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Burden of hospital-acquired SARS-CoV-2 infections in Germany: occurrence and outcomes of different variants

M. Bonsignore^{a,b}, S. Hohenstein^c, C. Kodde^{d,*}, J. Leiner^c, K. Schwegmann^e,
A. Bollmann^c, R. Möller^f, R. Kuhlen^f, I. Nachtigall^{g,h}

^a Department of Infectiology and Infection Prevention, Helios Klinikum Duisburg, Duisburg, Germany

^b Center for Clinical and Translational Research, Helios Universitätsklinikum Wuppertal, University of Witten/Herdecke, Wuppertal, Germany

^c Heart Centre Leipzig at University of Leipzig and Helios Health Institute, Berlin, Germany

^d Department of Pneumology, Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring, Berlin, Germany

^e Central Department for Hygiene, Helios Kliniken, Hildesheim, Germany

^f Helios Health Institute, Berlin, Germany

^g Department of Infectious Diseases and Infection Prevention, HELIOS Hospital Emil-von-Behring, Berlin, Germany

^h Charité – Universitätsmedizin Berlin, Institute of Hygiene and Environmental Medicine, Berlin, Germany

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SUMMARY

Background: Avoiding in-hospital transmissions has been crucial in the COVID-19 pandemic. Little is known on the extent to which hospital-acquired SARS-CoV-2 variants have caused infections in Germany.

Aim: To analyse the occurrence and the outcomes of HAI with regard to different SARS-CoV-2 variants.

Methods: Patients with SARS-CoV-2 infections hospitalized between March 1st, 2020 and May 17th, 2022 in 79 hospitals of the Helios Group were included. Information on patients' characteristics and outcomes were retrieved from claims data. In accordance with the Robert Koch Institute, infections were classified as hospital-acquired when tested positive >6 days after admission and if no information hinted at a different source.

Findings: In all, 62,875 SARS-CoV-2 patients were analysed, of whom 10.6% had HAI. HAIs represented 14.7% of SARS-CoV-2 inpatients during the Wildtype period, 3.5% during Alpha (odds ratio: 0.21; 95% confidence interval: 0.19–0.24), 8.8% during Delta (2.70; 2.35–3.09) and 10.1% during Omicron (1.10; 1.03–1.19). When age and comorbidities were accounted for, HAI had lower odds for death than community-acquired infections (0.802; 0.740–0.866). Compared to the Wildtype period, HAIs during Omicron were associated with lower odds for ICU (0.78; 0.69–0.88), ventilation (0.47; 0.39–0.56), and death (0.33; 0.28–0.40).

Conclusion: Hospital-acquired SARS-CoV-2 infections occurred throughout the pandemic, affecting highly vulnerable patients. Although transmissibility increased with newer variants, the proportion of HAIs decreased, indicating improved infection prevention and/or

* Corresponding author. Address: Department of Pneumology, Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring, Walterhöferstraße 11, 14165 Berlin, Germany. Tel.: +49 8102/62495.

E-mail address: cathrin.kodde@helios-gesundheit.de (C. Kodde).

the effect of immunization. Furthermore, the Omicron period was associated with improved outcomes. However, the burden of hospital-acquired SARS-CoV-2 infections remains high.

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Introduction

When the novel SARS-CoV-2 started spreading throughout the world, its high transmissibility soon became apparent. Under unfavourable conditions, a single person was able to infect many others, causing so-called super-spreader events and outbreaks in different settings. This posed major challenges for hospitals to prevent nosocomial spread. Initially, knowledge about the disease and its transmission routes was scarce; this led to a wide variety of prevention measures being employed, including some that now seem superfluous, such as the use of coveralls or thermographic cameras or even setting up separate hospitals for the treatment of COVID-19 patients. At the beginning of the pandemic, there was broad consensus among the scientific community that the transmission occurred mainly via droplets, as in other respiratory viruses and in rare cases via other body fluids or indirectly via surfaces [1]. The focus of prevention measures rested therefore on separation and isolation, the use of surgical masks, face shields, protective gowns, frequent handwashing and enhanced environment disinfection protocols [2,3]. Increasing evidence of super-spreader events with transmissions among persons without direct contact and over significant distances made the airborne route appear increasingly plausible [4,5]. This shifted the emphasis on measures such as masks with higher filtration capability (FFP2 or KN95 masks) and towards improving indoor air using frequent ventilation and filtration.

