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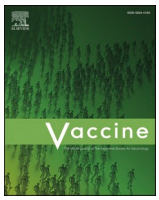

Vaccine protection against COVID-19 mortality in relation to time since last booster dose among nursing home residents in Sweden – A case-control study over 35 months

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SUMMARY

Background: The implementation of COVID-19 vaccination among older persons at nursing homes has lowered the infection-associated mortality considerably, but emerging virus variants and decline in vaccine-induced immunity over time necessitate examination of future booster dosing strategies. The overall aim of this study was to assess vaccine protection against COVID-19 mortality in relation to time elapsed since the last booster dose.

Methods: All older persons living in nursing homes in Sweden at any time point December 27th, 2020 - December 4th, 2023 were included. For each case (5256 COVID-19 and 85,745 all-cause deaths), up to 10 controls were sampled randomly from this population, matched with respect to birth year, sex and county. The matched case-control sets were analyzed for vaccination history with conditional logistic regression, with further adjustment for co-morbidties and prior SARS-CoV-2 infection.

Findings: Vaccination status (unvaccinated vs. vaccinated), $\geq$ 90 days since last vaccine dose, a co-morbidity score $\geq$ 2, and no previous SARS-CoV-2 infection were associated with death occurring within 30 days of a positive test. The odds ratio (OR) for COVID-19 death was 2.4 (95 % confidende interval [CI] 1.8–3.2) when contrasting at least 365 days with less than 90 days since the last vaccine dose.

Interpretation: Waning vaccine protection was observed already 90 days after the last vaccine dose among older people living in nursing homes. The reported ORs imply that more than one third of all COVID-19 deaths could in the investigated setting have been possible to prevent by more frequent vaccine boosting during 2022–2023.

1. Introduction

Early in the coronavirus disease 2019 (COVID-19) pandemic, older people living at nursing homes were identified as a particularly vulnerable group with high case fatality [1]. In the management of the pandemic, focus has for long been on optimizing vaccine dosing, particularly for older individuals with an elevated risk of severe disease [2]. In Sweden, COVID-19-associated crude 30-day mortality was initially nearly 40 % among nursing home residents, and the odds associated with living in a nursing home was 12 times higher than for individuals living independently, after controlling for other risk factors [3,4]. While older age has been associated with decreased SARS-CoV-2 antibody persistence after repeated vaccinations [5], not all epidemiological studies have shown a faster waning of protection against severe disease at older age [6]. However, the absolute risk of severe outcomes is undoubtedly much higher among old and frail individuals also after

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repeated vaccinations. As an example, the infection-associated 30-day mortality was still as high as 8–9 % among nursing home residents after the initial administrations of COVID-19 booster vaccinations [7]. Repeated monitoring of emerging virus variants and the vaccine-induced immunity among older persons together with a meticulous evaluation of implemented booster dosing strategies is thus warranted [8–11].

The overall aim of this study was to assess vaccine protection against COVID-19 mortality among older people living in nursing homes in relation to time elapsed since the last booster dose, to inform public health policies on how best to shield the most vulnerable older adults in the society.

2. Methods

2.1. Study design

This study was based on a dynamic population of all people living in a nursing home at any time during the follow up period between December 27th, 2020 when COVID-19 vaccinations started and August 31^{sth}, 2023 and born in 1959 or earlier (165,755 individuals in total). Individuals who died or moved from a nursing home to a regular dwelling were censored on the date of death or relocation. Follow up data on vaccinations, positive SARS-CoV-2 test results and deaths were available for the study population until December 4th, 2023, while data on entry and exit from nursing homes were only available until end of August 2023. Consequently, from September 2023 until end of follow up, there were no new entries into the study population and nursing home residents on August 31st, 2023 were considered to stay until death or end of follow up. The number of individuals living at a nursing home in our study population was 78,697 on December 27th, 2020, and 81,129 on August 31st, 2023. The size of study population then decreased to 76,786 by December 4th, 2023.

