Vaccination Setting of Patients with Autoimmune Diseases in Times of Severe Acute Respiratory Syndrome Coronavirus Type 2 Pandemic Using the Example of Multiple Sclerosis Patients: A Longitudinal Multicenter Study

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Keywords

Multiple sclerosis · Severe acute respiratory syndrome coronavirus type 2 · Vaccination · COVID-19 · Vaccination willingness

Abstract

Background: Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection represents a serious health risk, especially in chronically ill people. Multiple sclerosis (MS) is the most common chronic immune-mediated neurological disease. Vaccinations play an important role in the therapeutic MS management. This study aimed at determining MS patients' attitudes toward vaccinations and governmental measures before and during the SARS-CoV-2 pandemic, including associations with sociodemographic and clinical variables. **Methods:** In a longitudinal, multicenter study, 200 MS patients were investigated regarding their vaccination attitudes before and after the first wave of the SARS-CoV-2 pandemic. Data on vaccination status and burden (physical, psychological, and social) experienced as caused by the pandemic and related governmental safety

measures were registered. **Results:** Patients with progressive MS felt significantly more pandemic-burdened than patients with relapsing-onset MS ($p < 0.001$). Older patients were more frequently willing to get vaccinated against SARS-CoV-2 than younger patients ($p < 0.001$). After the first pandemic wave, patients with pre-pandemic willingness to comply with vaccination recommendations were more likely to accept recommended standard vaccinations (60% vs. 36%) and a possible SARS-CoV-2 vaccination than pre-pandemic nonwilling patients (66.7% vs. 42.0%). **Conclusions:** The vaccination topic was not immediately present in many patients before the pandemic. MS patients need comprehensive and understandable education meeting their concerns using evidence-based and convincing arguments on the subject of vaccination, particularly younger patients. Older patients are already more often willing to become vaccinated. Complete vaccination status is necessary to avoid multiple infections.

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Introduction

About 3–5% of the population is affected by about 100 autoimmune diseases (AIs) worldwide [1]. Multiple sclerosis (MS) represents the most common AI of the central nervous system with demyelinating and inflammatory central nervous system processes [2–4]. The diverse symptomatology reveals, for instance, sensory and visual disturbances, paresis, and neuropsychological deficits [5].

Since the approval of the first disease-modifying drug (DMD) in 1993 [6], numerous other immunomodulatory and symptomatic drugs for the treatment of MS have been added to the therapeutic spectrum [7]. The risk of infections while treated with a DMD is a major issue in MS management [8–10]. Therefore, the vaccination status of MS patients before the start of an immunomodulatory therapy is a factor of high priority. Although an association between vaccination and onset of MS [11] was previously assumed, the current state of research suggests none [12–15].

Flu jab rates among German chronically ill patients varied from 19 (MS) to 44% (chronic kidney disease) in 2017/2018. Women showed higher vaccination rates than men, with the lowest rates among 20- to 29-year olds [16]. This is far from the target flu jab coverage of 75% of EU residents. Particularly older and more disabled patients with MS appeared to be at increased risk for severe acute respiratory syndrome coronavirus type 2 (SARS CoV-2) infection with more complicated disease courses [17–25].

This study aimed to answer the following questions: (a) Was vaccination a matter of concern among German MS patients prior to the SARS CoV-2 pandemic? (b) What attitudes do MS patients express toward governmental measures against this pandemic, toward vaccination in general, and toward an upcoming anti-SARS CoV-2 vaccination? (c) What sociodemographic and clinical variables are associated with attitudes toward anti-SARS CoV-2 vaccination?

Methods

Study Population and Design

This longitudinal, prospective, and multicenter study was conducted at the Department of Neurology (section of Neuroimmunology) of the University Medical Centre of Rostock (Germany) and the Department of Neurology of the Ecumenical Hainich Hospital, Mühlhausen (Germany). Two hundred patients aged ≥ 18 years and diagnosed with clinically isolated syndrome (CIS) or MS according to the revised McDonald criteria [4] were included after voluntarily consenting to participate in this study. In

June/July 2020, these 200 patients were surveyed on the perceived impact of SARS CoV-2 safety measures in Germany (e.g., mandatory wearing of masks in public, distance regulation in shops, limitation of purchasing, and service options) and on changes in personal attitudes toward standard vaccinations since the onset of the SARS CoV-2 pandemic. The same 200 patients were already examined as part of an ongoing cross-sectional multicenter study of CIS/MS patients on both polypharmacy and vaccination status as well as vaccination attitude in Rostock and Mühlhausen from June 2019 (online suppl. Document 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519582). In the original study starting in June 2019, patients were initially recruited during regular visits to institutional MS clinics and wards. All patients voluntarily signed an informed consent form prior to enrollment in the study.

