Original Article

Vaccine-Induced or Hybrid Immunity and COVID-19-Associated Mortality During the Omicron Wave

A Retrospective Observational Study in the Elderly

Maximilian Weigert, Andreas Beyerlein, Katharina Katz, Rickmer Schulte, Wolfgang Hartl*, Helmut Küchenhoff*

Summary

Background: It is not yet entirely clear to what extent vaccine-induced or hybrid immunity offers protection from death during the omicron wave of the COVID-19 pandemic in Germany.

Methods: In this retrospective study, we evaluated 470 159 cases aged ≥ 60 years in the German federal state of Bavaria who tested positive for SARS-CoV-2 between 1 January and 30 June 2022. Cox models were used to estimate adjusted hazard ratios (aHR) for dying within 60 days of the infection, depending on sex, age, time of infection, and different levels of immunity.

Results: Over the period of observation, 3836 COVID-19-associated deaths were registered (case fatality rate 0.82%). The risk of death was significantly lower in cases with a higher level of immunity than in unvaccinated cases (aHR for a full primary level of immunity if reached less than 6 months before the date of the infection: 0.30, 95% confidence interval [0.23; 0.39]; if reached more than 6 months before: aHR 0.46 [0.35; 0.60]). A boosted level of immunity lowered the risk of death even further (if reached less than 3 months before the infection: aHR 0.17 [0.15; 0.20]; if reached more than 3 months before: aHR 0.25 [0.21; 0.29]).

Conclusion: Among elderly persons in Bavaria, a higher immunity level was associated with a substantial degree of protection against death during the Omicron wave; however, the strength of protection may have diminished somewhat over time.

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To date, knowledge on the effectiveness of vaccinations or hybrid immunity (immunity acquired from prior infection and vaccination) during the Omicron wave has been derived mainly from international studies (1).

In Germany, vaccine effectiveness studies have so far focused on hospitalization or in-hospital mortality of patients predominantly infected during the Delta wave (2, 3). Analyses by the Robert Koch Institute (RKI) rely on methods for aggregated data which contain no information on preceding SARS-CoV-2 infections, and do not allow adjustment of risks for individual age and gender or analysis of the time between vaccination and infection (4).

In the study presented here we investigated individual data, which do not involve these limitations. Thus we were able to assess the effectiveness of different levels of immunity with regard to the risk of death during the Omicron wave. We specifically studied the elderly population, i.e., the group mostly frequently affected by a severe course of COVID-19.

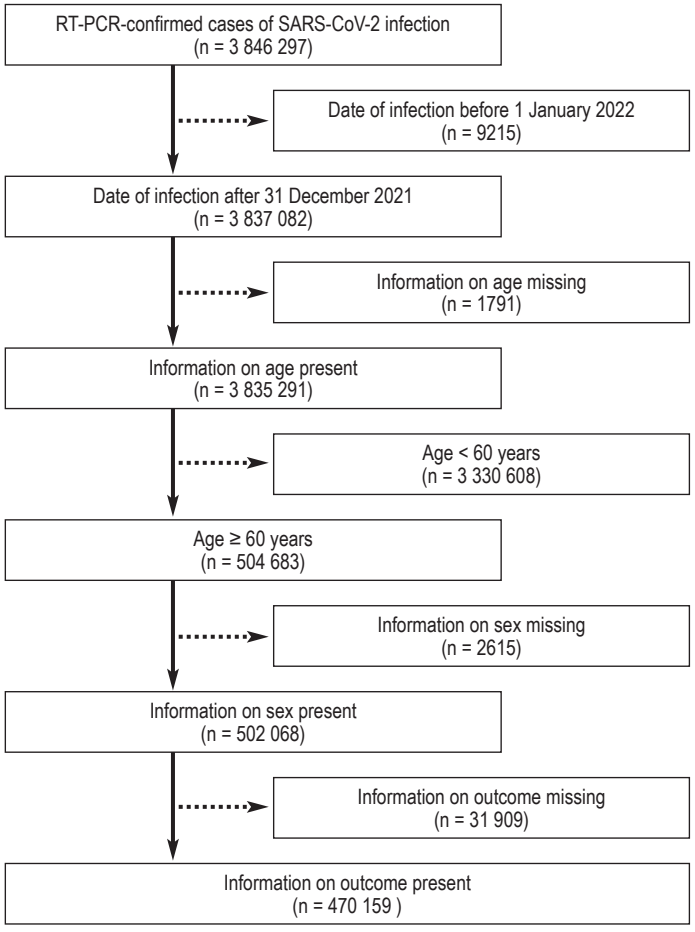
Methods

Study design and target group

In this retrospective cohort study, we analyzed all SARS-CoV-2 cases confirmed by real-time polymerase chain reaction (RT-PCR) that were officially reported and registered in Bavaria according to the German Infection Protection Act (*Infektionsschutzgesetz*, IfSG) between 1 January and 30 June 2022 (whether or not the persons concerned had suffered from COVID-19). From the beginning of January, infections caused by the rapidly dominating Omicron BA.1 and BA.2 variants initially increased rapidly; by the end of June, their relative frequencies had fallen to below 10% and the Omicron BA.5 variant predominated (5, 6).

For infection surveillance purposes, information was available at the Bavarian Health and Food Safety Authority (*Landesamt für Gesundheit und Lebensmittelsicherheit*, LGL). The final data extraction took place on 7 September 2022. For reasons of data protection, individual age information was merged into 5-year age categories at data extraction.

FIGURE 1



Flowchart of case selection according to the STROBE criteria

Data management

The data comprised all deaths for which—according to medical judgment—COVID-19 had been the direct or indirect cause or for which the cause was unknown or could not be determined.

Hereinafter, "date of infection" describes the approximate date of infection, defined as either the calendar date on which an infection was reported or the date on which the first symptoms had appeared (whichever was the earlier). The outcome variable was survival time, up to day 60 after the date of infection. Therefore, the observation period was from 1 January 2022 to 29 August 2022 (60 days after 30 June 2022).

The individual level of immunity was classified as follows: unknown; unvaccinated; incomplete primary level of immunity (one vaccination without a preceding SARS-CoV-2 infection); full primary level of immunity (two vaccinations or one vaccination in combination with a reported preceding SARS-CoV-2 infection), achieved either more or less than 6 months before the date of infection; or boosted level of immunity (three or four vaccinations, or two vaccinations in combination with a preceding SARS-CoV-2 infection) achieved either more or less than 3 months before the date of infection. Cases with a previous SARS-CoV-2 infection, but without vaccination, were counted as unvaccinated.