Nursing home residents were together with their caregivers and frontline health care workers the first to become vaccinated in Sweden, starting in late December 2020. They were then followed by the general population stratified by age- and risk groups. Three different vaccines have been used in Sweden: BNT16b2 mRNA (Comirnaty, Pfizer-BioNTech), mRNA-1273 (Spikevax, Moderna) and ChAdOx1-SARS-CoV-2 (Vaxzevria, AstraZeneca). The initial two doses were generally administered within 42 days of each other. From September 1st, 2021, a third dose was offered, starting with nursing home residents, older people living independently and immunocompromised persons. The national recommendation was two additional doses per year both in 2022 and 2023, but with regional variation in implementation. Some nursing home residents have been given up to ten doses during the follow up period. The median number of doses in the study population on 31st August 2023 was 6 (79 % had received 5 or 6 doses); 86 % of the 415,553 administrated doses were BNT16b2 mRNA, 12 % were mRNA-1273.

2.2. Data sources

This is a register-based study where different data sources were linked using the personal identification number assigned to all Swedish residents at birth or immigration [12]. Individual-level data on country of birth, civil status and residential area were obtained from the Swedish Total Population Register. Data on vaccination date, type of vaccine and dose number were obtained from the National Vaccination Register, and data on positive SARS-CoV-2 test results from the infection reporting register SMINet, both mandatory registers kept at the Public Health Agency of Sweden. Vital status and death dates were obtained from the Swedish Tax Authority. In line with the definition used by the Public Health Agency of Sweden, deaths occurring within 30 days of a positive SARS-CoV-2 test was considered as a COVID-19 death. The National Board of Health and Welfare provided monthly data on individual independence (lives independently, with home care or at a nursing home). They also provided data on co-morbidities from the National Patient Register [13] at the beginning of each year 2021–2023. Co-morbidities were defined from diagnoses in inpatient or specialized outpatient care at any time point during the previous five years in the following disease groups (see Supplementary Table S1 for a detailed list): cardiovascular diseases, diabetes or obesity, respiratory diseases, cancer or immunosuppressed states, dementia, other neurological diseases, kidney diseases, liver diseases, and other conditions and diseases (Down syndrome, HIV, sickle cell anaemia, drug addiction, thalassaemia or mental health disorder). The number of co-morbidities (0–9) in these groupings was counted and used in the analyses.

2.3. Case-control sampling

To avoid conflation of varying infection pressure and dominating variant of concern (VOC) over time in the population with waning vaccine effectiveness, we used continuous density case-control sampling [14]. The sampling was based on the dynamic study population (open cohort) where for any given month, all people born 1959 or earlier and living in a nursing home the month before were included. All deaths, irrespective of cause, occurring during the month were classified as cases. Any death occurring within 30 days of a positive SARS-CoV-2 laboratory test (PCR and/or antigen test) was further classified a COVID-19 death. For each case, up to 10 controls who were still alive at the end of the calendar month when case's death occurred were sampled randomly from the population, matched with respect to birth year (before 1925, 1925–1929 in five-year groups until 1955–1959), sex and county. The implicit matching on calendar month accounts for the seasonality of infection pressure. Sampling was done with replacement, which implies that individuals can appear as controls in multiple matched sets and also appear as cases subsequently.

2.4. Statistical analysis

We used conditional logistic regression (Stata SE 14.2, Stata Corp, command *clogit*) for the 1:10 case-control matched sets and accounted for individual clustering that stems from the control sampling with replacement. We estimated the odds ratio (OR) together with 95 % confidence interval (CI) for the association between vaccination history, and COVID-19 and all-cause mortality. Vaccination history was characterized as the number of days since the last dose was obtained, continuous or grouped as <90 (reference category), 90–179, 180–269, 270–364, $\geq$ 365 days or as unvaccinated. Only doses received at least 7 days before the case date were counted within each matched set when vaccination history was assessed. Estimates were obtained with further adjustment for number of doses, (0, 1, 2, 3 or at least 4), prior infection exceeding 90 days since case date, and number of comorbidities (0, 1, 2, 3 or at least 4). The continuous association between the number days ($\geq$ 90) since last dose and COVID-19 mortality was illustrated using fractional polynomials with linear, quadratic and logarithmic terms [15]. The association between vaccination history and mortality was also investigated separately among males and females and among persons younger than 80 years.