Data Acquisition

MS-related clinical (e.g., MS course type, Expanded Disability Status Scale [EDSS] score [26], and disease duration), sociodemographic (e.g., age, sex, education, and occupation), and basic vaccination-related data were collected in 2019 (baseline) by anamnesis, patient records, and structured patient interviews. The MS patients were called before and asked to provide their vaccination card (the current one and the child vaccination card if available) during their clinical appointment or inpatient treatment for a check of vaccination completeness, based on the current recommendations by the Standing Committee in Vaccination (STIKO) of the Robert-Koch-Institute, the German National Institute for Investigation and Prevention of Infectious Diseases, that is, furthermore responsible for health monitoring [27]. This procedure aimed to evaluate the current vaccination status as accurate as possible and to identify how many of the 200 patients do not have a vaccination card at all. Furthermore, participants were asked about their beliefs about their own vaccination status (before the vaccination card check), and about their attitudes toward vaccination in general.

A short questionnaire was created to assess the impact of SARS CoV-2 pandemic (in terms of fears, burden, or change in attitudes toward vaccination) after the first wave of SARS CoV-2 pandemic in June and July 2020 (online suppl. Document 1). The Trauma Screening Questionnaire (TSQ) [28] was adapted to assess the burden of the SARS CoV-2 pandemic and the associated information and limiting societal measures. The formulation of each item has clearly been focused on the SARS CoV-2 pandemic and the original alternative response model was changed to a 5-point scale with 0 = not at all to 4 = very much. The TSQ consists of 10 symptom items (5 arousal and 5 re-experiencing items) to assess post-traumatic stress disorder symptoms. It is recommended for screening survivors of traumatic stress. A sum-score was calculated as an indicator of the burden associated with the measures initiated to limit the rate of infection within the country and living with the risk of becoming infected and suffering from a severe SARS CoV-2 comorbidity in addition to existing MS. The questionnaires used for data collection in the 2 survey periods (2019 and 2020) were added to the supplement (online suppl. Document 1).

Statistics

Interval scaled descriptive data were presented by means and standard deviations. Ordinal or nominal data were expressed as

Table 1. Sociodemographic and clinical variables by sex (mean $\pm$ SD)

	Total	Females	Males
N	200	131	69
Age, years	48.2 $\pm$ 12.7	46.4 $\pm$ 14.5	48.7 $\pm$ 12.4
Disease duration, years	11.7 $\pm$ 8.6	12.2 $\pm$ 8.3	11.0 $\pm$ 9.1
EDSS score	3.5 $\pm$ 2.3	3.5 $\pm$ 2.4	3.5 $\pm$ 2.2
Education, years	10.4 $\pm$ 1.1	10.5 $\pm$ 1.1	10.4 $\pm$ 1.3
Intensity physical burden	1.6 $\pm$ 1.2	1.7 $\pm$ 1.2	1.4 $\pm$ 1.2
Intensity psychological burden	1.6 $\pm$ 1.2	1.7 $\pm$ 1.2	1.5 $\pm$ 1.2
Intensity social burden	1.4 $\pm$ 1.3	1.5 $\pm$ 1.3	1.4 $\pm$ 1.3
MS course type, %			
CIS	5.5	4.6	7.2
RRMS	64.0	66.4	59.4
SPMS	23.0	24.4	20.3
PPMS	7.5	4.6	13.0
Number of comorbid diseases	1.9 $\pm$ 1.7	2.0 $\pm$ 1.8	1.6 $\pm$ 1.6
DMD use			
Yes	60.2%	56.5%	66.7%
Trauma score	17.8 $\pm$ 6.4	17.7 $\pm$ 6.5	17.8 $\pm$ 6.2

