In the current analysis, only fully vaccinated NHR/NHS participating in the SCOPE study were included. Participants were defined as fully vaccinated 14 days after complete vaccination (i.e., completion of the primary course vaccination), as at this time optimal protection is expected [12]. For the SARS-CoV-2 seroreversion analysis, we further excluded participants with missing baseline seropositivity data (first antibody measurement timepoint after being fully vaccinated). A detailed participant flow is shown in Supplementary Fig. 2.

2.3. Ethical considerations

The SCOPE study was approved by the Ethics Committee of the Ghent University Hospital (reference number BC-08719) and conducted according to the principles outlined in the Declaration of Helsinki. Each participant signed an informed consent form after being informed about the goal of the study and the study procedures. For participants who were incapable of signing, such as NHR with dementia, consent was given by their legal representative.

2.4. Data collection

2.4.1. Antibody testing

We assessed the presence of SARS-CoV-2 antibodies in capillary blood using point-of-care COVID-19 IgG/IgM rapid test cassettes (Healgen Scientific LLC, Houston, USA), with a reported sensitivity of 94.4 % (95 % confidence interval (CI): 88 %–97 %) and specificity of 96.6 % (95 % CI: 91 %–99 %) [13]. Capillary blood was collected by a finger prick using an 18G lancet (Sarstedt Inc., Nümbrecht, Germany). Testing was performed by trained study personnel, or in case a participant was absent during the study visit, sampling was performed by a trained nursing staff member. Sample collection started on February 1st, 2021, in a staggered way, so that all visit-specific samples were collected within the first ± four weeks after the first sample. Follow-up samples in April, June, August, October, and December 2021 were collected 60 ± 7, 120 ± 7, 180 ± 7, 240 ± 7 and 300 ± 7 days after the NH collection in February 2021, respectively.

2.4.2. Questionnaire

Every participant was asked to complete an online questionnaire (LimeSurvey version 3.22) on the day of antibody testing. For NHR, the NH head nurse(s) completed the questionnaires based on their medical file. At baseline, sociodemographic data (e.g., age, sex, job type (for NHS), care dependency level (for NHR, evaluated using the KATZ index), residing in a dementia ward (for NHR)) and COVID-19 relevant comorbidities (cardiovascular disease, diabetes, hypertension, immunosuppression, severe renal/lung/cardiac disease, active cancer) were recorded [14,15]. In addition, at every test round, participants were asked about their COVID-19 vaccination status (number of doses, date, vaccine type by brand name) and infection status (as assessed by previous PCR, antigen test, or CT-scan, with the respective test results, and date of testing). In case a NHR deceased during follow-up, date of death and cause (COVID-19 related/non-COVID-19 related) was asked.

2.5. Statistical analysis

Patient characteristics were analyzed descriptively. Median age was calculated with the interquartile range (IQR), and minimum and maximum. The categorical variables were described using absolute (n) and relative frequencies (%). An alpha of 0.05 was chosen with a *p*-value less than 0.05 indicating statistical significance. The analyses to assess persistence of the SARS-CoV-2 antibody response were performed in R, version 4.1.1, using the icenReg package (version 2.0.15). The analyses to assess all-cause mortality were performed in R, version 4.2.0, using the survival (version 3.3–1) and survminer (version 0.4.9) packages.

Persistence of the SARS-CoV-2 antibody response | Parametric exponential survival models with interval censoring were fitted to assess the persistence of the SARS-CoV-2 antibody response in fully vaccinated NHR/NHS, with seroreversion as the event of interest. Seroreversion was defined as having a (first) negative antibody rapid test result after being fully vaccinated. Participants that dropped-out, deceased or received a booster vaccine during follow-up were censored at the study-specific interval. Hazard ratios (HR) for seroreversion (with 95 % CI) were calculated using a Cox proportional hazards (Cox PH) model (semi-parametric) stratified for NHR and NHS and adjusted for the following a priori selected variables: self-reported history of SARS-CoV-2 infection

at complete vaccination, presence of comorbidities, sex, age class (per interval of 10 years), and care dependency level at the start of the study (latter for NHR only). Survival models were visualized with 95 % CI, stratified for NHR and NHS on the first tier, and stratified for the previously mentioned variables on the second tier. The proportion of seroreverters (with 95 % CI) was calculated 120 and 240 days after being fully vaccinated (as 238 days was the mean number of days between fully vaccinated administration of booster dose), stratified for the previously mentioned variables. A Last Observation Carried Forward (LOCF) principle was used in case of missing survey data.

