



A case series of severe breakthrough infections observed in nine patients with COVID-19 in a southwestern German university hospital

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Abstract

Purpose Vaccination is the key element for protection against COVID-19. Increased vaccination breakthroughs raise the question of whether additional prevention is necessary in case of individual risk factors for a severe course with hospitalization or death despite vaccination.

Methods Since July 13, 2021, there is an extended reporting requirement by German law. We analyzed our hospitalized patients with vaccine breakthrough infection during the first 8 weeks.

Results Nine of 67 patients (13.4%) hospitalized for COVID-19 (median age 75 years) were fully vaccinated. Five of these patients received intensive care; two patients died. All had received two doses of BNT162b2 vaccines (Pfizer-BioNTech). There was a median of 99 days between complete immunization and symptom onset. All patients suffered from \geq three comorbidities. Six patients (66.7%) showed a negative Anti-SARS-CoV-2-N titer at the time of vaccine breakthrough, five of these also had Anti-SARS-CoV-2-S titers $<$ 100 U/ml. All determinable cases were Delta variant B.1.617.2.

Conclusion Advanced age, underlying cardiorespiratory disease, and the Delta variant of SARS-CoV-2 were associated with hospitalization of our patients, suffering from vaccine breakthrough infection. Avoidance of face masks, lack of immunization of close contacts, and travel to high-risk areas have been observed as modifiable behavioural circumstances. Consistent personal protective measures, vaccination of close caregivers, and increased awareness might be effective measures in addition to COVID-19 booster vaccination for patients at a high risk to suffer a severe course of infection.

Keywords COVID-19 · Vaccination · Vaccine breakthrough · Risk factors · Preventive measures

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Introduction

Vaccination has been the effective key element to protect the population against COVID-19 since December 27, 2020 [1–3]. In Germany, the mRNA vaccine BNT162b2 (Pfizer-BioNTech) was applied quite predominantly, for which a protective effect for 95% of the vaccinated against the wild type of SARS-CoV-2 was described [4]. As early as April 2021, Hacisuleyman et al. reported two vaccine breakthroughs by different SARS-CoV-2 variants after complete vaccination with an mRNA vaccine [5].

On July 11, 2021, the German Federal Ministry of Health issued the ordinance on the extended reporting obligation according to Sect. 6 of the Infection Protection Act (IfSG) for hospitalized COVID-19 patients with vaccination breakthrough [6]. Thus, a nationwide registration of cases with vaccination breakthrough started. Since July 13, 2021, an extended reporting dataset has been sent to the health authorities by the hospitals.

The dominance of the Delta variant and the renewed increase in the number of cases since September 2021, despite a rate of 66.7% (as of 10-30-2021) of fully vaccinated adults [7], raise the question as to which individuals are at risk for severe COVID-19 disease despite vaccination. The aim of this work is to use a collective of fully vaccinated hospitalized COVID-19 patients to describe potential predisposing factors for severe COVID-19 courses after vaccine breakthrough and to identify modifiable risk factors that promote vaccine breakthrough. This will provide a basis for recommending flanking preventive measures in addition to vaccination of individuals at risk.

Methods

At the University Hospital Mannheim, the demographic data of all hospitalized COVID-19 patients are recorded daily in the Department of Hygiene. In calendar week (CW) 28–36, the subgroup of all hospitalized patients with a vaccination breakthrough was analyzed prospectively (07-13-2021 to 09-06-2021). In accordance with the definition of the Public Health Institute for Germany [Robert Koch Institute (RKI)], a vaccination breakthrough was defined as SARS-CoV-2 infection confirmed by PCR with clinical symptoms of COVID-19 disease that occurred in fully vaccinated persons, i.e. at least 14 days after completion of a vaccination series [8].

Data collection included sex, age, body mass index (BMI), number and specificity of pre-existing comorbidities, vaccination status and vaccine used. Furthermore, the PCR results with the associated cycle threshold (Ct) values

(cobas[®] SARS-CoV-2, Roche Diagnostics GmbH, Germany; Cepheid Gene Xpert[®] Xpress SARS-CoV-2, Cepheid, Germany) at the time of vaccination breakthrough and the result of the SARS-CoV-2 mutation diagnostics were extracted from the findings of the infection diagnostics performed as standard. In addition, anti-SARS-CoV-2 N and anti-SARS-CoV-2 S levels (Cobas e601 analyzer, Roche, Germany) were analyzed in all patients at the time of hospital admission. The information recorded during the interview of the patient and/or a first-degree relative included the use of medical masks in daily life, immunization of close contacts, travel history before vaccination breakthrough and the temporal latency between onset of COVID-19-specific symptoms and consultation of a physician (Table 1).