Statistical analysis

For the main analysis we evaluated all cases older than 59 years, and defined a separate category for cases with unknown level of immunity. The inclusion of this category allowed us to use additional information that was contained in the confounder variables.

Furthermore, we performed separate analyses for cases older than 79 years and for cases in which the level of immunity was known. In two sensitivity analyses, we respectively evaluated 30-day instead of 60-day mortality and considered only those fatalities in which COVID-19 was reported as the direct cause of death.

Cox proportional hazard regression models (7) were used to estimate the adjusted hazard ratio (aHR), effectiveness, and absolute risk reduction (with 95% confidence intervals [CI]). Associations with the level of immunity were adjusted for sex, age, and date of infection. Effectiveness was defined as the relative reduction in the risk of death (in comparison with "unvaccinated") in the infected Bavarian population over 59 and 79 years of age, respectively.

The methods used are described in detail in the *eMethods* supplement.

Results

Between 1 January and 30 June 2022, 3 846 297 cases with a positive RT-PCR test result were registered in Bavaria. Of these, 470 159 cases could be included in the main analysis *(Figure 1)*. In this group, 248 312 persons (52.8%) were female and 48 (0.01%) were diverse; 94 457 persons (20.1%) were older than 79 years at the date of infection. Of the infected persons, 1.7% had had a preceding SARS-CoV-2 infection.

Death during the observation period occurred in 3836 cases (60-day case fatality rate [CFR] 0.82%). Of these deaths, 25% were observed in persons aged 90 years or older. The median time between the date of infection and death was 8 days (interquartile range 4–14 days).

COVID-19 was the direct cause of death in 2663 cases (69.4%) and an indirect cause in 871 cases (22.7%). In 302 cases (7.9%), the cause of death was unknown or could not be determined.

The demographic data and fatality rates according to the level of immunity are presented in *Table 1*. In the majority of persons (n = 343 018, 73.0%) the level of immunity was unknown. Among those with a known level, 79 083 (62.2%) had a boosted level of immunity, 15 652 a full primary level of immunity (12.3%), and 19 561 had not been vaccinated (15.4%). Kaplan–Meier graphs for survival probabilities *(eFigure 1)* showed a significant but unadjusted association between an increasing level of immunity and a better survival rate.

Multivariable analysis

As none of the persons with diverse sex had died, these cases were not included in the Cox model. After adjustment, the risk of death was significantly higher for men than for women (aHR 1.70, [1.59–1.81]. We observed significant non-linear associations of the risk of death with both age and date of infection *(Figure 2)*.

Table 2 and *Figure 3* present aHR, effectiveness, and absolute risk reduction (related to the risk of death within 60 days among persons with a positive RT-PCR test result in the respective age category) depending on the level of immunity. Compared with unvaccinated persons, an increasing level of immunity was associated with a significantly decreasing risk of death (aHR falling from 0.42 [0.35; 0.50] to a minimum of 0.17 [0.15; 0.20] depending on the level) and with increasing effectiveness and absolute risk reduction (effectiveness with an incomplete primary level of immunity: 56.7% [48.9; 63.5]; with a boosted level of immunity reached less than 3 months before the date of infection: 81.9% [78.8; 84.7]). There was also evidence for some waning of protection.

In the subgroup without persons with an unknown level of immunity, results remained largely unchanged; protection appeared to be generally weaker across all levels of immunity, however, in persons older than 79 years. In this age group, the effectiveness was 65.5% if a full primary level of immunity had been established within 6 months before the date of infection, and fell to 45.4% with longer periods of time.

Sensitivity analyses yielded findings qualitatively similar to those of the main analysis *(eFigures 2–5)*. Quantitatively, however, protection was stronger for all levels of immunity when only fatalities in which COVID-19 had been the direct cause of death were considered.

TABLE 1

Demographic characteristics and COVID-19-related fatality rates among cases over 59 years of age in Bavaria, Germany (between January and June 2022)

Clinical variable	COVID-19-related death within 60 days after date of infection	
	Yes	No
Sex		
Female	1851 (0.7%)	246 461 (99.3%)
Male	1985 (0.9%)	219 814 (99.1%)
Diverse	0 (0%)	48 (100%)
Age (years)		
60–79	1079 (0.3%)	374 623 (99.7%)
≥80	2757 (2.9%)	91 700 (97.1%)
Level of immunity*		
Unknown	2644 (0.8%)	340 374 (99.2%)
Unvaccinated	511 (2.6%)	19 050 (97.4%)
Incomplete primary level of immunity	165 (1.3%)	12 680 (98.7%)
Full primary level of immunity established more than 6 months before date of infection	63 (1.4%)	4593 (98.6%)
Full primary level of immunity established less than 6 months before date of infection	63 (0.6%)	10 933 (99.4%)
Boosted level of immunity established more than 3 months before date of infection	186 (0.6%)	30 493 (99.4%)
Boosted level of immunity established less than 3 months before date of infection	204 (0.4%)	48 200 (99.6%)

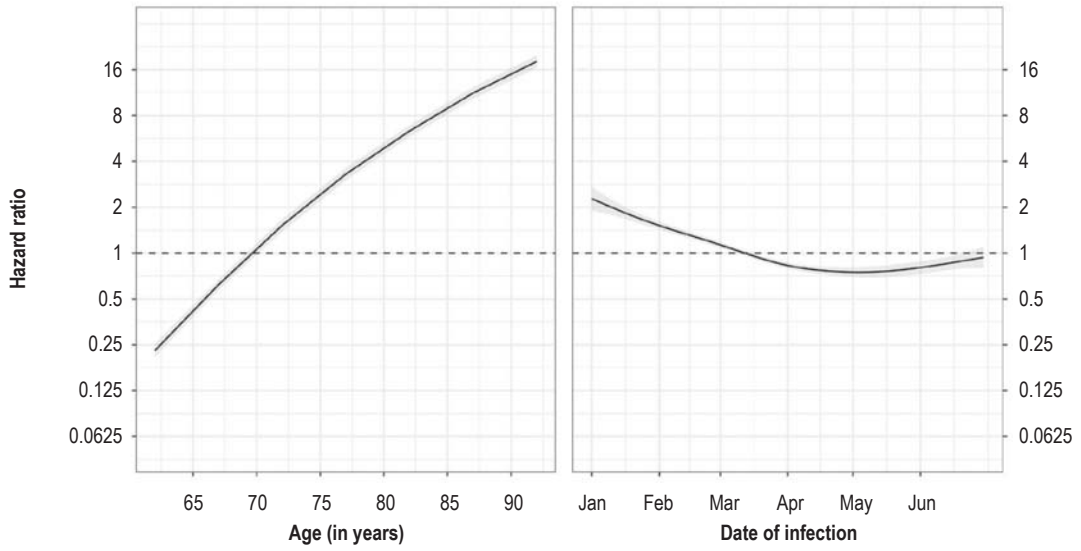
* The level of immunity was defined by vaccination status with or without a reported preceding SARS-CoV-2 infection