All-cause mortality | All-cause mortality was assessed using survival analysis with reported death as the event of interest. The mortality rate and 95 % CI were calculated as the number of deceased NHR over the total number of included NHR. COVID-19 mortality was descriptively reported. HR for all-cause mortality (with 95 % CI) were calculated using a Cox PH model, adjusted for the following a priori selected predictors: age class (per interval of 10 years), sex, comorbidity (both number and type), self-reported history of SARS-CoV-2 infection at complete vaccination, breakthrough SARS-CoV-2 infection, residing in a dementia ward, and (grouped) care dependency level. Breakthrough SARS-CoV-2 infection was defined as a self-reported positive test (PCR, antigen test, CT-scan) after complete vaccination. For NHR who did not experience the event of interest, the censoring date was the date of the last follow-up visit. Two Cox PH models were calculated: in model 1 the type of comorbidity, and in model 2 the number of comorbidities (none, one, two or more) was included as predictor. Survival curves were estimated based on the days between full vaccination and death and visualized with 95 % CI, stratified for sex, age class, severe renal/lung/cardiac disease, cancer, and care dependency level. Missing data is reported per variable, complete case analysis was performed. Sensitivity analysis was performed to address the drop-out rate in survivors, comparing mortality rate with and without dropouts, after which we decided not to perform multiple imputation for missing data.

3. Results

3.1. Participation

In the SCOPE study, 3008 (1640 NHR; 1368 NHS) participants were recruited. The participant flow is shown in Supplementary Fig. 2.

3.2. Cohort characteristics at baseline

Participant characteristics are described in Supplementary Table 1. Participant characteristics, separated for survivors and non-survivors (mortality analysis) and seroreverters and non-seroreverters (seroreversion analysis), are shown in Supplementary Table 2.

3.3. Persistence of the antibody response after primary course COVID-19 vaccination in NHR and NHS: survival analyses

3.3.1. SARS-CoV-2 seroreversion in NHR vs. NHS after primary course COVID-19 vaccination

The SARS-CoV-2 antibody response after COVID-19 vaccination among NHR and NHS is shown in Fig. 1, reported with the proportion of seroreverters 120 and 240 days after vaccination. NHS had a 47 % lower hazard to serorevert after COVID-19 vaccination compared to NHR (Cox PH ratio 0.53 (95 % CI 0.45–0.62)) in the 10 months after vaccination.

3.3.2. Predictors for SARS-CoV-2 seroreversion after primary course COVID-19 vaccination in NHR and NHS

Fig. 2 presents the antibody response in NHR and NHS after primary course COVID-19 vaccination stratified for significant predictors, reported with the proportion of seroreverters 120 and 240 days after vaccination. The Cox Proportional HR are presented in Table 1.

Infection naïve NHR/NHS had significantly higher chances of seroreverting after vaccination (Fig. 2A/B). This was most prominent for NHR, as NHR with history of SARS-CoV-2 infection had a 89 % lower hazard to serorevert after vaccination compared to infection naïve NHR.