CIS, clinically isolated syndrome; DMD, disease-modifying drug; EDSS, expanded disability status scale; N, number of patients; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

percentages within categories. Associations between interval data and ordinal (e.g., intensity of burden) or nominal data were calculated by 1-way analysis of variance (ANOVA) with related post hoc tests depending on equality of variances (equal variances: Tuckey' b; unequal variances: Games-Howell). Relationships between ordinal or nominal data were defined by χ^2 tests or contingency coefficients, respectively. The cutoff indicating significant results was set to $p = 0.050$. All calculations were performed by SPSS, version 25.

Results

Demographic and Clinical Characteristics

Substantial sociodemographic information of the included MS patients, clinical variables, and vaccination attitude data are presented in Tables 1 and 2. The mean age of patients was 47.2 ± 13.8 years, time since first MS diagnosis was 11.7 ± 8.6 years and mean EDSS score was 3.5 ± 2.3 . For MS course type, a total of 5.5% resulted as CIS, 64.0% as relapsing-remitting MS (RRMS), 23.0% as secondary progressive MS (SPMS), and 7.5% as primary progressive MS (PPMS). Vaccination cards were available for 90% of patients analyzed.

The MS course type was substantially related to the age of the patients (1-way ANOVA $F(3/195) = 9.26$; $p < 0.001$), with patients with SPMS or PPMS being older

than patients with CIS or RRMS, as indicated by post hoc tests. Furthermore, the MS course type was significantly associated with disease duration (1-way ANOVA $F(3/195) = 7.72$; $p < 0.001$).

Indicators for Attitudes toward Vaccinations Prior to Start of the SARS CoV-2 Pandemic

Slightly less than one-third of the sample (27.5%) received vaccination advice from a physician (general practitioner or specialist) within the 12 months prior this investigation (27.5%) and 38% indicated a desire for vaccination advice. However, vaccination was not a topic of concern for most participants prior to the SARS CoV-2 pandemic: 19.5% of the patients last thought about vaccination within the last month, 40.5% within the last year, and 40.0% >1 year ago. One-third of the MS patients (32%) reported experiencing health problems of any kind after a vaccination. Three-quarters of patients expressed their willingness to comply with the governmental recommendations for vaccinations and only 2.0% showed a general refusal to get vaccinated at all. About two-thirds of participants (64.5%) had a documented complete tetanus vaccination status (defined as basic immunization in childhood and booster every 10 years), whereas only 13.5% had a documented complete flu jab status.

Table 2. Clinical, vaccination, and SARS CoV-2 related variables by sex (%)

	Total	Females	Males	$p^{\chi^2/Fi}$ value
<i>N</i>	200	131	69	
Vaccination card available (yes), %	90.0	91.6	87.0	0.327
Health problems after vaccination (yes), %	34.0	39.0	24.6	0.059
Willingness to comply with recommended vaccinations (yes), %	75.0	76.3	72.5	0.607
Tetanus vaccination (complete), %	64.5	63.4	66.7	0.756
Flu jab (complete), %	13.5	13.7	13.0	1.000
Changed attitudes due to SARS CoV-2 pandemic (yes), %	32.5	31.3	34.8	0.636
Governmental measures evaluated as somewhat or completely appropriate, %	72.0	70.3	75.4	0.509
Willingness to get vaccinated against SARS CoV-2, %				
Yes – likely or for sure	60.5	57.3	66.7	
Not known	17.0	19.8	11.6	0.286
No – unlikely or highly unlikely	22.5	22.9	21.7	
Changed attitudes toward vaccination recommendations, %				
Negative change	6.5	5.4	8.7	
Unchanged	39.5	38.9	40.6	0.412
Positive change	6.0	4.6	8.7	
Have ever been in favor	48.0	51.1	42.0	

χ , χ^2 test; Fi, Fisher's exact test; MS, multiple sclerosis; *N*, number of patients; SARS CoV-2, severe acute respiratory syndrome coronavirus type 2.