Despite an increasing understanding of the infection, its transmission mechanisms and the corresponding tailoring of precautions, outbreaks have continued to occur throughout the pandemic in care facilities and hospitals. Little is yet known about the total burden of these infections in Germany during the pandemic. This study analyses the occurrence and the outcomes of hospital-acquired SARS-CoV-2 infections within a large hospital group, as well as the influence of virus variants.

Methods

This study is a retrospective analysis based on claims and surveillance data. We included all inpatients hospitalized with the International Classification of Diseases (ICD-10) code U07.1 (polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection) as main or secondary diagnosis in 79 hospitals of the Helios Group between March 1st, 2020 and May 17th, 2022. Helios is a privately owned company with hospitals spread throughout Germany. Its proportion of basic to tertiary care is comparable to the overall distribution of hospitals in the country, treatment in Helios hospitals being covered by all German health insurances. Patients from the claims data retrieval were linked to patients documented in the iNOK database, this being a Helios' own, group-wide, intranet-based surveillance programme, in which trained infection control nurses document daily new patients with a SARS-CoV-2 infection. In accordance with the criteria of the Robert Koch

Institute, infections were classified as being hospital-acquired as follows:

- Positive SARS-CoV-2 PCR after day 6 of the inpatient stay and no other obvious source of infection, e.g. previously infected household members or visitors;
- Positive SARS-CoV-2 PCR on day 3–6 of hospital stay and strong suspicion of transmission in hospital;
- Readmission of a patient with a positive SARS-CoV-2 PCR ≤ 6 days after discharge and strong suspicion of transmission in hospital [6].

Claims and surveillance data were linked by a double-pseudonymized case number.

Information on sex, age, comorbidities, treatment in an intensive care unit (ICU), mechanical ventilation, and death were retrieved from claims data. Mechanical ventilation was defined as ventilation with pressure support via either invasive devices such as tracheal tube or tracheostomy, or use of non-invasive devices. Mortality was defined as death during the same hospital stay. Cases with discharge due to hospital transfer were excluded from the calculation of the mortality rate. Claims data on comorbidity was summarized by the Elixhauser Comorbidity Index, a score for categorizing patient comorbidities based on ICD-10 codes [7]. As surrogate parameter for the number of patients with symptoms among those infected with SARS-CoV-2, the documentation of a severe acute respiratory infection (SARI) was included, as defined by the ICD-10-codes J09-J22 according to the method of SARI surveillance [8].

For further analysis, each patient was associated with the variant that was prevalent at the time of becoming infected. Actual results of variant analyses were not available. The time-period of predominance of each variant was derived from the weekly reports of the Robert Koch Institute on variant development in Germany as follows:

- (1) Wild type period: February 4th, 2020 to March 7th, 2021
- (2) Alpha period: March 8th, 2021 to June 25th, 2021
- (3) Delta period: June 26th, 2021 to January 2nd, 2022
- (4) Omicron period: January 3rd, 2022 to present [9].

Statistics

Inferential statistics were based on generalized linear mixed models (GLMMs) specifying hospitals as random factor [10]. Effects were estimated with the lme4 package (version 1.1–26) in the R environment for statistical computing (version 4.0.2, 64-bit build) [11,12]. For all tests a two-tailed 5% error criterion for significance was applied. For the description of the patient characteristics of the cohorts, χ^2 -tests were employed for binary variables and analysis of variance for numeric variables. Proportions, means, standard deviations, and *P*-values are reported.

For the comparison of outcomes, logistic GLMMs with logit link function were used. Proportions, odds ratios together with confidence intervals and *P*-values are reported.