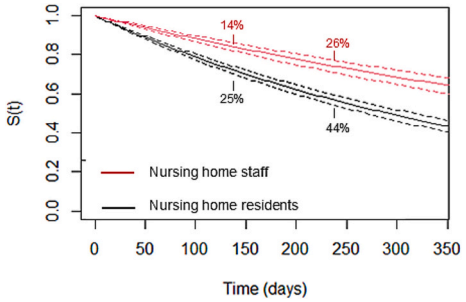

Fig. 1. Survival analysis: persistence of the SARS-CoV-2 antibody response after primary course COVID-19 vaccination in nursing home residents (black) and nursing home staff (red). The survival plot (parametric exponential model) shows the probability of SARS-CoV-2 seropositivity (S(t), Y-axis) in function of the days after being fully vaccinated (14 days after primary course COVID-19 vaccination) (X-axis). Survival curves are shown with 95 % confidence interval (dotted lines). The percentages of seroreverters 120 and 240 days after being fully vaccinated are shown on the graph. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Survival analysis by age category showed an increased hazard to serorevert with older age (Fig. 2C/3D) and NHR with a low care dependence level (O, A, B) had significantly lower chances of seroreverting compared to those with high care dependency levels (C, Cd, D) (Fig. 2E).

NHR/NHS with ≥1 comorbidity did not have a significantly increased risk to serorevert compared to NHR/NHS without comorbidity (Table 1).

3.4. All-cause mortality

3.4.1. All-cause mortality rate and COVID-19 mortality after primary course COVID-19 vaccination in NHR

The all-cause mortality rate over a period of 10 months in NHR in our study was 14 % (95 % CI 13–16 %, 229/1596). COVID-19 infection was the cause of death in 2 % (95 % CI 0–3 %, 4/229) of deceased NHR (Supplementary Fig. 2).

3.4.2. Predictors for all-cause mortality after primary course COVID-19 vaccination in NHR

Table 2 presents the results of the Cox PH model 1 including the type of comorbidity as a predictor. Being male (Fig. 3A) and older age class, 80–89 and > 90 years, (Fig. 3B) were associated with a higher hazard of all-cause mortality, irrespective of history of SARS-CoV-2 or breakthrough infection. Furthermore, severe renal/lung/cardiac disease (Fig. 3C), and active cancer (Fig. 3D) were associated with a higher hazard compared to NHR without these predictors. Whereas low care dependency level (care group O, A, or B) was associated with a lower hazard compared to high care dependency level (Fig. 3E). The results of model 2 are presented in Supplementary Table 3, similar predictors were found, but number of comorbidities was not significant.

Sensitivity analysis was performed to assess the impact of dropouts in survivors. The mortality rate when excluding dropouts in survivors was 15 % (95 CI 13 %–17 %, 229/1557). The Cox PH model when excluding dropouts showed the same predictors to be statistically significant to predict mortality as described above (Supplementary Table 4 and 5).