Discussion

A key finding of our study was that—compared with unvaccinated persons, and after adjusting for age, gender, and date of infection—an increasing level of immunity was associated with a decreasing risk of death, and with increasing effectiveness and absolute risk reduction. The maximum effectiveness was about 82% in cases that had reached a boosted level of immunity less than 3 months before the date of infection (minimal CFR 0.4%). Even with a full primary level of immunity established more than half a year before the date of infection, the effectiveness was still above 50% (CFR 1.4%).

Qualitatively, the direction of our results on primary and boosted levels of immunity is in line with observations from numerous other international studies which have studied vaccine effectiveness with regard to death (some of them specifically in elderly patients [(8–18]). Since only 1.7% of the elderly infected persons reported a preceding SARS-CoV-2 infection, it is likely that the associations we found between level of immunity and survival were determined largely by vaccination status.

FIGURE 2



Adjusted hazard ratio for COVID-19-related death (with 95% confidence bands as gray areas), depending on age (left) and date of infection (right) (among cases in which the level of immunity was unknown). The values on the y-axis follow a logarithmic scale.

Generally, our findings are also in line with the preliminary results of the German COViK study (19). However, there are differences concerning the waning of immune protection, possibly attributable to the low number of participants (770 patients), and to differences regarding the endpoints (risk of hospitalization).

Our results suggest that there may be some waning of protection from death 6 months after a full primary level of immunity has been achieved. Effectiveness decreased from 69% before this point in time to 53% thereafter, with, however, slightly overlapping 95% confidence intervals. Three months after boosting, effectiveness fell slightly, yet significantly, from 82% to 75%.

In cases over the age of 79 years, the effectiveness of a full primary level of immunity fell particularly sharply after 6 months, from around 66% to 45% (in line with longitudinal observations during the Delta wave [(20, 21]). Generally, however, the effectiveness of vaccinations against death during the Omicron wave (75–82%) was 15–20% less than that observed during the Delta wave (22) or in the registration studies performed in 2020 (23). However, comparison with the latter studies is limited, for example, by the fact that we could only evaluate infected cases.

As an incidental finding, we identified a significant, slightly U-shaped change of mortality risk during the period under study. There are numerous potential explanations, including:

- Simultaneous changes in the dominating SARS-CoV-2 variant (the risk of death may be lower for infections with the Omicron variant and its sublines than with the Delta variant, still fading at the beginning of 2022 [24–29], and lower with the Omicron BA.1/BA.2 variants than with the BA.5 variant [30, 31]).
- Seasonal effects (lower air pollution and higher humidity during the summer reduce virus transmission in high-risk subjects with impaired immune nasopharyngeal defense in the nasopharyngeal mucosa [32–34]).
- Changes in testing behavior and thus in the test positivity rate: higher rates (and therefore higher underreporting) may lead to delayed diagnosis in high-risk patients (35, 36).

Limitations

As with any retrospective observational analysis, there was the possibility of confounding due to various unmeasured covariates, e.g., timing of recommendations for vaccination, type of SARS-CoV-2 variant, therapy goal changes, comorbidities (for instance severe immunosuppression), health/risk behavior, socioeconomic status, ethnicity, body mass index (BMI), or a time-varying testing behavior which is related to the number of unrecognized infections. Our results may have also been affected by uneven temporal distribution of a second booster vaccination, by healthy vaccinee bias, or by incorrect classification of the cause of death.

Some of these covariates, however, are presumably of minor importance for the validity of our results. The healthy vaccinee bias is unlikely to cause

TABLE 2

Adjusted hazard ratios, effectiveness, and absolute risk reduction for COVID-19-related death within 60 days after the date of infection according to the level of immunity* and adjusted for age, gender, and date of infection

Level of immunity	Inclusion of cases in which the level of immunity was unknown	Age categories (years)	Adjusted hazard ratio (95% CI)	Effectiveness (%) (95% CI)	Absolute risk reduction (%) (95% CI)
Unvaccinated	Reference				
Unknown	Not applicable	All (≥ 60)	0.28 [0.25; 0.31]	71.0 [68.0; 73.7]	1.8 [1.6; 2.1]
		≥ 80	0.29 [0.25; 0.32]	70.0 [66.2; 73.1]	6.2 [5.3; 7.1]
Incomplete primary level of immunity	Yes	All (≥ 60)	0.42 [0.35; 0.50]	56.7 [48.9; 63.5]	1.5 [1.2; 1.8]
		≥ 80	0.43 [0.35; 0.53]	55.6 [45.9; 64.2]	4.9 [3.8; 6.0]
	No	All (≥ 60)	0.40 [0.34; 0.48]	58.2 [50.9; 64.7]	1.4 [1.2; 1.7]
Full primary level of immunity established more than 6 months before date of infection	Yes	All (≥ 60)	0.46 [0.35; 0.60]	52.8 [40.2; 65.0]	1.4 [1.2; 1.8]
		≥ 80	0.53 [0.40; 0.71]	45.4 [29.8; 59.3]	4.0 [2.6; 5.4]
	No	All (≥ 60)	0.45 [0.35; 0.58]	53.7 [41.9; 65.3]	1.3 [1.0; 1.7]
Full primary level of immunity established less than 6 months before date of infection	Yes	All (≥ 60)	0.30 [0.23; 0.39]	69.1 [61.1; 76.1]	1.8 [1.5; 2.1]
		≥ 80	0.33 [0.24; 0.46]	65.5 [53.6; 75.4]	5.8 [4.5; 7.0]
	No	All (≥ 60)	0.31 [0.24; 0.40]	68.2 [59.4; 76.1]	1.7 [1.3; 2.0]
Boosted level of immunity established more than 3 months before date of infection	Yes	All (≥ 60)	0.25 [0.21; 0.29]	74.5 [70.1; 78.7]	1.9 [1.7; 2.2]
		≥ 80	0.27 [0.22; 0.33]	71.8 [66.0; 77.0]	6.4 [5.4; 7.3]
	No	All (≥ 60)	0.23 [0.19; 0.27]	76.5 [72.1; 78.8]	1.9 [1.7; 2.2]
Boosted level of immunity established less than 3 months before date of infection	Yes	All (≥ 60)	0.17 [0.15; 0.20]	81.9 [78.8; 84.7]	2.1 [1.9; 2.4]
		≥ 80	0.21 [0.17; 0.26]	77.8 [73.5; 81.8]	6.9 [6.0; 7.8]
	No	All (≥ 60)	0.17 [0.15; 0.20]	81.9 [78.8; 84.7]	2.0 [1.8; 2.3]