Based on the obtained OR estimates, we calculated the population preventable fraction (PPF) [16]. In this context, the PPF yields estimates of the number and proportion of all deaths that theoretically would have been possible to prevent by a vaccination strategy where all individuals had their last dose in the reference category (less than 90 days ago). Standard errors and hence confidence intervals for PPF [17] were approximated from a regression model where days since last vaccine was dichotomized (more vs. less than 90 days).

Role of the funding source.

The funders of the study played no role in the design of the study, data collection or analysis, decision to publish, or writing of the report.

3. Results

In total, 85745 deaths occurred in the study population of nursing home residents during follow up (December 27th, 2020 and December 4th, 2023), of which 5256 (6.1 %) occurred within 30 days of a positive SARS-CoV-2 test. The monthly COVID-19 mortality exhibited peaks in January 2021, February 2022 and December 2022 with 124, 74 and 57 deaths per 10,000 persons, respectively (Fig. 1). The total number of deaths and the COVID-19 deaths were matched with 857,140 and 52,535 controls, respectively (Table 1). The proportion of males was higher among COVID-19 deaths than among all deaths (46 % vs. 39 %), but the age distributions were similar.

Analysis of the complete follow-up period showed that vaccination status (unvaccinated vs. vaccinated), ≥ 90 days since last vaccine dose, a co-morbidity score ≥ 2, and having no previous SARS-CoV-2 infection were associated with COVID-19 death (Table 2). As an example, the OR for COVID-19 death was 2.4 (95 % CI 1.8–3.2) when contrasting at least 365 days with less than 90 days since the last vaccine dose. This estimate was similar among males (OR 2.3, 95 % CI 1.5–3.5), females (OR 2.5, 95 % CI 1.7–3.7) and among persons younger than 80 years (OR 2.7, 95 % CI 1.5–4.8), see Supplementary Table S2 and S3. As illustrated in Fig. 2, the elevated COVID-19 mortality reached a plateau 270–300 days after the last dose with an OR around 2.5. The number of vaccine doses beyond one, was not independently associated with COVID-19 death when taking time since last dose into account. Importantly, prior SARS-CoV-2 infection was associated with markedly lower COVID-19 mortality. All ORs were generally attenuated but still evaluated in the analyses for all-cause mortality (Table 2).

Associations between vaccination status, time since last vaccine dose and COVID-19 mortality are presented stratified by calendar year 2021–2023 in Table 3. The increase in COVID-19 mortality was not observed until 180 days since last dose in 2021 but was observed already after 90 days in 2022. The pattern for 2023 was largely similar as for 2022 but more statistically uncertain. For 2021, the estimates imply that 46 % (95 % CI 38–53 %) of the COVID-19 deaths could have been prevented with a faster vaccine roll out. The vast majority of the excess deaths in 2021 thus occurred among persons still unvaccinated (634 / 711; 89 %) and fewer among vaccinated with their last dose more than 90 days ago (77 / 711; 11 %; Table 3). In 2022–2023, an estimated 36 % (95 % CI 23–46 %) of all COVID-19 deaths were theoretically possible to prevent, that is 1319 out of 3696 deaths (955 / 2661 in 2022 and 364 / 1035 in 2023). The majority of the preventable deaths in 2022–2023 occurred among vaccinated who had their last vaccine dose more than 90 days ago (1064 / 1319; 81 %).

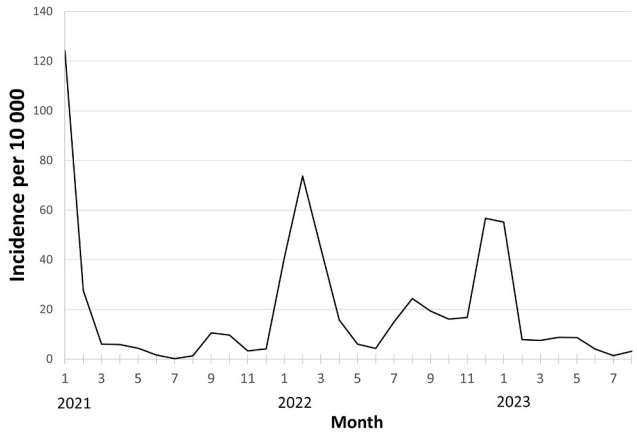

Fig. 1. COVID-19 related mortality, deaths per 10,000 individuals and month, among older people living in nursing homes in Sweden January 2021 – August 2023.