Logistic GLMMs were used for multivariable analysis of binary outcomes. The analysis of weekly HAI proportions was done via beta regression. Numerical predictors were centred on their mean and scaled to unit variance.

Statistics for Elixhauser Comorbidity Index are reported. For this index, the Agency for Healthcare Research and Quality (AHRQ) algorithm was applied [13].

Ethics

The local ethics Committee (vote: AZ490/20-ek) and Helios Kliniken GmbH data protection authority approved data use for this study.

Table 1

Characteristics and outcome of patients with community-acquired versus hospital-acquired SARS-CoV-2 infections

Variant/variable	Community-acquired infection (CAI)	Hospital-acquired infection (HAI)	OR (95% CI) HAI vs CAI	<i>P</i> -value
All	56,223	6652 (10.6%)	n/a	n/a
Age (years) (mean ± SD)	62.5 ± 22.8	72.5 ± 17.0	n/a	<0.01
Sex (male)	28,625 (50.9%)	3415 (51.3%)	n/a	ns
ECI	8.8 ± 10.7	15.8 ± 13.7	n/a	<0.01
SARI	31,918 (56.8%)	2794 (42.0%)	0.57 (0.54–0.60)	<0.001
ICU	11,581 (20.6%)	2305 (34.7%)	1.99 (1.88–2.11)	<0.001
Mechanical ventilation	7727 (13.7%)	892 (13.4%)	0.92 (0.85–0.99)	0.032
Mortality	7228 (14.5%)	1234 (20.9%)	1.53 (1.43–1.64)	<0.001
Wildtype	18,299	3,143 (14.7%)	n/a	n/a
Age (years) (mean ± SD)	67.9 ± 19.3	73.7 ± 15.3	n/a	<0.01
Sex (male)	9396 (51.3%)	1560 (49.6%)	n/a	ns
ECI (mean ± SD)	10.4 ± 11.1	16.8 ± 13.4	n/a	<0.01
SARI	13,173 (72.0%)	1721 (54.8%)	0.48 (0.44–0.52)	<0.001
ICU	4450 (24.3%)	1150 (36.6%)	1.74 (1.60–1.89)	<0.001
Mechanical ventilation	3046 (16.6%)	511 (16.3%)	0.92 (0.81–1.02)	ns
Mortality	3310 (20.2%)	760 (27.9%)	1.49 (1.35–1.63)	<0.001
Alpha	7,567	274 (3.5%)	n/a	n/a
Age (years) (mean ± SD)	61.0 ± 19.5	71.1 ± 19.0	n/a	<0.01
Sex (male)	4091 (54.1%)	134 (48.9%)	n/a	ns
ECI (mean ± SD)	8.7 ± 10.5	15.2 ± 13.3	n/a	<0.01
SARI	5662 (74.8%)	122 (44.5%)	0.30 (0.23–0.40)	<0.001
ICU	2005 (26.5%)	90 (32.8%)	1.53 (1.17–2.01)	0.002
Mechanical ventilation	1610 (21.3%)	44 (16.1%)	0.76 (0.54–1.06)	ns
Mortality	957 (14.1%)	50 (20.4%)	1.65 (1.18–2.30)	0.003
Delta	11,285	1,085 (8.8%)	n/a	n/a
Age (years) (mean ± SD)	60.9 ± 22.5	69.4 ± 19.3	n/a	<0.01
Sex (male)	5921 (52.5%)	586 (54.0%)	n/a	ns
ECI (mean ± SD)	8.7 ± 10.5	15.7 ± 14.8	n/a	<0.01
SARI	7340 (65.0%)	406 (37.4%)	0.33 (0.28–0.37)	<0.001
ICU	2616 (23.2%)	375 (34.6%)	1.72 (1.49–1.98)	<0.001
Mechanical ventilation	2068 (18.3%)	151 (13.9%)	0.69 (0.57–0.82)	<0.001
Mortality	1678 (16.6%)	201 (20.2%)	1.24 (1.05–1.47)	0.012
Omicron	19,072	2,150 (10.1%)	n/a	<0.01
Age (years) (mean ± SD)	58.9 ± 26.2	72.5 ± 17.7	n/a	<0.01
Sex (male)	9219 (48.4%)	1135 (52.8%)	n/a	<0.01
ECI (mean ± SD)	7.5 ± 10.3	14.3 ± 13.5	n/a	<0.01
SARI	5743 (30.1%)	545 (25.3%)	0.77 (0.69–0.85)	<0.001
ICU	2510 (13.2%)	690 (32.1%)	2.93 (2.64–3.35)	<0.001
Mechanical ventilation	1003 (5.3%)	186 (8.7%)	1.58 (1.33–1.86)	<0.001
Mortality	1283 (7.7%)	223 (11.4%)	1.51 (1.30–1.76)	<0.001