The study was approved by the Research Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Germany (No. 2021-850).

The aforementioned patient data were extracted from the hospital information system (SAP, Walldorf, Germany) and processed strictly pseudonymised for the analysis.

Results

During the observation period, a total of nine (seven men, two women) out of 67 (13.4%) patients hospitalized for COVID-19 showed vaccine breakthrough. The median age of those affected was 75 years (range 44–90 years) (Table 1). All had three or more comorbidities: seven had heart failure and/or arrhythmias treated with medication (77.8%), six had hypertension (66.7%), and four had diabetes mellitus (44.4%). Only two of the nine patients had a BMI > 30 kg/m². Two patients with kidney transplantation and two with prostate malignancy (44.4%) had impaired immune competence. In three further patients (30%) a compromised immune status can be assumed due to severe chronic renal insufficiency (one of these patients was on dialysis).

All hospitalized patients affected by a vaccine breakthrough were vaccinated with the mRNA vaccine BNT162b2 (Pfizer-BioNTech). The median interval between the first and second vaccination was 21 days (range 21–29 days). The median interval between complete immunization [8] and the onset of the first COVID-19 symptoms was 99 days (range 38–211).

The first symptoms occurred at a median of four days (range 1–11 days) before admission to hospital; none of the aforementioned cases had been to a physician prior to hospital admission in view of their symptoms. The leading symptoms at the time of hospital admission were dyspnoea (77.8%), fever (66.7%) and cough (44.4%).

The Ct values of the PCR on nasopharyngeal swabs were ≤ 20 in seven of nine patients on admission to hospital.

Table 1 Hospitalized patients with COVID-19-infection und vaccination breakthrough (CW 28–36)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Sex	Male	Male	Male	Male	Male	Female	Female	Male	Male
Age (yr)	75	80	44	62	62	84	90	85	72
Coexisting conditions									
- Heart failure	+	+	+	+	+	-	+	-	+
- Arrhythmia	+	+	-	+	+	-	+	+	+
- Hypertension	+	+	+	-	-	+	+	-	+
- Diabetes mellitus	+	-	-	+	+	-	+	-	-
- Renal insufficiency (chronic)	+	+	-	-	-	-	+	-	+
- Sleep apnoea	+	-	-	-	-	-	+	-	+
- Anaemia	-	+	-	+	+	-	+	+	-
- Malignancy (Prostate)	-	-	-	-	+	-	-	-	+
- Transplantation (Kidney)	-	-	+	+	-	-	-	-	-
- Stroke	+	-	-	-	-	-	-	-	-
- M. Parkinson	-	-	-	-	-	+	-	-	-
- Impaired immune status (drugs)	-	-	+	+	-	-	-	-	-
- Hyperlipidaemia	-	-	-	-	-	-	-	-	-
- Dementia	-	+	-	-	-	+	+	-	-
- Nicotine abuse	-	-	-	-	-	-	-	-	-
- Arterial occlusive disease	+	-	-	-	-	-	-	+	-
- BMI > 30 kg/m ²	-	-	-	-	-	-	+	-	+
Vaccine	BNT162b2 (Pfizer-BioNTech)	BNT 162b2 (Pfizer-BioNTech)	BNT162b2 (Pfizer-BioNTech)	BNT162b2 (Pfizer-BioNTech)	BNT162b2 (Pfizer-BioNTech)	BNT162b2 (Pfizer-BioNTech)	BNT162b2 (Pfizer-BioNTech)	BNT162b2 (Pfizer-BioNTech)	BNT162b2 (Pfizer-BioNTech)
Time from first to second vaccine dose [d]	21	21	22	29	21	21	24	22	21
Time from second vaccination to infection [d]	60	99	70	104	38	211	134	131	63