Table 1
Characteristics of the cases (COVID-19 and all-cause deaths) and controls on the date of the death (cases) or matched case date (controls). Cases and controls were matched (1:10) with respect to calendar time, sex, age and region.

	Deaths, COVID-19		Deaths, all-cause	
	Cases	Controls	Cases	Controls
Total, n	5256	52,535	85,745	857,140
Age (years)				
< 80	997 (19)	9870 (19)	15,590 (18)	157,369 (18)
80–84	892 (17)	9299 (18)	14,800 (17)	150,309 (18)
85–89	1312 (25)	13,094 (25)	20,809 (24)	210,766 (25)
90–94	1317 (25)	13,079 (25)	21,598 (25)	214,305 (25)
95–99	615 (12)	6124 (12)	10,752 (13)	105,102 (12)
100+	123 (2.3)	1069 (2.0)	2196 (2.6)	19,289 (2.2)
Sex				
Females	2827 (54)	28,270 (54)	52,537 (61)	525,348 (61)
Males	2429 (46)	24,265 (46)	33,208 (39)	331,792 (39)
Born abroad	621 (11.8)	6000 (11.4)	9494 (11.1)	98,908 (11.5)
Nursing home, length of stay (months)	13 (1–36)	14 (2–36)	17 (1–40)	17 (2–40)
Comorbidities (number)				
0	2976 (57)	32,537 (62)	48,093 (56)	532,932 (62)
1	781 (15)	8237 (16)	13,137 (15)	133,611 (16)
2	730 (14)	6358 (12)	11,929 (14)	103,961 (12)
3	464 (8.8)	3735 (7.1)	8096 (9.4)	59,486 (6.9)
≥ 4	305 (5.8)	1668 (3.2)	4490 (5.2)	27,150 (3.2)
Number of vaccine doses				
0	1190 (23)	7584 (14)	6133 (7.2)	48,920 (5.7)
1	398 (7.6)	4928 (9.4)	3231 (3.8)	31,003 (3.6)
2	467 (8.9)	4981 (9.5)	18,357 (21)	185,515 (22)
3	1155 (22)	12,381 (24)	15,494 (18)	153,984 (18)
≥ 4	2046 (39)	22,661 (43)	42,530 (50)	437,718 (51)
Time since last dose, days[a]				
≥ 365	183 (4.5)	1345 (3.0)	3624 (4.6)	31,699 (3.9)
270–364	176 (4.3)	1372 (3.1)	3574 (4.5)	27,591 (3.4)
180–269	562 (14)	4626 (10)	14,071 (18)	129,647 (16)
90–179	1906 (47)	19,698 (44)	28,574 (36)	291,589 (36)
< 90	1239 (30)	17,910 (40)	29,769 (37)	327,694 (41)
SARS-CoV-2 infection				
Current	5256 (100)	2415 (4.6)	5256 (6.1)	16,959 (2.0)
Prior	429 (8.2)	12,308 (23.4)	22,024 (26)	240,271 (28)

[a] Vaccinated with at least 1 dose.

4. Discussion

In this population-based study of all 5256 COVID-19 deaths occurring in Swedish nursing homes together with their age and sex-matched controls we find that waning in vaccine protection was already evident 90 days after the last vaccine dose given. Among persons who had their

Table 2
Conditional logistic regression for the association between vaccination history and mortality (COVID-19 and all cause deaths) during the complete follow up period (December 27th, 2020 – December 4th, 2023). The analysis was matched (1:10) for age, sex and county and further adjusted for comorbidities and prior SARS-CoV-2 infection. Results are presented as odds ratios (ORs).