OR, odds ratio; CI, confidence interval; ECI, Elixhauser Comorbidity Index; SARI, severe acute respiratory infection; ICU, intensive care unit; SD, standard deviation; n/a, not applicable; ns, not significant.

Results

Occurrence of hospital-acquired SARS-CoV-2 infections

In total, 62,875 patients with a PCR-confirmed SARS-CoV-2 infection were included. In 6652 (11.8%) of these, the infection was categorized as hospital-acquired (HAI) (Table 1).

The number of HAIs varied during the pandemic. It peaked during the Wildtype period (208 HAIs per week) and Omicron period (229 HAIs per week) (Figure 1A). Generally, the number of HAIs increased with the number of community-acquired infections (CAIs) (odds ratio (OR): 2.871; 95% confidence interval (CI): 2.680–3.071; *P* < 0.001). However, the proportion of HAIs among all inpatients did not remain constant,

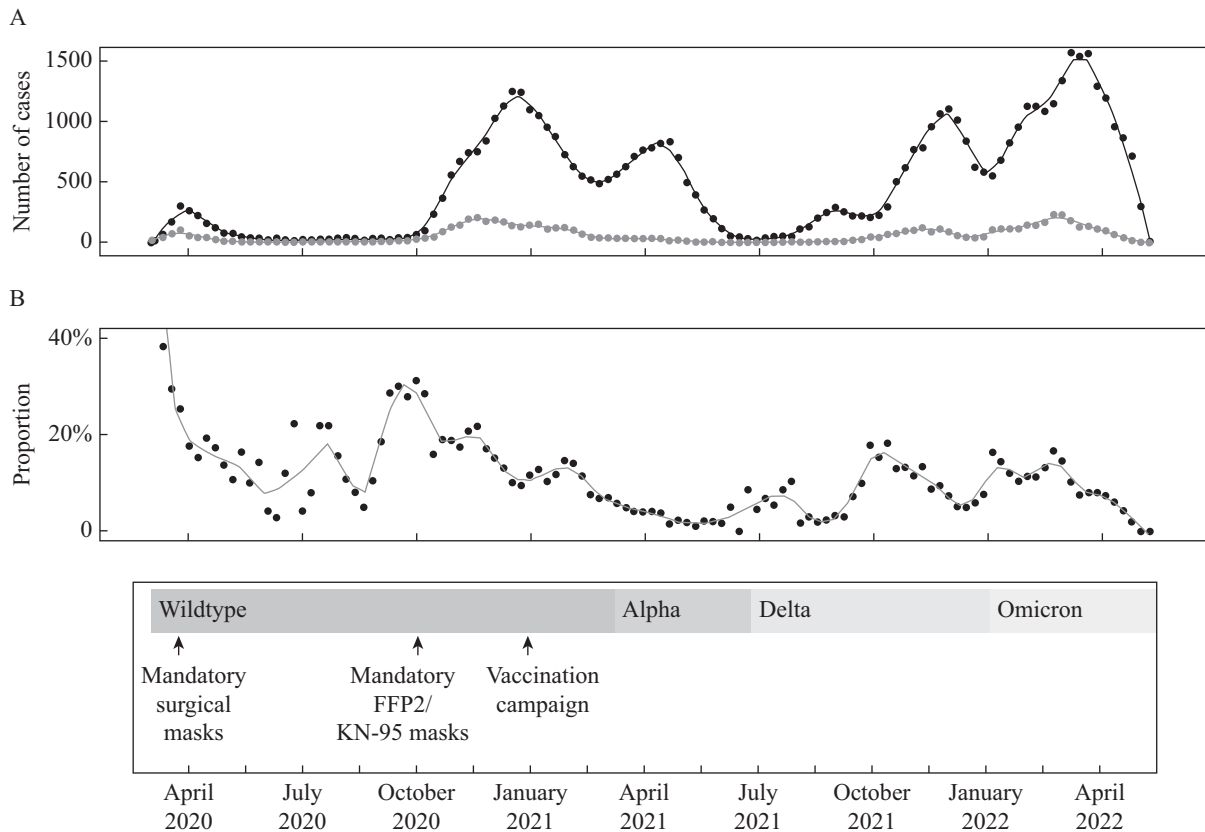


Figure 1. (A) Weekly incidences of community-acquired (black line) and hospital-acquired (grey line) infections. (B) Proportion of hospital-acquired infections to all hospitalized patients with SARS-CoV2. The smooth curves were generated via LOESS (locally weighted scatterplot smoothing).

varying between zero and 31.2% (Figure 1B). There was no association between the proportion of HAIs and the number of CAIs, i.e. periods with a high number of inpatients with CAIs were neither associated with more nor with fewer transmissions (OR: 0.968; 95% CI: 0.830–1.123; $P = 0.667$). Rather, the fluctuations in the proportions were determined by the variants. During the Wildtype period, the proportion of HAIs was highest, on average 14.7%; this decreased to 3.5% during Alpha (OR: 0.21; 95% CI: 0.19–0.24; $P < 0.001$) and increased again to 8.8% during Delta (2.70; 2.35–3.09; $P < 0.001$) and then to 10.1% during Omicron (1.10; 1.03–1.19; $P = 0.015$).

Outcomes of hospital-acquired SARS-CoV-2 infections