Table 1 (continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Use of medical masks before vaccination breakthrough	-	+	-	+	+	-	-	-	-
Immunization of close contacts before vaccination breakthrough	+	+	-	-	-	+	+	-	+
Travel history before vaccination breakthrough	Wife, Daughter-in-law	Wife	Wife, daughter	Single	Wife, daughter	Husband	Daughter	Daughter	Wife
Onset of COVID-19-specific symptoms and consultation of a physician [d]	1	1	11	9	7	1	1	5	4
Symptoms of COVID-19-infection and vaccination breakthrough	Fever, dyspnoea	Cough, dyspnoea	Fever, cough, dyspnoea	Fever, cough, dyspnoea	Dyspnoea	Fever, cough	Fever, dyspnoea	Dyspnoea	Fever, dyspnoea, diarrhoea
Reason for PCR testing	+	+	+	+	+	+	+	+	+
-Clinical suspicion									
Intensive care (day of hospitalization)	+(3) +/7	+(2) -	+(4) -	- -	+(11) +/2	- -	- -	- -	+(4) +/3
-Mechanical ventilation [d]	20/23	14/15	17/19	17/20	33/35	13/15	16/18	16/18	19/20
Ct values N1/N2 at the time of vaccination breakthrough	Day 2; > 250 Positive	Day 3; 250 Positive	Day 3; 0,4 Negative	Day 2; < 0,4 Negative	Day 3; > 250 Positive	Day 1; 42 Negative	Day 2; 73 Negative	Day 1; > 250 Negative	Day 1; 93 Negative
Anti-SARS-CoV-2-S [U/ml]									
Anti-SARS-CoV-2-N [COI]	B.1.617.2 (Delta)	B.1.617.2 (Delta)	B.1.617.2 (Delta)	B.1.617.2 (Delta)	Not determined	B.1.617.2 (Delta)	B.1.617.2 (Delta)	B.1.617.2 (Delta)	B.1.617.2 (Delta)
VOC									

Table 1 (continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Outcome	-	+(38)	+(19)	+(22)	+(30)	+(5)	+(12)	+(8)	-
-Discharge [d]	+(13)	-	-	-	-	-	-	-	+(7)
-Exitus letalis [d]	-	-	-	-	-	-	-	-	-

CW calendar week, yr year, + yes, - no, BMI Body Mass Index, d day, Ct Cycle threshold, S spike, N nucleocapsid, COI cutoff index, VOC Variants of Concern

In all patients, the anti-SARS-CoV-2-S and anti-SARS-CoV-2-N titers against the viral spike protein and the viral nucleocapsid protein, respectively, were determined in the first 72 h of hospitalization. In six cases (66.6%), the anti-SARS-CoV-2-N titer was negative, results suggest no signs of former infection or effect on vaccination; in five cases, the anti-SARS-CoV-2-S titer was below 100 U/ml. The absence of titers of both antibodies was observed in two patients under drug immunosuppression after kidney transplantation (nos. 3,4) as well as one patient with metastasised malignant primary disease (no. 9); the two other patients with negative antibody titers (nos. 6,7) had no obvious indication of a restriction of their immunocompetence. In contrast, three patients had positive anti-SARS-CoV-2-N and anti-SARS-CoV-2-S titers ≥ 250 U/ml. Interestingly, this was also true for the only patient requiring chronic dialysis (no. 2) and one patient with non-metastatic prostate carcinoma (no. 5).

Variant detection using sequencing was technically feasible in eight cases and consistently showed the Delta variant (B.1.617.2).

Intensive care was required for five of the nine patients (all male). All had severe heart failure as predisposing factors; this was combined with chronic renal failure (nos. 1, 2, 9), condition after organ transplantation (no. 3) or malignancy (nos. 5, 9). Two of these patients (nos. 1, 9) required invasive ventilation due to COVID-19-related hypoxia; both died as a consequence of cardiorespiratory failure despite previous vaccination.

The median duration of inpatient treatment until discharge or death was 19 days (range 5–38 days).

The extended medical history showed that after vaccination, the majority of patients (66.7%) refrained from using medical masks for contacts outside their own household. Three patients (33.3%) had admitted to have travelled to a high-risk area according to RKI [9] within the last three weeks. Four (44.4%) reported that one or more immediate contacts in their domestic environment had not been vaccinated at all.

Discussion

As of September 8, 2021, 61.6% of the adult population had been fully vaccinated according to the RKI [8]. The protective effect of complete vaccination against death from COVID-19 disease was stated by the RKI at this time to be 100% for adults < 60 years of age and 91% for adults ≥ 60 years of age; the protective effect against hospitalization due to COVID-19 was estimated to be 96% and 94%, respectively, for the two age groups [8].