Impact of the SARS CoV-2 Pandemic and Attitudes toward Vaccinations during First Wave of Pandemic

Experienced psychological, physical, or social burden caused by the SARS CoV-2 pandemic and the governmental safety measures implemented were each reported as high or very high by 28.5% of the MS patients, respectively. Attitudes toward SARS CoV-2 safety measures changed due to the pandemic course in 32.5% of the sample. 72.0% evaluated the governmental safety measures as somewhat or completely appropriate. 60.5% of the patients reported that they would accept a vaccination against SARS CoV-2 when a recommended vaccine will be available (23.5% likely and 37.0% for sure). 6.5% of the sample indicated that the SARS CoV-2 pandemic caused their current negative attitudes toward standard vaccination, while 48.0% reported that they had always been in favor of a recommended vaccination program. Another 6.0% would accept a general recommended vaccination program now and 39.5% indicated that their attitudes did not change due to the pandemic. The more burdened the patients felt about the SARS CoV-2 pandemic and the related governmental safety measures, the substantially higher was their perceived distress in terms of trauma-related symptoms (1-way ANOVA psychologically: $F [4/195] = 25.25$; $p < 0.001$; physically: $F [4/195] = 8.70$; $p < 0.001$; socially: $F [4/195] = 11.30$; $p < 0.001$). Patients who indicated that their attitudes toward vaccination did

change due to SARS CoV-2-related problems (pandemic itself and safety measures) reported a significantly higher trauma score on the adapted TSQ ($F [1/196] = 33.90$; $p < 0.001$).

Associations between Sociodemographic and Clinical Variables and Attitudes toward the SARS CoV-2 Pandemic

MS disease course was significantly associated with trauma score indicating post-traumatic stress disorder symptom intensity (1-way ANOVA $F [3/195] = 41.90$; $p < 0.001$). The symptom intensity is related to the changed social and health conditions due to the experience of the SARS CoV-2 pandemic and the related governmental safety measures. CIS patients reported the lowest impact, followed by RRMS, whereas patients with progressive MS (SPMS and PPMS) indicated the highest symptom level based on post hoc tests results. Additionally, patients who had experienced any vaccination-related health problems in the past reported significantly higher stress symptom levels than those without any vaccination reactions (1-way ANOVA $F [2/195] = 7.66$; $p < 0.001$). Furthermore, MS disease duration was substantially related to the perceived adequacy of the federal pandemic-related safety measures (1-way ANOVA $F [4/194] = 2.66$; $p = 0.034$). Patients who experienced the measures as somewhat inappropriate had a longer MS disease duration than pa-

Fig. 1. SARS CoV-2 vaccination willingness in MS patients. The willingness to get vaccinated against SARS CoV-2 when a safe, recommended vaccine will be available is shown for patients that are willing to comply with the governmentally recommended vaccinations ($N = 150$) (**a**) and for patients that are not willing to follow the governmental recommendations ($N = 50$) (**b**). In recommendation followers, the proportion of patients that wanted to get a SARS CoV-2 vaccination “for sure” was much higher than in recommendation deniers (40.7% vs. 26.0%). In recommendation deniers, the proportion of patients that indicated a SARS CoV-2 vaccination as “highly unlikely” was >3 times as high as in recommendation followers (28.0% vs. 8.7%). SARS CoV-2, severe acute respiratory syndrome coronavirus type 2; MS, multiple sclerosis.

tients who experienced the measures as completely appropriate. Moreover, age was significantly positively associated with the willingness to get vaccinated against SARS CoV-2 (1-way ANOVA $F [4/195] = 5.82$; $p < 0.001$).

Attitudes toward the SARS CoV-2 Pandemic Comparing Patients with and without Willingness to Comply with Recommended Vaccinations