* The level of immunity was defined by the vaccination status with or without a preceding SARS-CoV-2 infection. In addition, cases in which the level of immunity was unknown were or were not included. The results are presented according to different age categories (≥ 60 years or ≥ 80 years). The effectiveness of the level of immunity is defined as the relative reduction of the risk of death (compared with "unvaccinated") in the infected Bavarian population ≥ 60 years or ≥ 80 years. CI, Confidence interval

substantial overestimation of the risk of death (14). Moreover, the frequency of severe immunosuppression is low in mixed populations (< 2%) (8), and in comparable studies adjustment for sociodemographic characteristics or ethnicity had only a small effect on the association of, for example, SARS-CoV-2 variants with the risk of death (25, 37). The unfavorable association between BMI and the prognosis of infected cases may well be less relevant in vaccinated cases (38, 39).

Furthermore, we could not adjust for the individual vaccination schedules (e.g., type and order of the vaccines administered). However, differences in the effects on risk of death may exist only between mRNA-based and vector-based vaccines (40, e1, e2), with ChAdOx1 being used in Germany only until December 2021 (e3).

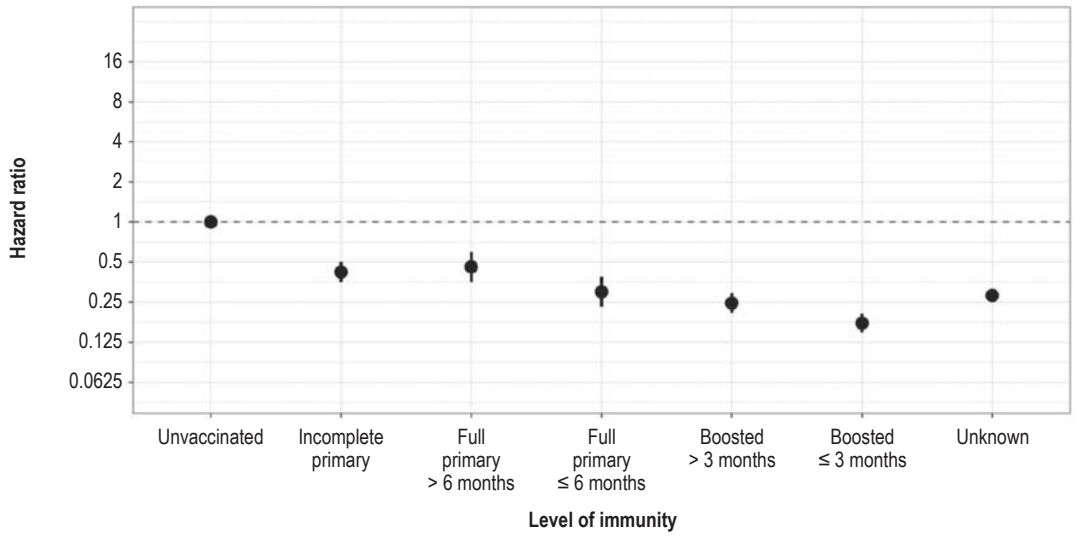
To examine the risk of misclassification/underreporting of death from COVID-19 (e4–e6), we performed a sensitivity analysis in which we considered only those fatalities in which COVID-19 had been the direct cause of death. This sensitivity analysis yielded results qualitatively similar to those of the main analysis *(eFigures 4 and 5)*.

By adjusting our results for age, it is likely that we considered at least a certain portion of the chronic comorbidities that have distinctly higher rates of occurrence with increasing age (e7) (in general, comorbidities are much less important for a worse prognosis than advanced age, especially after booster vaccinations [37]); this adjustment also enabled the consideration of therapy goal changes causing the premature death of patients. Advanced age is by far the most important predictor for such therapy restrictions (e8).

By adjusting our results for the date of infection, we took account of:

- The timing of vaccine recommendations by Germany's Standing Commission on Vaccination (STIKO), which in early 2022 propagated earlier rollout of booster vaccinations for high-risk groups.
- Effects arising from changes in the distribution of SARS-CoV-2 variants (Delta, Omicron BA.1/BA.2/BA.5) during the observation period.
- The fact that, after 12 February 2022, individual RT-PCR testing was free of charge only if a preceding rapid antigen test or pooled testing of

FIGURE 3



Adjusted hazard ratio for COVID-19-related death (with 95% confidence intervals) depending on the level of immunity (among cases in which the level of immunity was unknown) and with "unvaccinated" as reference category. The values on the y-axis follow a logarithmic scale.

samples by RT-PCR had yielded a positive result (e9). Persons who had voluntary RT-PCR tests after this date may on average have been sicker and thus at higher risk of more severe COVID-19. This would lead to an increasing overestimation of fatality rates, but not necessarily to a bias in the estimation of effectiveness.

- The fact that successively, in the last few months of the registration period, around 17% of the elderly Bavarian population received a second booster vaccination (e10). We were unable to distinguish between cases with one and those with two booster vaccinations. Since a fourth dose of a COVID-19 vaccine may further reduce the risk of death after an Omicron infection also in the elderly (18, 40, e11, e12), and since second boosters were predominantly not administered until spring 2022, we may have overestimated the benefits of a boosted level of immunity established less than 3 months before the date of infection.