During the stated observation period (CW 28–36), nine of 67 COVID-19 cases (13.4%) requiring hospitalization had a vaccine breakthrough. Based on a vaccination rate of 61.6%

in the adult population at this time [8], the proportion of vaccine breakthroughs among hospitalized COVID-19 cases was higher than expected in our cohort, given the vaccine effectiveness against hospitalization estimated by the RKI at this time [8]. However, it is largely consistent with calculations from later German reporting data in CW 33–38 [10]. It therefore makes sense to consider the individual risks of patients for a vaccination breakthrough as well as for the severity of the course of the disease.

At that point of time in our collective, as in Farinholt et al. [11], severe vaccine breakthroughs were caused by the Delta variant. This finding may be consistent with a lower vaccination effectiveness against the Delta variant of SARS-CoV-2, which is particularly pronounced in the group of older patients, as American surveillance data show [12]. In the COVID-19 cases registered by the RKI, the dominance of the Delta variant is also reflected in an increasing proportion of vaccine breakthroughs in the 37–40th calendar week [13]. Whether the predominance of Delta per se or the decreasing effectiveness of the vaccination over time were responsible for the increasing number of breakthrough infections observed at that time cannot be derived from our limited database.

Both in an Israeli study by Bross-Nissimov et al. [14] and in the group of patients with a severe course of COVID-19 analyzed by us, all those affected had received vaccination with Pfizer-BNT162b2 (Comirnaty[®]), as had the patient collective from Qatar described by Butt et al. [15, 16]. Of the 80,181 vaccine breakthroughs registered with the RKI by October 14, 2021, 66.16% were observed after vaccination with Comirnaty[®] [13]. These findings may not only be due to the high proportion of vaccinations with BNT162b2 per se, the comparative data of Andrews et al. [17] suggest.

The mortality rate of hospitalized patients with vaccine breakthrough was the same in our own as well as the Israeli patient group at 22% [14]. The rate was also similar to a group of 2741 unvaccinated hospitalized US patients as early as 2020, in which PCR-confirmed COVID-19 disease led to death or hospice discharge in 24.3% of cases [18]. A comparison with the data from Qatar is not possible due to a purely PCR-based definition of vaccine breakthrough [15, 16].

As in our own collective, the Israeli work predominantly involved male patients with a median age > 70 years [14]. Hypertension, diabetes mellitus and heart failure were the three leading predisposing factors for hospitalization for COVID-19 after vaccine breakthrough in both collectives; the proportion of immunocompromised patients was also largely concordant at 40% and 44%, respectively. A BMI > 30 kg/m² was less relevant, with rates of 30% and 22.2%, respectively, contrary to the literature [19]. The time between complete immunisation and the first symptoms of vaccine breakthrough was significantly longer in

our own collective, with a median of 99 days than in the Israeli study (39.5 days) [14]. However, in both cases the period of six months after complete vaccination recommended for booster vaccination by the German Standing Committee on Vaccination (STIKO) at the RKI had not yet been reached [20].

The need for intensive therapy also corresponds in both collectives with 53% and 55.5% respectively. This means that the proportion of patients requiring intensive care is even significantly higher than in the study by Petrilli et al. [18], who observed a critical illness in 36.1% of hospitalized COVID-19 patients without prior vaccination. Very similar to what was described in the case series by Kim et al. [21] and Wolff et al. [22], one explanation for this may lie in the high number of comorbidities and the time latency until medical treatment of COVID-19 sufferers with vaccination breakthrough.

Brosh-Nissimov et al. [14] analyzed the (Ig)-G anti-spike (S) titer (Diasorin/ Abbott) for 69 of the 152 hospitalized patients with vaccine breakthrough. Patients with a severe course (intensive therapy or death) tended to show a lower titer, but without statistical significance. In our own collective, the anti-SARS-CoV-2-S titer (Cobas e601, Roche) was also low at the beginning of treatment due to COVID-19 in five of nine patients. In four of these five patients, immunodeficiency could be assumed based on the medical history of the individual. Due to vaccination failure Malin et al. [23] reported on patients with humoral immunodeficiency (e.g. B-cell related malignancies) and the inability to mount sufficient amounts of SARS-CoV-2 neutralizing antibodies. Passive immunization with SARS-CoV-2 neutralizing monoclonal antibodies may be a rational treatment approach for these patients. According to the STIKO [10], a booster vaccination has been recommended after a period of six months. However, in eight out of nine cases—similar to the Israeli patient collective [14] and the case series by Kim et al. [21]—the vaccination breakthrough already occurred before six months had elapsed. In line with this, Longlune et al. [24] advocate a significantly earlier booster vaccination after two vaccinations with Pfizer-BioNTech.