Among patients with HAIs, 42.0% developed a severe acute respiratory infection (SARI), 34.7% were treated in ICU, 13.4% were ventilated, and 20.9% died (Table I). Compared to patients with CAIs, they were diagnosed less frequently with SARI (OR: 0.57; 95% CI: 0.54–0.60) and received less frequently mechanical ventilation (0.92; 0.85–0.99), but were treated more often in ICU (1.99; 1.88–2.12). Mortality was higher among patients with HAI (1.52; 1.43–1.64). However, patients with HAI were on average 10.0 years older and had an ECI 7.0 points higher ($P < 0.01$) than patients with CAI. When age, sex, and ECI were controlled for (Table II, multivariable analyses), HAIs were associated with a higher risk for ICU (1.44; 1.35–1.53), but with a lower risk for ventilation (0.597; 0.55–0.65) and death (0.80; 0.74–0.87).

The outcomes of HAI differed between the various periods of variant dominance similarly to CAIs (Table I). ICU and mortality rates were highest during the Wildtype period (ICU: 36.6%, mortality: 27.9%). Outcomes became more favourable with each new variant. During the Omicron period, ICU rate fell to 32.1% and mortality rate to 11.4%. Compared to infections during the Wildtype period, HAIs during Omicron had the least odds for intensive care (OR: 0.78; 95% CI: 0.69–0.88; $P < 0.001$), ventilation (0.47; 0.39–0.56; $P < 0.001$), SARI (0.29; 0.25–0.33; $P < 0.001$) and death (0.33; 0.28–0.40; $P < 0.001$).

Discussion

In all, 62,875 patients treated with SARS-CoV-2 in the hospitals of the Helios group were analysed. Of these, around 11% had acquired the infection during the hospital stay. Earlier studies focusing on the first wave described proportions of HAIs of 12% in Wuhan and of 15–20% in England [14–18]. On the other hand, a single centre study from Boston detected only one HAI among nearly 10,000 inpatients during the first weeks of the pandemic [19].