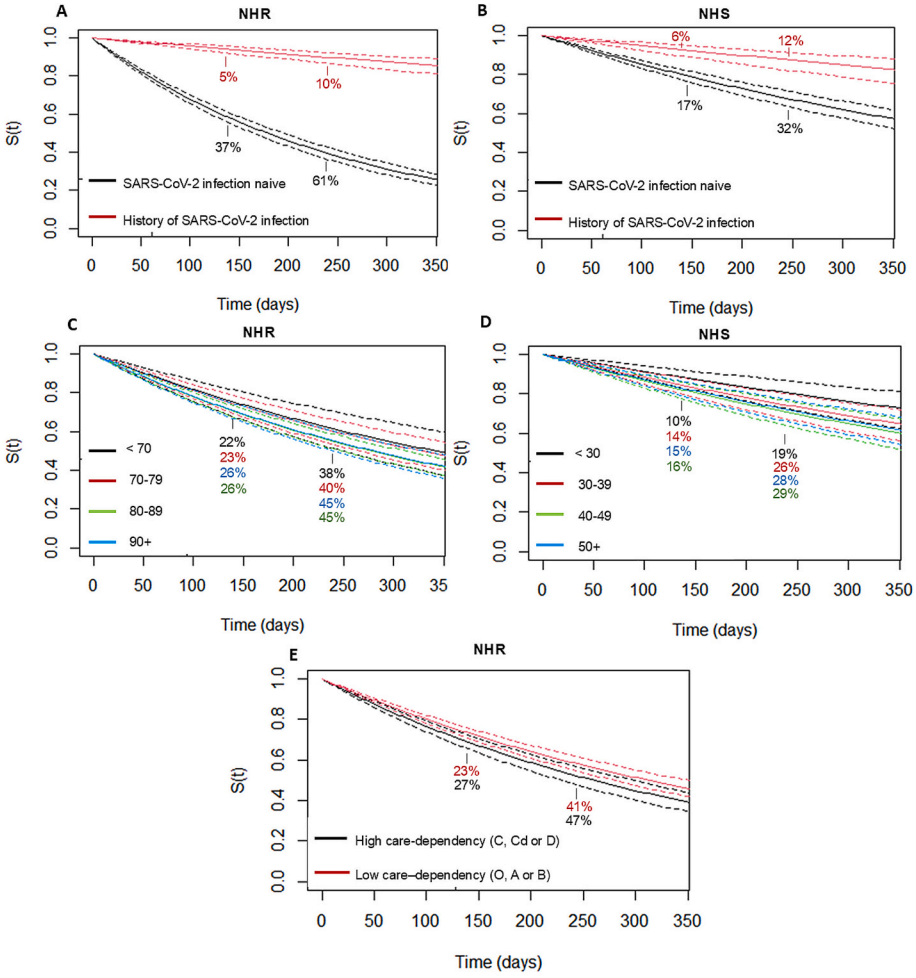

Fig. 2. Overview: persistence of the SARS-CoV-2 antibody response after primary course COVID-19 vaccination among: nursing home residents (NHR) (Fig. 2A) and nursing home staff (NHS) (Fig. 2B) with/without history of SARS-CoV-2 infection, NHR (Fig. 2C) and NHS (Fig. 2D) of different age categories in years, NHR with high/low care dependency levels (Fig. 2E). The survival plots (parametric exponential model) show the probability of SARS-CoV-2 seropositivity (Y-axis) in function of the days after being fully vaccinated (14 days after primary course COVID-19 vaccination) (X-axis). Survival curves are shown with their 95 % confidence interval (dotted lines). The percentages of seroreverters 120 and 240 days after being fully vaccinated are shown on the graph. (For interpretation of this figure in colour, the reader is referred to the web version of this article.)

4. Discussion

4.1. Main findings

In this study, we found that NHR were 47 % more likely to seroревert within 10 months after COVID-19 vaccination, compared to NHS, who are generally younger and healthier. Notably, infection naïve NHR/NHS, NHR/NHS of older age and NHR with a high care dependency level were more likely to seroревert. The most substantial difference was observed between infection naïve and previously infected NHR, where 61 % of infection naïve NHR seroreverted 240 days post-vaccination, compared to 10 % previously infected. Furthermore, 229 NHR died over a period of 10 months, corresponding to a 14 % (95 % CI 13–16 %) mortality rate. In only 2 % COVID-19 was the reported cause of death. Older age, being male, severe renal/lung/cardiac disease, active cancer or high care dependency level were significant predictors for all-cause mortality, irrespective of history of SARS-CoV-2 or breakthrough infection.

4.2. Interpretation

Persistence of the SARS-CoV-2 antibody response | Our findings align with previously published work regarding the immune response after primary course COVID-19 vaccination in NHR. Firstly, other cross-sectional studies have identified a different antibody response between NHR and NHS, with more NHR having a lower or null response shortly after BNT162b2 vaccination compared to NHS [10,16,17].

Additionally, our study shows that previously infected NHR/NHS had a more durable antibody response compared to infection naïve individuals. Similar to our findings, several studies found that NHR/NHS, previously infected, had higher antibody concentrations after primary course vaccination than infection naïve NHR/NHS [18–22]. This was most prominently observed in NHR [18,20,22].

Moreover, we found that NHR >90 years old had a significantly higher hazard to seroревert after vaccination compared to NHR <70 years old, echoing previous findings associating advanced age with a poor antibody response [19,23–25]. Age-dependent trends were also observed in NHS, although not statistically significant for all age categories. Nevertheless, other studies among healthcare workers have previously reported higher SARS-CoV-2 antibody response among younger individuals [26,27].