Among the MS patients analyzed, 75.0% ($N = 150$) were willing to comply with the governmentally recommended vaccinations, whereas 25.0% ($N = 50$) were unwilling to follow the recommendations. Those MS patients, who were treated by DMDs at the baseline investigation (60.2%), were more often willing to follow the recommended vaccination advice than those not on DMDs (willingness for recommended vaccinations when on DMDs: 64.0%; when not on DMDs: 36.0%; $\chi^2 [1] = 4.00$, $p = 0.046$). Treatment with any kind of DMD at baseline was not associated with any attitude variables in the follow-up investigation. Willingness to comply with the governmentally recommended vaccinations was not significantly associated with an attitude change toward the SARS CoV-2 pandemic between the two assessments ($\chi^2 [1] = 0.07$; $p = 0.794$). There was a slight tendency for patients who were willing to comply with recommended standard vaccinations prior to the pandemic to evaluate the pandemic-related safety measures as appropriate compared to unwilling patients (75.3% vs. 62.0%; $p = 0.101$). General attitudes toward standard vaccinations were unchanged in 36.7% of patients with pre-pandemic

willingness to comply with vaccination recommendations (vs. 48.0% in patients without willingness) after the first wave of the pandemic. Furthermore, 16.0% of the pre-pandemic unwilling patients developed attitudes against recommended standard vaccinations during the pandemic (vs. 3.1% among willing patients). After the first pandemic wave, 60.0% of patients with pre-pandemic willingness to comply with recommended vaccinations accepted recommended standard vaccinations versus 36.0% among unwilling patients ($\chi^2 [4] = 15.39$; $p = 0.004$). Willingness to comply with the recommended vaccinations prior to the SARS CoV-2 pandemic was significantly associated with the expressed intention to get the anti-SARS CoV-2 vaccination when a safe, recommended vaccine will be available ($\chi^2 [4] = 14.59$; $p = 0.006$), see Figure 1.

Discussion

Vaccination was not a topic of concern among MS patients in the time prior to the SARS CoV-2 pandemic. Nevertheless, three quarters of the participants indicated their willingness to comply with governmental vaccination recommendations. However, vaccination coverage rates for tetanus (STIKO recommendation: basic immunization as a child or adolescent, booster every 10 years from the age of 18 years) and flu jab (STIKO recommendation: annual vaccination from the age of 60 years) [27] were substantially lower in MS patients than in the gen-

eral population, even in 2008–2011 in Germany or worldwide in 2019 [29–31]. Since the protection by vaccinations is recommended for MS patients, our findings indicate some shortcomings in the treatment and care of these patients. Neurologists treating MS patients should probably pay more attention to the vaccination status of their patients in their routine practice.

A substantially larger proportion of the MS patients indicated agreement with the governmental safety measures (e.g., mandatory wearing of masks in public, distance regulation in stores, limitation of shopping, and service options) to get control over the SARS CoV-2 infection rate compared with individuals from the general population since June 2020 (72% vs. 25%) [32]. This might partly be explained, on the one hand, by the fact that MS patients are more often aware of their own position of higher risk for severe disease course in case of infection than individuals from the general population [22, 33]. Furthermore, acceptance of governmental safety measures as well as recommended vaccinations could be understood as a preconscious avoidance attitude as nonacceptance of the measures could lead to inter- and intrapersonal conflicts [34] with the potential of increased inner tension that could have a negative impact on the immune system. International representative surveys with 480,000 participants confirmed that during the SARS CoV-2 pandemic, there was a clear willingness to trade off civil and personal liberties, related to increased exposure to health risks [35].

Almost the half of participants stated that their attitudes toward vaccination recommendations had not changed, since the start of the SARS CoV-2 pandemic and that they had always been in favor of federal recommendations on vaccinations. This suggests that the experience of the pandemic was not at all closely associated with attitudes toward a vaccination program. However, less than two-thirds expressed their willingness to get vaccinated against SARS CoV-2, when a recommended vaccine will be available. This proportion of MS patients willing to get vaccinated against SARS CoV-2 would probably not be sufficient for the formation of herd immunity [36]. This seems to contradict the previously expressed acceptance of the government recommendations for standard vaccinations. The attitudes of MS patients toward the SARS CoV-2 pandemic appear to be somewhat complex and inconsistent.

The obviously confounded variables age and disease duration were positively associated with both acceptance of safety measures and willingness to get vaccinated against SARS CoV-2. Especially older patients were more often willing to become vaccinated. This could be due to the fact that older people are at higher risk of developing

a more severe course of SARS CoV-2 [37]. The risk becomes even higher if they suffer from comorbid conditions, such as hypertension since the older the patients were, the more comorbid illnesses they had [38–41].