	Deaths, COVID-19 OR (95 % CI)	Deaths, all cause OR (95 % CI)
Unvaccinated	5.5 (3.5–8.5)	1.6 (1.5–1.8)
Vaccinated		
Number of vaccine doses		
1	2.0 (1.2–3.2)	1.2 (1.0–1.3)
2	1.0 (0.66–1.6)	0.95 (0.84–1.1)
3	0.94 (0.71–1.2)	1.0 (0.93–1.1)
≥ 4	Ref.	Ref.
Time since last dose, days		
≥ 365	2.4 (1.8–3.2)	1.4 (1.3–1.5)
270–364	2.2 (1.7–2.8)	1.6 (1.5–1.7)
180–269	2.4 (1.9–3.1)	1.4 (1.3–1.5)
90–179	1.8 (1.3–2.3)	1.2 (1.1–1.3)
< 90	Ref.	Ref
Comorbidities		
≥ 4	2.2 (1.9–2.5)	1.91 (1.83–1.98)
3	1.4 (1.2–1.6)	1.55 (1.50–1.60)
2	1.3 (1.2–1.4)	1.29 (1.26–1.33)
1	1.0 (0.93–1.1)	1.10 (1.07–1.12)
0	Ref.	Ref.
Prior SARS-CoV-2 infection	0.25 (0.22–0.28)	0.86 (0.84–0.88)

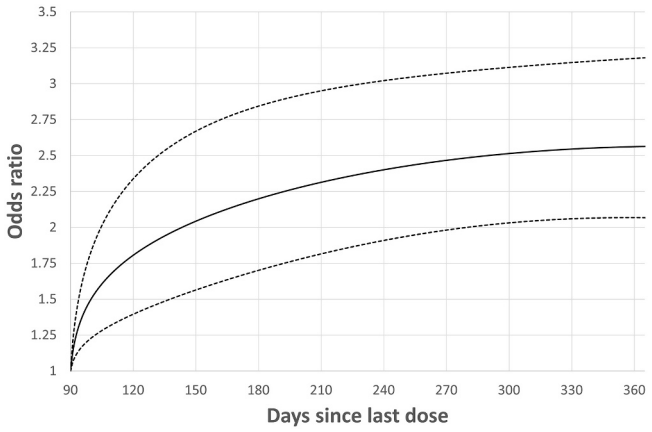

Fig. 2. Association between time since last vaccine dose and COVID-19 mortality. Odds ratios from conditional logistic regression with exposure variable expressed as fractional polynomials (linear, quadratic and logarithmic terms), matched (1:10) for age, sex and county and further adjustment for number of vaccine doses, prior SARS-CoV-2 infection and comorbidities. Dotted curves represent 95 % confidence bands.

last dose more than a year ago, the COVID-mortality was more than twofold compared to those who had their vaccine protection updated less than 90 days ago, irrespective of sex, age, and number of vaccine doses. Our findings suggest that a more efficient vaccination strategy has the potential to prevent a substantial number of COVID-19 deaths.

Our finding that an estimated 46 % of all COVID-19 deaths theoretically would have been prevented in 2021 with the last dose no more than 90 days ago is remarkable but should be interpreted with caution as most excess deaths occurred among the unvaccinated before they had been offered the vaccine. The results for 2022–2023 are more likely to represent the effect of timely administration of additional booster doses in a population with a already high uptake of the vaccine. This said, the estimated 36 % preventable COVID-19 deaths for this period is still remarkable.

Our study thus adds to the evidence on waning patterns in vaccine protection against COVID-19 death [6,18,19]. Among people living in nursing homes investigated in our study, waning started earlier compared to other studies conducted in Sweden including all age groups [6,19]. The short duration of vaccine protection among nursing home residents and the high proportion of preventable deaths under a scenario with more frequent booster doses has important implications for vaccination strategies for nursing home residents and other population groups with similar vulnerability. It may call for booster doses not only once a year, but rather twice, ideally with a timing adjusted for patterns of seasonal variation of COVID-19 to maintain sufficient protection. The nursing home population investigated in this study is relatively easy to reach with vaccinations as they have a 24–7 service by nurses and care assistants, whereas maintaining sufficient protection in equally vulnerable groups who live independently in the society can be more challenging. Vaccines with longer duration of protection would alleviate problems related to booster dosing with optimal timing.