In analogy with care dependency, literature shows that frailty in NHR is associated with lower antibody responses after vaccination [25,28]. Indeed, it has been described before that frailty is associated with adaptive immune system alterations, and suggested as predictor for poor vaccine response [29–31].

Table 1
Hazard to seroreverter after primary course COVID-19 vaccination in nursing home residents ($n = 1535$) and nursing home staff ($n = 1140$) in Belgium.

	Nursing home residents[a]		Nursing home staff[b]	
	Hazard ratio	95 % Confidence Interval	Hazard ratio	95 % Confidence Interval
SARS-CoV-2 history of infection	0.11	0.08–0.14	0.37	0.24–0.91
At least one comorbidity	1.03	0.86–1.23	1.32	0.91–1.91
Age 30–39	NA	NA	1.65	0.93–2.93
Age 40–49	NA	NA	1.84	1.05–3.22
Age 50+	NA	NA	1.71	0.99–2.96
Age 70–79	1.29	0.88–1.89	NA	NA
Age 80–89	1.41	1.00–1.98	NA	NA
Age 90+	1.50	1.03–2.17	NA	NA
Male	1.14	0.93–1.40	1.17	0.76–1.82
Low care dependency level (O, A, B)	0.80	0.67–0.96	NA	NA

NA: not applicable. [a]Reference for nursing home residents: SARS-CoV-2 infection naïve, no comorbidities, age < 70 years old, female, care level C, Cd, D. [b]Reference for nursing home staff: SARS-CoV-2 infection naïve, no comorbidities, age < 30 years old, female. Hazard ratios are calculated using Cox proportional hazard model with a 95 % confidence interval to assess the association with seroreversion. Underlined hazard ratios are statistically significant ($p < 0.05$).

Table 2
Cox proportional hazard ratios stratified for nursing home residents: hazard of all-cause mortality after primary course COVID-19 vaccination: model 1.

	Nursing home residents[a]	
Predictors	Hazard Ratio	95 % Confidence Interval
Age 70–79	1.51	0.70–3.25
Age 80–89	2.08	1.03–4.16
Age 90+	3.25	1.60–6.60
Male	1.60	1.17–2.18
History of SARS-CoV-2 infection[b]	0.87	0.65–1.16
Breakthrough infection[c]	0.81	0.36–1.84
Comorbidity:		
Cardiovascular disease	1.07	0.81–1.41
Diabetes	0.99	0.68–1.44
Hypertension	0.87	0.64–1.17
Severe renal/lung/cardiac disease	1.70	1.18–2.46
Immunosuppression	1.22	0.56–2.67
Active cancer	1.92	1.16–3.17
Residing in dementia ward	1.25	0.89–1.75
Low care dependency level (O, A, B)	0.51	0.39–0.68

Hazard ratios are calculated with a 95 % confidence interval to assess the association with all-cause mortality. Underlined hazard ratios are statistically significant ($p < 0.05$).

[a] Reference for nursing home residents: age < 70 years old, female, SARS-CoV-2 infection naïve, no breakthrough infection, no cardiovascular disease, no diabetes, no hypertension, no severe renal/lung/cardiac disease, no immunosuppression, no active cancer, not residing in dementia ward, care level C, Cd, D. [b]History of SARS-CoV-2 infection was defined as a self-reported infection before complete vaccination. [c]Breakthrough SARS-CoV-2 infection was defined as a self-reported positive test result (PCR, antigen test, or CT-scan) after complete vaccination.

While our model did not show an increased hazard for seroreversion based on sex, the underrepresentation of males in our cohort may limit our findings. Some studies have reported higher antibody prevalence/concentration among females, however, all were conducted in working-age populations [32–34].