To estimate the total occurrence of HAIs in Germany, the number of patients hospitalized since the beginning would be needed. However, due to incomplete reporting, the exact number is not known. Based on the total number of infections in the population and on the proportion of hospitalizations among the available reports, it can be roughly estimated that

Table II

Multivariable analyses of risk factors for intensive care, mechanical ventilation and mortality, among all inpatients with SARS-CoV-2

Variable	Intensive care		Mechanical ventilation		Mortality	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Male sex	1.627 (1.560–1.695)	<0.001	1.834 (1.740–1.928)	<0.001	1.620 (1.540–1.708)	<0.001
Age	1.038 (1.010–1.064)	0.004	0.961 (0.930–0.991)	0.010	1.057 (1.050–1.059)	<0.001
Elixhauser Comorbidity Index	1.814 (1.770–1.854)	<0.001	1.940 (1.890–1.990)	<0.001	1.057 (1.050–1.059)	<0.001
Hospital- vs community-acquired	1.439 (1.350–1.530)	<0.001	0.597 (0.550–0.649)	<0.001	0.802 (0.740–0.866)	<0.001
Alpha vs Wildtype	1.290 (1.210–1.375)	<0.001	1.548 (1.440–1.661)	<0.001	0.914 (0.840–0.994)	0.037
Delta vs Wildtype	1.054 (1.000–1.114)	0.065	1.224 (1.150–1.303)	<0.001	1.007 (0.940–1.078)	ns
Omicron vs Wildtype	0.577 (0.550–0.608)	<0.001	0.323 (0.300–0.347)	<0.001	0.362 (0.340–0.388)	<0.001

OR, odds ratio; 95% CI, confidence interval; ns, not significant.

about 915,000 COVID-19 patients have been hospitalized since the beginning of the pandemic and until April 2022 [9]. Assuming a similar burden of HAIs in all hospitals in Germany, up to 110,000 patients might have been affected by hospital-acquired SARS-CoV-2 infections in Germany since the beginning of the pandemic.

HAIs have occurred despite comprehensive infection control programmes. The hospital architecture in Germany is far from ideal regarding infections with an airborne transmission route: most rooms are designed to accommodate two or three patients and mechanically ventilated rooms are usual only in units for intensive care or stem cell transplants. A major problem is a low nurse-to-patient ratio. Germany introduced a law regulating this ratio only in 2019 and suspended it during the first months of the pandemic. The legally required standard of one nurse per two patients in ICU and one per 10 in medical–surgical units is still lower than the given average in other European countries or the USA [20]. Low nurse-to-patient ratios have been associated with a higher risk for HAI [21–23].

Some of the measures taken – e.g. universal masking, screening of patients and personnel, increased hand hygiene and frequent room ventilation – created high costs and discomfort, but usually no major harm. Others – e.g. quarantine and isolation, visitors' limitations, postponing elective treatments and the limitation of in-hospital meetings and teachings – had severe consequences for patients and staff alike, such as anxiety, depression, delirium, suicide risk, and insufficient or delayed medical treatment [24–28]. Which prevention measures were most effective, which proved superfluous and what additional efforts (if any) should have been implemented remain to be evaluated. At this time, it seems hardly conceivable that even more severe restrictions could have been imposed on patients, relatives and healthcare workers to prevent HAIs.

Occurrence of HAI during different periods of variant predominance

The highest numbers of HAI per week occurred during the Omicron period in March/April 2022. This period also saw the highest numbers of inpatients with SARS-CoV-2 and of infections in the population since the beginning of the pandemic [29]. More infected people among staff and visitors unfortunately led to more HAIs. However, the proportion of HAIs among all inpatients with SARS-CoV-2 was highest during the first and second wave of the pandemic, i.e. during the Wildtype period, decreased during the Alpha period, and increased again

with Delta and Omicron. At the same time, with each new variant the coronavirus became more contagious. Estimations on the original virus reported a basic reproductive number (R_0 : the average number of people to whom an infected person will pass the virus in a totally naïve population and in the absence of preventive measures) of around 2–3 [30,31]. R_0 reached 4–5 with the Alpha variant, 5–8 with Delta, and 9–10 with Omicron [32–34]. The major decrease in the proportion of HAIs during Alpha can probably be attributed to improvements in prevention measures and in outbreak management, but above all to the vaccination campaign, which focused during the first months of 2021 on healthcare workers and persons at risk, providing initially a high level of protection against the infection. The later rebound is probably the consequence of the increase in transmissibility associated with Delta and Omicron.