As another limitation, our data were restricted with respect to completeness and quality. These parameters may have varied, both over time and across regions, depending on different conditions such as temporary staff shortages in the offices of local health authorities.

The primary goal of data collection was infection surveillance, so that especially in periods of high incidence (particularly during the Omicron wave), data such as contact details or date of infection was accorded higher priority than other information. This may, for example, explain the large proportion of missing data for level of immunity.

Strengths

Our analyses were performed on a recent, large, and population-based dataset. To our knowledge, this is the first German cohort study to analyze the association between individual level of immunity and survival time, age, and gender during the Omicron wave. By adjusting for the date of infection, we could implicitly take account of potential time-dependent effects, thereby improving the validity of our results.

Conclusion

Our results demonstrate that a full primary level of immunity offers significant protection against COVID-19-related mortality in Bavaria, even in persons over 80 years of age. Protection in this subgroup may fall below 50%, however, if such a level of immunity was established more than 6 months before the time of infection. A boosted level of immunity provided further protection at all ages, but became slightly weaker after 3 months.

Ethical approval and consent to participate

This retrospective analysis of pseudonymized data was approved by the local institutional review board of LMU Munich. The need for informed consent was waived (project no. 22–0429). All applicable data protection regulations were followed to ensure that patients' rights regarding their data were respected.

Availability of data and materials

The analysis code deposited at time of publication is available in an open source repository on GitHub at https://github.com/MaxWeigert/COVID-19_immunity_mortality.

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Dedication
This work is dedicated to Prof. Dr. Karl-Walter Jauch, Munich, chairman of the Bavarian Vaccination Committee, on the occasion of his 70th birthday.

Conflict of interest statement
The authors declare that no conflict of interests exist.

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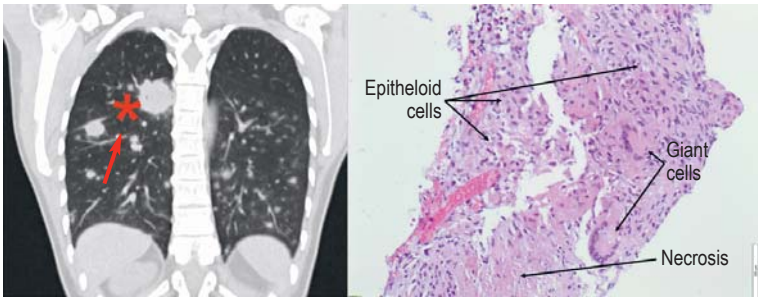
► **Supplementary material**
eReferences, eMethods und eFigures:
www.aerzteblatt-international.de/arztebl.m2023.0051

CLINICAL SNAPSHOT

Necrotizing Sarcoid Granulomatosis (NSG)

A 37-year-old female high-school teacher with a 3-week history of increasing dyspnea on exertion, arthralgia in virtually all joints, subfebrile temperature, and fatigue was admitted as an inpatient. No other abnormalities were striking from a clinical perspective, and only C-reactive protein (CRP) was elevated in laboratory tests. Computed tomography (CT) revealed multiple pulmonary nodules, some with an inflammatory halo between 1 cm (arrow) and 4 cm in diameter (asterisk). CT-guided biopsy 9 days later demonstrated significant progression of the granulomatous lesions. Histopathological analysis revealed extensive necrotizing epithelioid cell granulomatosis. Mycobacterial infection and Epstein-Barr virus-related lymphoproliferation could be excluded.



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Left figure: Computed tomography of the chest with contrast medium. Coronal plane. Pulmonary nodules, some with an inflammatory halo. The granulomatous lesions are shown by the arrow and asterisk.
Right figure: Histological image of lung tissue. Signs of necrotizing granuloma: epithelioid cells, giant cells, and necrosis.

Immunosuppressive therapy with prednisolone and azathioprine was performed. On CT at 3 months, the rapid clinical improvement was accompanied by only residual pulmonary nodules. Necrotizing sarcoid granulomatosis (NSG) is a rare differential diagnosis of granulomatous lung diseases. The histopathological analysis of tissue samples as well as the exclusion of infectious/malignant causes are essential. Multiple pulmonary nodules on computed tomography, the absence of extrapulmonary involvement, typical histopathological findings, and nonspecific clinical symptoms all contribute to the confirmation of the diagnosis.

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Supplementary material to:

Vaccine-Induced or Hybrid Immunity and COVID-19-Associated Mortality During the Omicron Wave

A Retrospective Observational Study in the Elderly

by Maximilian Weigert, Andreas Beyerlein, Katharina Katz, Rickmer Schulte, Wolfgang Hartl*, and Helmut Küchenhoff*

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eMETHODS

Study design and population

This study constituted a secondary analysis of pseudonymized data collected for the surveillance of mandatorily notifiable infectious diseases according to the German Infection Protection Act (*Infektionsschutzgesetz*, IfSG) and managed by the Bavarian Health and Food Safety Authority (*Landesamt für Gesundheit und Lebensmittelsicherheit*, LGL). All institutions named in the IfSG are obliged inform the public health departments of positive SARS-CoV-2 RT-PCR test results and of the associated demographic variables. For each individual case, the local public health departments received personal information such as name and address and were obliged to record further information, e.g., sex, age, vaccination status, date of last vaccination, date of symptom onset, SARS-CoV-2 infection history (first infection or re-infection) and date of probably or possibly COVID-19-related death. The LGL collected the pseudonymized data of all RT-PCR-confirmed cases of SARS-CoV-2 recorded by the local Bavarian public health departments on a daily basis.

Between January and June 2022, a total of 3 846 297 infections were reported to the LGL in Bavaria. This number corresponds to about 29% of all Bavarian residents (e13), under the assumption that repeated infections in the same person within the 6 months from January to June 2022 were very rare. This appears likely, particularly because the local public health departments were advised to classify a case as a person with a persistent infection, if multiple positive PCR tests had been reported within 3 months for the same person and if no contradicting information (e.g., from viral genome sequencing) was available. Since the highest risk of death was observed in COVID-19 patients over 59 years of age (e14, 37), and since more than 95% of the deaths in Germany during the Omicron wave had occurred in patients older than 59 years (e15), we restricted our analyses to this age group.