A major strength of the present study was the extensive individual-level register data on both COVID-19 related and all-cause mortality with almost three years of follow up for the entire population of nursing home residents in Sweden. A limitation was that we only assessed the COVID-19 related death risk based on register data on co-morbidities obtained from inpatient and specialized inpatient care. Additional data on impaired cognitive and physical functioning would make it possible to stratify the risk further [3,20]. However, a more detailed risk assessment would most likely not change the main conclusion of our study, as vaccination recommendations for the nursing home settings were given on the basis of the care setting with a high risk of infection outbreaks among highly vulnerable persons, rather than on individual risks. It should also be stressed that the attenuation in the association between vaccination and non-COVID-19 related deaths speaks against selection in who received booster doses as a major explanation for the pattern of waning protection that we observed. Another limitation was that we could not incorporate data on immunological response. Repeated capillary blood sampling in subgroups, in combination with register data for the full population, has the potential to stratify the mortality risk further and inform policy on optimal timing of the vaccine doses [21]. Finally, misclassification of exposure (vaccination status), outcome (COVID-19 death) and important covariates (such as prior SARS-CoV-2 infection) should always be considered as potential sources of bias. However, such misclassifications are in this register-based setting unlikely to have substantially influenced the findings.

In conclusion, time since the last vaccine dose was associated with COVID-19 deaths in the Swedish nursing home population favoring short intervals of mRNA vaccine boosting for maximal protection.

CRediT authorship contribution statement

Jonas Björk: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Dominik Dietler:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Carl Bonander:** Writing – review & editing, Methodology, Conceptualization. **Mahnaz Moghaddassi:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Fredrik Kahn:** Writing – review & editing, Funding acquisition, Conceptualization. **Malin Inghammar:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Anders F. Johansson:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

Ethical standards

Ethical approval for the study was obtained from the Swedish Ethical Review Authority (no. 2021-00055) with amendment (no. 2022-00564-02). All personal data were handled and analyzed pseudonymized,

Table 3
Conditional logistic regression for the association between vaccination history and COVID-19 mortality, matched (1:10) for age, sex and county and further adjusted for comorbidities and prior SARS-CoV-2 infection, stratified by year during follow up (December 27th, 2020 – December 4th, 2023). Results are presented as odds ratios (ORs) and population preventable fractions (PPFs) with less than 90 days since last vaccine dose as reference category.

	2021[a,b]			2022			2023		
	Cases, n	OR (95 % CI)	PPF[c], n (%)	Cases, n	OR (95 % CI)	PPF[c], n (%)	Cases, n	OR (95 % CI)	PPF[c], n (%)
Unvaccinated	869 (56)	3.7 (2.6–5.4)	634 (40.6)	264 (9.9)	5.7 (4.0–8.2)	218 (8.2)	57 (5.5)	2.9 (1.4–5.7)	37 (3.6)
Vaccinated									
Time since last dose, days									
≥ 365	0 (0)	–		83 (3.1)	2.1 (1.4–3.0)	43 (1.6)	100 (9.7)	2.1 (1.1–4.0)	52(5.1)
270–364	12 (0.8)	6.0 (2.5–15)	10 (0.6)	118 (4.4)	2.0 (1.5–2.8)	60 (2.3)	46 (4.4)	1.3 (0.63–2.8)	10 (1.0)
180–269	141 (9.0)	1.9 (0.53–6.4)	67 (4.3)	205 (7.7)	2.2 (1.7–2.9)	112 (4.2)	216 (21)	2.0 (1.1–3.6)	108 (10.4)
90–179	45 (2.9)	0.90 (0.33–2.5)	Negative	1391 (52)	1.6 (1.2–2.2)	522 (19.6)	470 (45)	1.5 (0.72–3.1)	157 (15.1)
< 90	493 (32)	Ref.		600 (23)	Ref.	Ref.	146 (14)	Ref.	
Total	1560		711 (45.6)	2661		955 (35.9)	1035		364 (35.2)

[a] Not adjusted for number of doses due to collinearity.
[b] 2021 includes cases/controls samled during December 27th, 2020 – December 31st, 2021.
[c] PPF = pc · (OR - 1) / OR, where pc is the proportion of cases in each exposure category.

which means that the key that allows for identification of individual persons were stored technically and organizationally separated from the research data.

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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.2025.128043.

Data availability

The authors do not have permission to share data.

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