Outcome of hospital-acquired SARS-CoV-2 infections

Twenty-one percent of patients with HAI died in association with it. Extrapolated to the estimated number of hospitalized patients with SARS-CoV-2, up to 23,000 might have died in connection with a hospital-acquired SARS-CoV-2 infection in Germany since beginning of the pandemic. This would correspond to the order of magnitude of fatalities anticipated to result in the same period from all other common HAIs combined, such as surgical site infections, pneumonia, and urinary tract infections, including those caused by multidrug-resistant organisms [35].

However, not all deaths of patients with a hospital-acquired SARS-CoV-2 infection will have been caused directly by the infection. When the risk factors for an adverse outcome – age, gender and comorbidities – were accounted for, HAIs were associated with lower odds for death than CAIs. Furthermore, patients with HAI were less likely to be diagnosed with a severe respiratory infection. Both features indicate that there might have been a greater proportion among patients with HAI than among those with CAI, in whom the infection was a secondary if not incidental finding, perhaps detected in the course of routine testing and with no greater clinical relevance. These patients likely had other reasons for being hospitalized than a SARS-CoV-2 infection, leading to intensive care, mechanical ventilation, and death independently from a SARS-CoV-2 infection.

The Omicron period was associated with a significantly more favourable disease course. This is concordant to other studies comparing the outcome of Omicron to earlier variants [36,37]. In addition to an attenuated virulence of the coronavirus, this

development is probably due to the increasing immunization of the population. Furthermore, during the Omicron period, only a quarter of the patients with HAI were diagnosed with a severe respiratory infection, indicating an increasing proportion of secondary findings. However, in spite of the decreasing relevance of HAIs and the more benign outcomes since the Omicron variant, the mortality rate of patients with HAI was still high.

Strengths and limitations of the study

To the best of our knowledge, this is the first study to analyse the occurrence and the outcome of hospital-acquired SARS-CoV-2 infections in a large cohort in Germany as well as to show the changes that came with new variants. However, there are limitations to the interpretation of the results.

The main parameter of the study – the classification of the infections into community-versus hospital-acquired – relies on an estimation. The criteria were set and all cases were evaluated individually, including patients' history, laboratory, and imaging results in doubtful cases. Still, in some cases, the route of infection could not be traced with absolute certainty. The high number of infection control nurses involved probably caused a high inter-rater variability. The median incubation period of the early variants was 5 days, of Delta 4.3 and of Omicron 3 days [38–40]. Patients might have been infected in the first day(s) after admission and still tested positive before day 7, leading to the misclassification as CAIs. Patients with disease manifestation after discharge were registered only when readmitted. On the other hand, ~25% of infections have an incubation period of more than seven days and some may therefore have been falsely allocated as hospital-acquired [38]. False-negative results in early stages of the disease or delayed testing, caused by limited access to testing early in the pandemic or by the lack of typical symptoms, will also have resulted in a misclassification into HAIs. As there was no universal and repetitive screening in the beginning of the pandemic, underreporting is probable.

In conclusion, the pandemic has represented an unprecedented challenge for healthcare workers and infection prevention and control teams in their efforts to avoid hospital spreading. In spite of extensive prevention measures, hospital-acquired SARS-CoV-2 infections have occurred since the beginning of the pandemic, affecting a highly vulnerable population group. Fortunately, although the transmissibility has increased with new variants, the proportion of HAIs has decreased, indicating an improvement in infection prevention. Furthermore, the Omicron period was associated with better outcomes. However, the burden of hospital-acquired SARS-CoV-2 infections remains high. Further research is urgently needed to define prevention measures adequate to lower this burden with the greatest benefit and least harm.

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