In the age group ≥ 60 years, around 14% of Bavarian residents had a positive test result between January and June 2022. Dividing this population into 5-year categories, the rate of positive tests was 20% at age 60 to 64 years, 14% at 65 to 69 years, 12% at 70 to 74 years, 10% at 75 to 79 years, 10% at 80 to 84 years, 12% at 85 to 89 years, and 16% at ≥ 90 years.

Fatalities

The IfSG obliges physicians to inform the local health authority of any death associated with a SARS-CoV-2 infection within one working day. Further investigations to clarify the cause of death were performed by the local health authority if needed. Cases in which death was most likely not caused by a SARS-CoV-2 infection (e.g., death after a traffic accident with no history of symptoms, or incidental detection of SARS-CoV-2 on hospital admission) were not to be reported to the health authorities as disease-related deaths. In consequence, these cases were not recorded as deaths; rather, they were counted as surviving.

Classification of cause of death was based on the judgment of the notifying physician. COVID-19 could have been the direct (leading) cause of death (if, for example, a patient had died from COVID-19 induced pneumonia). COVID-19 could also have been an indirect (potential) cause of death (e.g., if a patient with a positive SARS-CoV-2 PCR test result had died from infection-associated multiple organ dysfunction). According to the death notifications, the cause of death could also be unknown. If there was no information and the health authorities could not clarify the cause of death, the latter was classified as undetermined.

Calendar date of death

In an exploratory data analysis of all cases over 59 years of age in which the date of death followed or was identical to the date of infection, we found that the median time between the date of infection and the date of death was 8 days. If the date of infection was later than the date of death (242 cases) and thus implausible, we set it to 8 days before the date of death. If the calendar date of death was missing (37 cases), we set it to 8 days after the date of infection. In this way, we were able to include all recorded fatalities in the analysis.

Level of immunity

Cases with an incomplete primary level of immunity were defined as those who had had only one vaccination at least 2 weeks before the date of infection. Cases with a full primary level of immunity were defined as those who had had a first vaccination (or an earlier SARS-CoV-2 infection), and in whom a second (or first) vaccination had been administered at least 2 weeks before the date of infection (e16). Persons with a boosted level of immunity had to have a full primary level of immunity, and must have had an additional vaccination at least 7 days before the date of infection (e17). For persons who had received a booster vaccination, no information was available about whether it was a first or subsequent booster.

To investigate the time-dependent effectiveness of different levels of immunity, we analyzed these levels according to the time that had elapsed since administration of the most recent dose of vaccine. Studies conducted during the Delta wave showed evidence that protection against COVID-19-related severe disease decreased by less than 10% up to 6 months after the second vaccine dose (e1, e18). We chose a shorter time interval of 3 months to analyze the time-dependent effectiveness of a boosted level of immunity; some studies had reported a faster waning of first or second booster vaccination effect in persons infected by the Omicron variant (16, 17, e11, e19, e20).

Vaccines and timing of vaccination recommendations

Among the vaccine doses delivered up to the end of calendar week 26, Comirnaty (Pfizer-BioNTech; BNT162b2) had been the most popular vaccine given to qualifying individuals (134.5 million doses), followed by Spikevax (Moderna; mRNA-1273; 31.4 million doses), Vaxzevria (Oxford-AstraZeneca; ChAdOx1; 12.8 million doses), Jcovden (Janssen-Cilag/Johnson and Johnson, Ad26.COV2.S; 3.7 million doses), and Nuvaxovid (Novavax , NVX-CoV2373; 0.1 million doses) (e21, e22).

In Germany, the large-scale COVID-19 vaccination campaign started in January 2021. During the observation period,

on 17 February 2022, Germany's Standing Commission on Vaccination published a new recommendation: high-risk patients should receive a second booster vaccination (no less than 3 months after the first booster vaccination) (e21).

Statistical analysis

Hazard ratios describing differences in risk of death were estimated using Cox proportional hazard models (7). For categorical covariates, fixed effects were estimated. Date of infection and age were included in our model by means of penalized splines (e23) with four degrees of freedom. In this way, we also controlled for potential time-varying confounders. Estimates for adjusted absolute risk reduction and relative effectiveness were derived from the Cox models.

Since an explorative data analysis revealed that about 99% of the deaths had occurred during the first 60 days after the date of infection, we restricted our analysis to this phase of follow-up; this also reduced the risk of bias caused by violations of the proportional hazard assumption.