Additionally, in our model, having one or more comorbidities did not show an increase hazard for seroreversion. Nevertheless, other research suggests associations between comorbidity indices and lower vaccine responses [35,36]. Possibly, our study is underpowered to assess comorbidity as predictor for seroreversion as this considered an exploratory analysis, and the proportion of subjects having no comorbidity and ≥ 1 comorbidity was not equally distributed.

In our study, majority of NHR and NHS received a booster vaccine approximately eight months after primary vaccination. At this time, 43.5 % of NHR and 26.1 % of NHS seroreverted. Among infection naïve NHR, even 60.5 % of NHR seroreverted at the time the booster campaign was initiated. Retrospectively, our data underscores the necessity of timely booster vaccination, particularly among NHR, given that nearly half had no detectable antibodies. Others demonstrated that antibody levels significantly increased after booster administration in NH cohorts [37,38].

All-cause mortality | During the first year of the pandemic, COVID-19 was associated with all-cause mortality in NHR [39]. Although we did not collect data in 2020, Vandael et al. [1] reported 11,329 COVID-19 deaths among Belgian NHR between 11 March 2020 and 3 January 2021. In our study, COVID-19 was reported as the cause in only 2 % of all deaths, a finding that reflects the anticipated reduction in COVID-19-related mortality following the vaccination campaign. This low percentage aligns with the protective effect observed in literature, where vaccination significantly reduced severe outcomes and mortality in NHR [40,41]. A Swedish study assessed mortality 30 days after laboratory-confirmed COVID-19 diagnosis and observed a significant reduction in mortality after vaccination [40]. This low mortality rate underscores the efficacy of vaccination in this vulnerable population, despite their increased likelihood of seroreversion. Despite surviving COVID-19 infection, NHR can present an acceleration of the aging process [42]. In our study, we could not find an association between mortality and history of COVID-19 infection prior to vaccination. This was also seen in a Dutch study [43] conducted in 2020, showing that, contrary to 30-day mortality after SARS-CoV-2 infection, NHR who survived COVID-19 did not have an increased hazard of mortality six months after infection compared to COVID-negative NHR.

Different predictors for COVID-19 mortality in NHR have been identified. Male sex is associated with an increased mortality risk in NHR with COVID-19 [44]. However, a Dutch study compared 30-day mortality in NHR with and without COVID-19 and found being male to be an independent predictor for mortality, not specific to COVID-19 [45]. This was also seen in the study of Panagiotou et al. [46], and is in accordance to our results. Additionally, in the study by Reilev et al. [47], prior to the COVID-19 pandemic, male sex was associated with lower survival rates after NH admission. They also found that men had a greater burden of comorbidities, including a higher prevalence of stroke, alcohol use, and substance abuse, which likely contributed to their lower survival rates. Furthermore, consistent to our findings, increased age is associated with all-cause mortality in NHR after SARS-CoV-2 infection [46]. Additionally, underlying comorbidities, such as diabetes and chronic kidney disease were associated with increased risk of 30-day mortality in NHR in 2020 [46]. Moreover, during the first year of the pandemic, higher frailty was associated with a higher mortality risk in NHR, independently from COVID-19 infection [39,48,49]. Similarly, in our study, NHR with a high care dependency level had a higher all-cause mortality. It is important to note that being male, increased age, underlying comorbidities, and frailty were, not surprisingly, already identified as predictors for all-cause mortality in NHR before the COVID-19 pandemic [50].

4.3. Strengths and limitations

Our study was the largest longitudinal study collecting both serological and mortality data in Belgian NH after COVID-19 vaccine implementation. However, this study has limitations. In the current analysis, both a history of infection and cause of death were based on self-reporting. Therefore, the actual proportion of NHR/NHS with a previous SARS-CoV-2 infection and (COVID-19 related) death was