Our observations regarding the behaviour of patients before vaccination breakthrough reflect that a misconceived sense of security may have contributed to an increased risk of infection after complete vaccination. Limited use of personal protective equipment, especially refraining from wearing medical mouth-nose protection in public spaces, the lack of immunization of close contacts as well as travelling to high-risk areas indicate that the patients no longer assumed a relevant COVID-19 risk after vaccination despite their severely impaired health status. This is further emphasized by the fact that patients did not seek medical treatment until several days after the onset of COVID-19-specific symptoms.

This study is limited by the small number of patients at a single hospital, the retrospective analysis and the lack of a comparison group. However, the detailed analysis of the medical history and disease progression of patients with vaccine breakthrough allows conclusions to be drawn about the need for supplementary protective measures particularly for vulnerable collectives. The evaluation of behaviour prior to vaccination breakthrough shows that multimorbid and immunosuppressed patients, especially those aged > 70 years, should be sensitised to the continuing value of personal protective measures already at the time of vaccination.

Conclusion

In accordance the current literature we could identify important risk circumstances (e.g. advanced age, underlying cardiorespiratory disease, and the Delta variant of SARS-CoV-2) in our hospitalized patients, suffering from vaccine breakthrough infection. Additionally, avoidance of face masks, lack of immunization of close contacts, and travel to high-risk areas were observed as modifiable risk factors for COVID-19-infection despite vaccination. Thus, we may speculate, that consistent personal protective measures, vaccination of close caregivers, and increased awareness continue to appear reasonable for patients at a high risk for a severe course of COVID-19-infection.