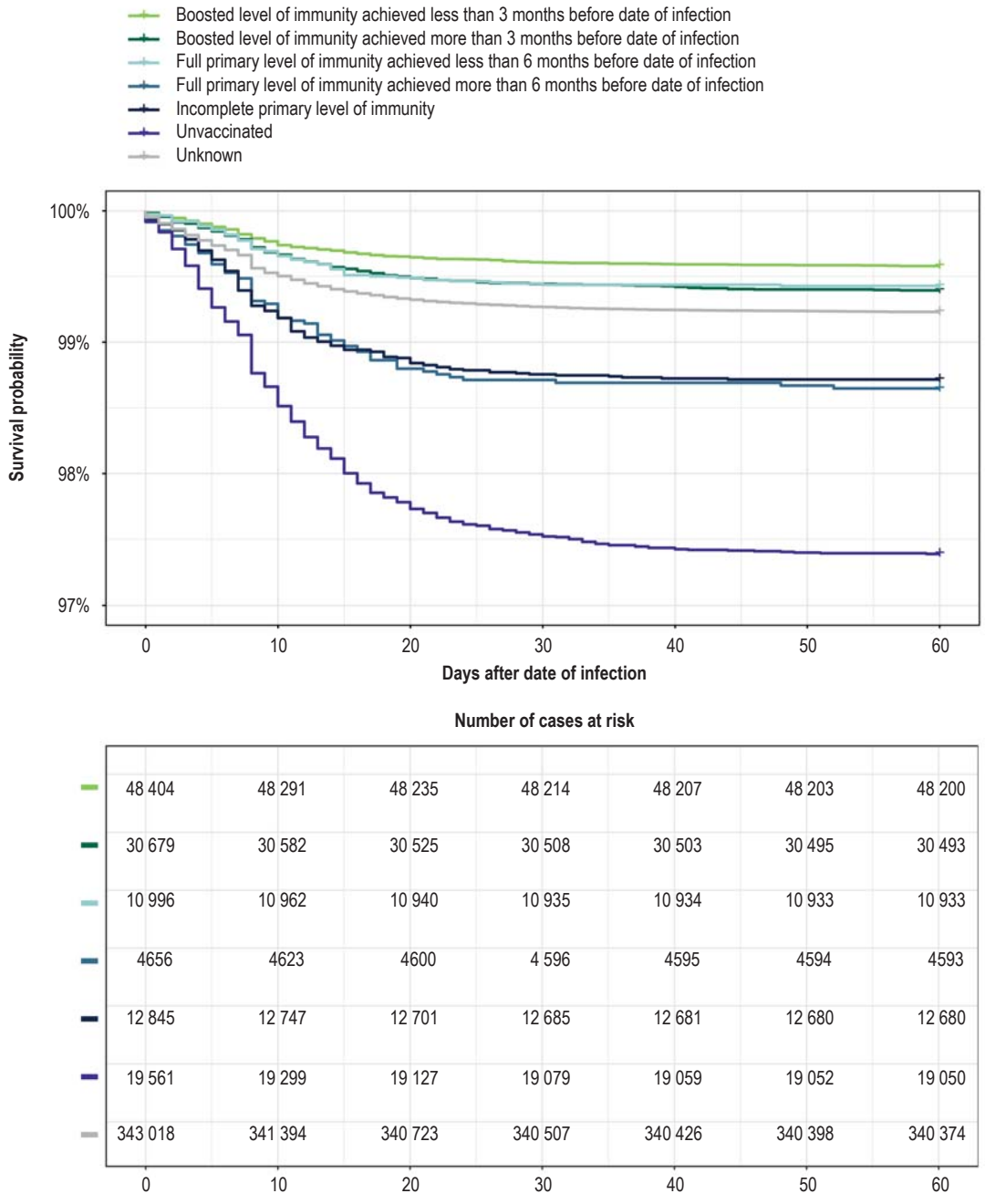
To evaluate the effect of a certain level of immunity, we first computed the adjusted absolute risk reduction for the whole population from our model. This was derived from the difference in the mean predicted probability of an event (i.e., occurrence of death) up to day 60 after the date of infection between the status "unvaccinated" and a status with a higher level of immunity (e24). The event probabilities were computed on the hypothetical premise that the entire population was either unvaccinated or had a certain—higher—level of immunity. Analogously, we defined the effectiveness of a certain level of immunity as the adjusted relative risk reduction in the infected Bavarian population, estimated using the same strategy as for absolute risk reduction (e25). The confidence intervals for both measures of risk reduction were calculated using a non-parametric bootstrap with 1000 bootstrap samples (e24).

We constructed a baseline model adjusting for sex, age category, level of immunity, and date of infection. We conducted separate analyses for cases over 79 years of age and for those in which this level of immunity was known, together with two sensitivity analyses to test the robustness of estimates for the SARS-CoV-2 infection-related risk of death:

- Analysis of 30-day mortality; there was evidence that with longer follow-up the results may be affected by violations of the proportional hazard assumption (e26).
- Use of a modified definition of the dependent variable; only those fatalities were considered for which the physicians had reported COVID-19 as the direct (leading) cause of death. Fatalities in which COVID-19 had not been the leading cause of death, or in which the cause of death was not identifiable or had not been determined, were treated as censored at the date of death.

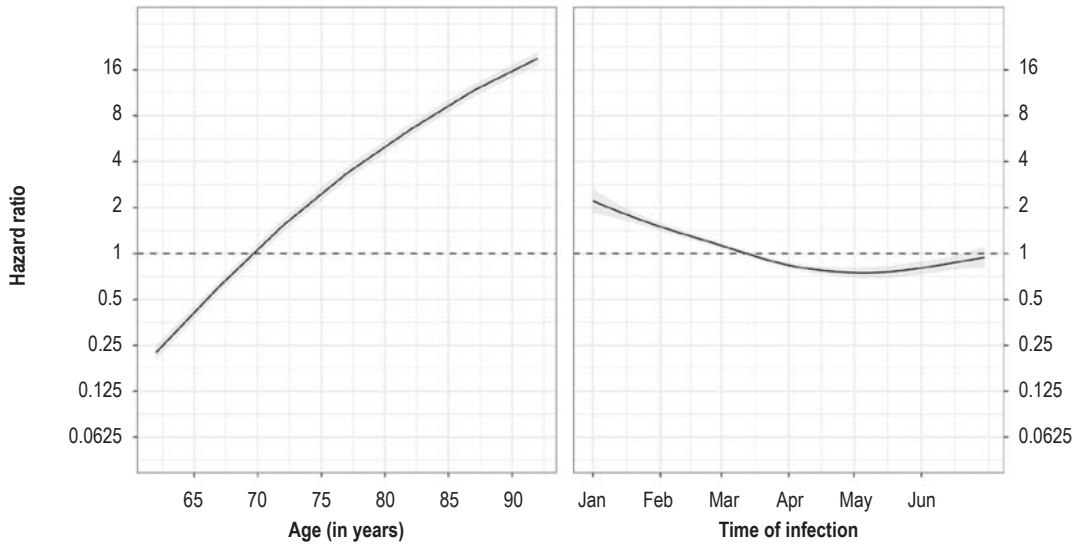
Cox regression models were estimated using the coxph function from the R package survival (version 3.4–0) (e27). The R package pec (version 2022.05.04) (e28) was used to predict event probabilities up to 60 days.

eFIGURE 1



COVID-19-related 60-day survival probabilities (Kaplan–Meier curves) for cases ≥ 60 years with a positive RT-PCR test result, depending on the level of immunity. Cases with diverse gender are included. Please note the selective presentation of the y-axis (97% to 100%).

eFIGURE 2



Adjusted hazard ratio for COVID-19-related death (with 95% confidence bands as gray areas), depending on age (left) and date of infection (right) (including cases in which the level of immunity was unknown). The values on the y-axis follow a logarithmic scale. Instead of 60-day mortality, 30-day mortality was analyzed.