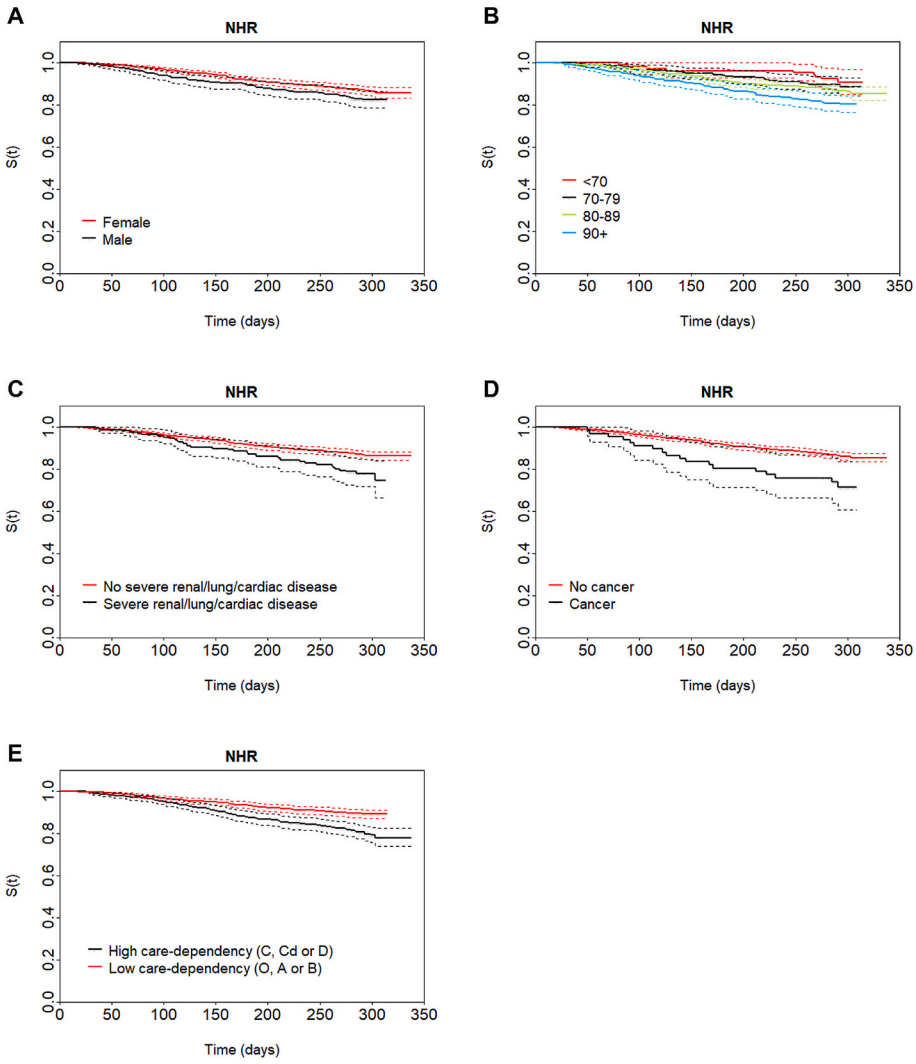

Fig. 3. Overview: survival curve for all-cause mortality in fully vaccinated nursing home residents (NHR): in female and male NHR (Fig. 3A), in NHR of different age categories in years (Fig. 3B), in NHR with/without severe renal/lung/cardiac disease (Fig. 3C), in NHR with/without cancer (Fig. 3D), and in NHR with high/low care dependency level (Fig. 3E). The survival plots show the proportion of NHR surviving (Y-axis) in function of the days after the COVID-19 vaccination (14 days after second dose was given) (X-axis). The survival curves are shown with their 95 % confidence interval (dotted lines). NHR, nursing home residents. (For interpretation of this figure in colour, the reader is referred to the web version of this article.)