Our data underline the recommendation of the RKI for booster vaccination against COVID-19 in view of the increasing number of severe vaccine breakthrough infections. Despite vaccination, it may be recommendable to encourage vulnerable individuals to take additional precautionary measures including behavioural adjustments to reduce the risk of contracting the virus and perhaps suffering a severe breakthrough infection.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The authors confirm that the study was approved by the Research Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Germany (No. 2021-850), and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Waize M, Scholz S, Wichmann O, et al. Die Impfung gegen COVID-19 in Deutschland zeigt eine hohe Wirksamkeit gegen SARS-CoV-2-Infektionen, Krankheitslast und Sterbefälle (Analyse der Impfeffekte im Zeitraum Januar bis Juli 2021). *Epid Bull.* 2021;35:3–10. <https://doi.org/10.25646/8887>.
2. Harder T, Koch J, Vygen-Bonnet S, et al. Wie gut schützt die COVID-19-Impfung vor SARS-CoV-2-Infektionen und SARS-CoV-2-Transmissionen? Systematischer Review und Evidenzsynthese. *Epid Bull.* 2021;19:13–23. <https://doi.org/10.25646/8442.2>.
3. Wichmann O, Scholz S, Waize M. Welche Impfquote ist notwendig, um COVID-19 zu kontrollieren? *Epid Bull.* 2021;27:3–13. <https://doi.org/10.25646/8742>.
4. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med.* 2020;383:2603–15. <https://doi.org/10.1056/NEJMoa2034577>.
5. Hacısuleyman E, Hale C, Saito Y, et al. Vaccine breakthrough infections with SARS-CoV-2 variants. *N Engl J Med.* 2021;384:212–8. <https://doi.org/10.1056/NEJMoa2105000>.
6. der Justiz B, für Verbraucherschutz. Bundesministerium für Gesundheit. Verordnung über die Erweiterung der Meldepflicht nach § 6 Absatz 1 Satz 1 Nummer 1 des Infektionsschutzgesetzes auf Hospitalisierungen in Bezug auf die Coronavirus-Krankheit-2019, vom 11. Juli, BAnz AT;12.07.2021 V1. Anlage. 2021;1:1–3.
7. <https://impfdashboard.de>. Zugegriffen: 30. Oktober 2021
8. https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Wochenbericht/Wochenbericht_2021-09-09.pdf. Zugegriffen am 01.11.2021
9. Bundesministerium der Justiz und für Verbraucherschutz. Bundesministerium für Gesundheit. Verordnung zum Schutz vor einreisebedingten Infektionsgefahren in Bezug auf das Coronavirus SARS-CoV-2 (Coronavirus-Einreiseverordnung-CoronaEinreiseV), vom 30. Juli 2021. BAnz AT;30.07.2021 V1:1–10
10. Koch J, Vygen-Bonnet S, Harder T, et al. STIKO-Empfehlung zur COVID-19-Auffrischimpfung mit einem mRNA-Impfstoff für Personen ≥ 70 Jahre und bestimmte Indikationsgruppen sowie Empfehlung zur Optimierung der Grundimmunisierung mit einem mRNA-Impfstoff nach vorausgegangener Impfung mit der COVID-19-Vaccine Janssen und die dazugehörige wissenschaftliche Begründung. *Epi Bull.* 2021;43:16–53. <https://doi.org/10.25646/9150>.
11. Farinholt T, Doddapaneni H, Qin X, et al. Transmission event of SARS-CoV-2 Delta variant reveals multiple vaccine breakthrough infections. *medRxiv.* 2021. <https://doi.org/10.1101/2021.06.28.21258780> (Update in: **BMC Med.**19(1):255. PMID: 34268529; PMCID: PMC8282118).
12. Scobie HM, Johnson AG, Suthar AB, et al. Monitoring incidence of COVID-19 cases, hospitalizations, and deaths, by vaccination status-13 U.S. Jurisdictions, April 4-July 17, 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:1284–90. <https://doi.org/10.15585/mmwr.mm7037e1>.
13. https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Wochenbericht/Wochenbericht_2021-10-14.pdf. Zugegriffen am 01.11.2021
14. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. *Clin Microbiol Infect.* 2021. <https://doi.org/10.1016/j.cmi.2021.06.036> (S1198-742X(21)00367-0).
15. Butt AA, Yan P, Shaikh OS, Mayr FB. Outcomes among patients with breakthrough SARS-CoV-2 infection after vaccination in a high-risk national population. *EclinicalMedicine.* 2021;40:

101117. <https://doi.org/10.1016/j.eclinm> (2021.101117.eCollection 2021 Oct).
16. Butt AA, Nafady-Hegao H, Chemaitelly H, et al. Outcomes among patients with breakthrough SARS-CoV-2 infection after vaccination. *Int J Infect Dis.* 2021;110:353–8. <https://doi.org/10.1016/j.ijid.2021.08.008>.
 17. Andrews N, Tessier, E, Stowe J et al (2021) Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. Preprint <http://daebi.de/MM57>
 18. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York: prospective cohort study. *BMJ.* 2020;369:m1966. <https://doi.org/10.1136/bmj.m1966>.
 19. Chetboun M, Raverdy V, Simonnet A, et al. BMI and pneumonia outcomes in critically ill COVID-19 patients: an international multicenter study. *Obesity.* 2021;29:1477–86. <https://doi.org/10.1002/oby.23223>.
 20. https://www.rki.de/DE/Content/Kommissionen/STIKO/Empfehlungen/PM_2021-10-07.html. Zugegriffen am 01.11.2021
 21. Kim PS, Schildhouse RJ, Saint S, et al. Vaccine breakthrough infections in veterans hospitalized with Coronavirus Infectious Disease-2019: a case series. *Am J Infect Control.* 2021. <https://doi.org/10.1016/j.ajic.2021.10.003> (S0196-6553(21)00646-5).
 22. Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for COVID-19 severity and fatality: a structured literature review. *Infection.* 2021;49:15–28. <https://doi.org/10.1007/s15010-020-01509>.
 23. Malin JJ, Di Christanziano V, Horn C, et al. SARS-CoV-2 neutralizing antibody treatment in COVID-19 patients with immunodeficiency due to B-cell non-Hodgkin lymphoma. *Blood Adv.* 2021. <https://doi.org/10.1182/bloodadvances.2021006655>.
 24. Longlune N, Nogier MB, Miedouge M, et al. High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. *Nephrol Dial Transplant.* 2021;36:1704–9. <https://doi.org/10.1093/ndt/gfab193>.