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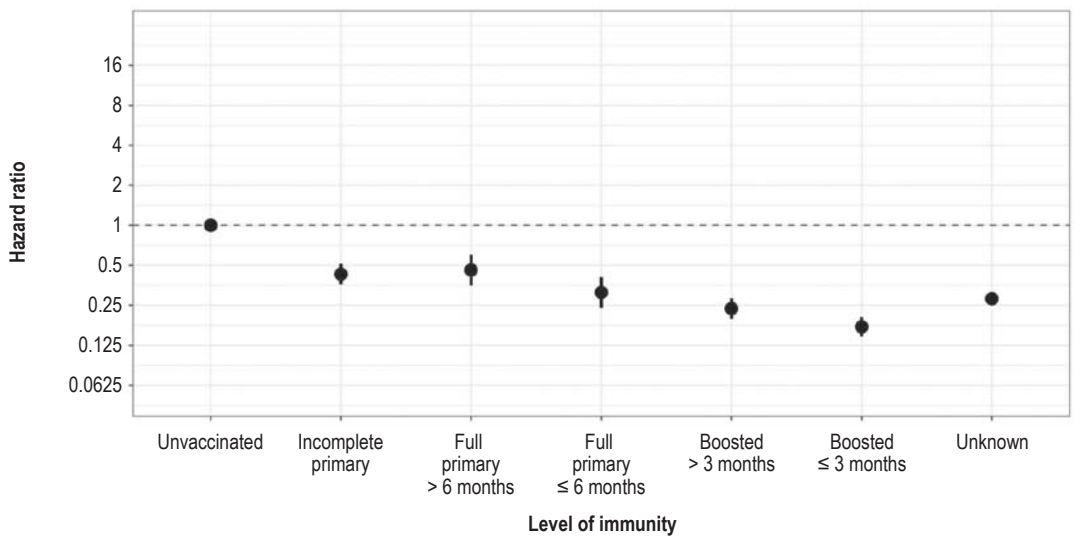
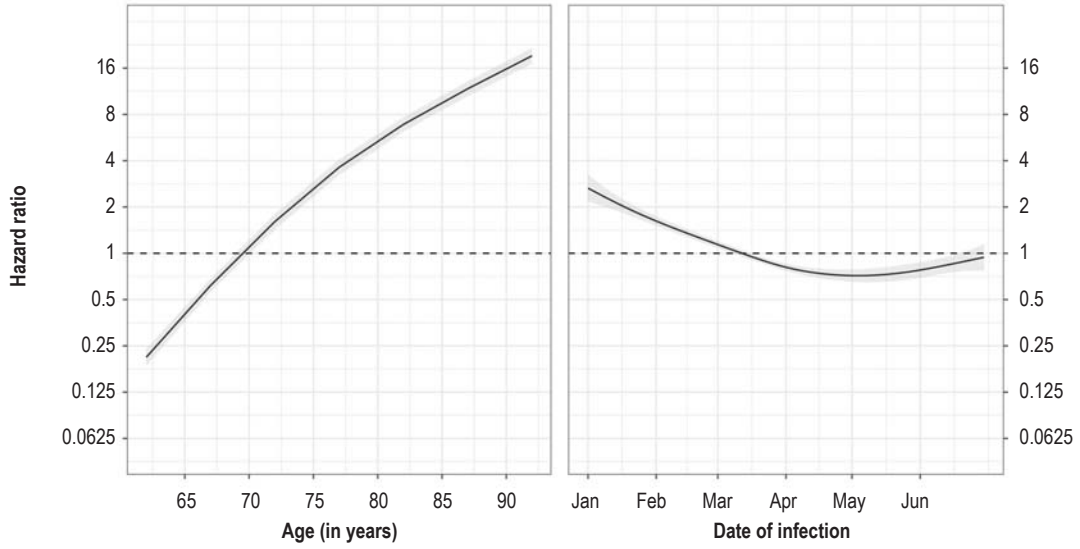
eFIGURE 3



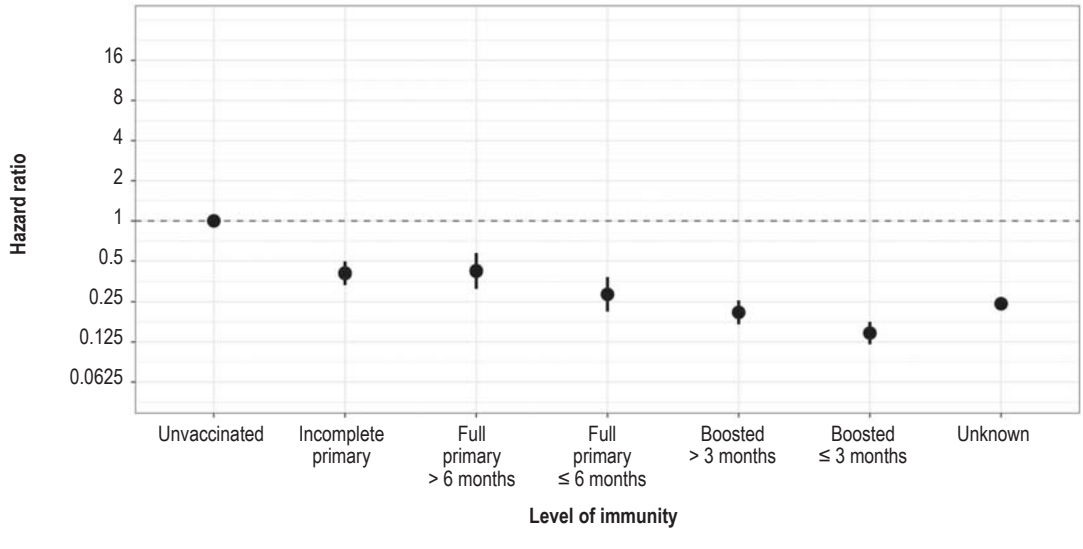
Adjusted hazard ratio for COVID-19-related death (with 95% confidence intervals) depending on the level of immunity (including cases in which the level of immunity was unknown) and with "unvaccinated" as reference category. The values on the y-axis follow a logarithmic scale. Instead of 60-day mortality, 30-day mortality was analyzed.

eFIGURE 4



Adjusted hazard ratio for COVID-19-related death (with 95% confidence bands as gray areas), depending on age (left) and date of infection (right) (including cases in which the level of immunity was unknown). The values on the y-axis follow a logarithmic scale. Only fatalities in which COVID-19 was the direct cause of death were analyzed.

eFIGURE 5



Adjusted hazard ratio for COVID-19-related death (with 95% confidence intervals) depending on the level of immunity (including cases in which the level of immunity was unknown) and with "unvaccinated" as reference category. The values on the y-axis follow a logarithmic scale. Only fatalities in which COVID-19 was the direct cause of death were analyzed.