probably underestimated due to asymptomatic infections/lack of systematic screening and reporting errors, respectively. Secondly, we used a point-of-care test to assess the presence of SARS-CoV-2 antibodies with a lower sensitivity compared to laboratory assays [13,51]. Therefore, seroreversion rate could be overestimated. Moreover, survival models were fitted up until 365 days post-vaccination, which was longer than the actual period of follow-up of 10 months. Therefore, visualization of the data towards the end of follow-up should be interpreted with caution, as it has a higher uncertainty. In specific for the seroreversion analysis, as participants who received a booster vaccine were censored, which was on average 238 days after being fully vaccinated. Additionally, interval censored survival analysis does not allow inclusion of time-dependent covariates, and therefore, breakthrough infection was not included in the survival analysis for seroreversion. Although the number of reported breakthrough infections during follow-up was low (3 % for NHR and 9 % for NHS), this might result in a slight underestimation of the true seroreversion rate. Furthermore, we assessed mortality during the second year of the pandemic, after a year in which mortality in NHR was high, thus introducing survival bias in this cohort [1]. Additionally, as far more NHR than NHS deceased in our cohort, it should be noted that survival bias could exist when comparing seroreversion among both groups. Different predictors used in the modelling strategies, such as care dependency and residing in a dementia ward, were assessed at baseline and were not monitored afterwards. Any changes over time (e.g. general state deterioration, resulting in higher care dependency) for the above predictors were not considered. Lastly, since the pandemic started, different variants of concern (VOC) with a different effect on disease severity and mortality have emerged [52]. We did not collect information on which VOC caused SARS-CoV-2 infection in our study. However, in Belgium the dominant VOC from February to July 2021 and from July to December 2021 was the Alpha and Delta variant, respectively [3].

4.4. Practical implications

Our study demonstrates the importance of a specific COVID-19 vaccine strategy for NHR, as they fail to mount a persistent vaccine-induced antibody response. A proactive approach should be implemented to monitor immunity levels and to identify potential gaps in protection and tailor vaccination strategies accordingly. Based on our results, priority for the administration of COVID-19 booster doses should be given to (infection naïve) NHR. Nevertheless, the COVID-19 related

mortality was minimal to non-existing in our observations. Therefore, although COVID-19 primary course vaccination might not elicit a durable antibody response, it did have clinical significant impact on COVID-19 mortality. Moreover, different predictors for all-cause mortality in vaccinated NHR were identified, irrespective of history of SARS-CoV-2 or breakthrough infection. Although these predictors were already associated with all-cause mortality in NHR prior to the pandemic, we believe that assessing them within this setting remains important in this vulnerable population. By assessment of predictors associated to seroreversion and mortality, targeted screening, prevention, and management strategies can be implemented in the future. These strategies should address advanced care planning and quality of life, mitigating the effects of isolation, and improve the well-being of this vulnerable population.

5. Conclusion

NHR were 47 % more likely to serorevert after COVID-19 vaccination, compared to NHS.

Specifically, infection naïve NHR/NHS, NHR/NHS of older age and NHR with a high care dependency level were more at risk to serorevert. The all-cause mortality rate among NHR was 14 %, which was associated with high age, being male, having severe renal/lung/cardiac disease, having active cancer or high care dependency level.

Sponsors role

Sciensano was involved in the design of this study, result interpretation and manuscript review.

Ethics approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Ghent University Hospital on December 11th, 2020 (BC-08719).

Consent to participate

Each participant signed an informed consent form after being informed about the goal of the study and the sampling procedures. For participants who were incapable of signing the consent form, such as nursing home residents with dementia, consent was given by their legal representative.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Eline Meyers: Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Liselore De Rop:** Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation. **Ellen Deschepper:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Els Duysburgh:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Tine De Burghgraeve:** Writing – review & editing, Project administration, Investigation. **Pauline Van Ngoc:** Writing – review & editing, Project administration, Investigation. **Marina Digregorio:** Writing – review & editing, Project administration, Investigation. **Anja Coen:** Writing – review & editing, Project administration, Investigation. **Nele De Clercq:** Writing – review & editing, Project administration, Investigation. **Steven Wallaert:** Writing – review & editing, Funding acquisition. **Laëtitia Buret:** Writing – review & editing, Supervision. **Samuel Coenen:** Writing – review & editing. **An De Sutter:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Beatrice Scholtes:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jan Y. Verbakel:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Piet Cools:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Stefan Heytens:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.126865.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request and with permission of Sciensano (Belgian Institute for Health).

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