The more traumatizing MS patients experienced the pandemic and related consequences due to safety measures, the more likely they were to change their attitudes toward vaccination in general. Furthermore, MS patients who previously experienced vaccination-related health problems felt more stressed by the pandemic. Behavioral and social burden might have caused additional concerns due to the threat that infection with SARS CoV-2 could negatively affect their health status. This, in turn, could have contributed to an attitude change [35, 42–53].

There is a tendency for those who accept the federal vaccination program to also experience the pandemic safety measures as appropriate. These patients very rarely developed an anti-attitude toward governmental vaccination recommendations due to SARS CoV-2 pandemic. Patients who were not willing to follow recommended vaccinations prior to the pandemic tended to develop a negative attitude regarding the safety measures (3.1% vs. 16%). Studies showed that awareness of the lower responsibility among people who do not get vaccinated increases the general vaccination willingness and may be due to concern for social well-being [54].

Documentation bias during the structured interview in 2019 among centers might have occurred due to the multicentric study design. This SARS CoV-2 pandemic-focused analysis was planned and conducted at the end of the first infection wave in Germany. Since vaccination in MS patients has been a scientifically controversial topic in recent years and because of the threat of SARS CoV-2, the authors developed a brief survey with items that covers psychological burden, including emotional disturbances and social distress; perceived attitude changes due to the pandemic and related safety measures. This gave the researchers the opportunity to obtain follow-up data. However, the psychometric properties of the items could not be comprehensively investigated before start of the data collection. The validity of the data might be limited since the majority of the data are self-reports by patients. However, the availability of substantial disease-related information as well as of information on attitudes toward vaccination in general, from a less stressful period of a comparably large sample, although convenient in nature, is strength of our study. To our knowledge, it represents the first follow-up study (pre-pandemic and pandemic) of attitudes toward vaccination related to the SARS CoV-2 pandemic among MS patients.

Conclusions

Although the majority of MS patients agreed to follow standard vaccination recommendations before the pandemic, the topic of vaccination was not of high importance for many of them at baseline. A reminder of vaccinations to be refreshed and recommended will be sufficient for some patients. However, others will need comprehensive and understandable information using evidence-based and convincing arguments about vaccinations. To address the patient's individual reservations seems to be important. This represents a time-consuming procedure, but will probably help to reduce infection rates and save lives. Effort should focus more on young rather than on old MS patients, since the older are already more often willing to become vaccinated. More advanced interventions are necessary to improve vaccination consumption among chronically ill individuals. Patients with progressive MS experienced more physical, social, and psychological distress than CIS or RRMS patients after the first pandemic wave. In addition, long disease duration was associated with increased refusal of federal safety measures to manage the pandemic. Willingness to get vaccinated against SARS CoV-2 was higher among patients with pre-pandemic willingness to comply with recommended standard vaccinations than among patients with pre-pandemic unwillingness. Moreover, in times when vaccination against SARS CoV-2 is not sufficiently available everywhere, flu jab as well as pneumococcal vaccination is important to protect against double infections. Studies on effects of anti-SARS CoV-2 vaccines on the different types of MS and on interactions of the vaccines with MS and the various immunotherapies need to be expanded.

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Statement of Ethics

The study was approved by the Ethics Committees of the University of Rostock (permit number A 2019-0048) and of the Physicians' Chamber of Thuringia and conducted according to the Declaration of Helsinki. All patients voluntarily signed an informed consent form prior to inclusion in the study.

Conflict of Interest Statement

The authors declare no conflicts of interest associated with this study.

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Author Contributions

F.H. substantially contributed to the conception, study design, and data interpretation. She drafted the introduction and discussion sections and critically revised the completed final draft for important intellectual content. U.K.Z. and N.F. substantially contributed to the conception, study design, and data interpretation. They critically revised the completed final draft for important intellectual content. J.B., B.S., P.M., and S.E.L. substantially contributed to the conception of the study. They critically revised the completed final draft for important intellectual content. J.R. substantially contributed to the conception, study design, and data interpretation. He conducted the data analysis. He drafted the methods and results sections and substantially contributed drafting the introduction and discussion sections and critically revised the completed final draft for important intellectual content.

Data Availability Statement

The datasets generated and analyzed in the current study are available from the corresponding author on reasonable request.

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