Aus der Klinik und Poliklinik für Neurologie der Universität Rostock

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Leiter: Prof. Dr. med. Uwe Klaus Zettl

Impfbereitschaft und Impfstatus bei Patienten mit Multipler Sklerose vor und während der SARS-CoV-2-Pandemie in Assoziation mit klinischen, soziodemografischen und psychologischen Faktoren

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Dekan Prof. Dr. med. Bernd J. Krause

1. **Gutachter: Prof. Dr. med. Uwe Klaus Zettl, Universität Rostock**
2. **Gutachter: Prof. Dr. Peter Kropp, Universität Rostock**
3. **Gutachter: PD. Dr. med. Florian Rakers, Universität Jena**

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1 Einleitung

Im Rahmen dieser Dissertation wurde die Impfbereitschaft von *People with Multiple Sclerosis* (PwMS) hinsichtlich Standardimpfungen sowie der spezifischen Impfung gegen das *Severe Acute Respiratory Syndrome Coronavirus type 2* (SARS-CoV-2) untersucht. Dabei wurden soziodemografische und klinische Daten sowie Persönlichkeitsmerkmale berücksichtigt, um ein umfassendes Bild der Faktoren zu erhalten, die das Impfverhalten in dieser Patientengruppe beeinflussen können.

Kapitel 1.1 gibt eine Einführung in die Multiple Sklerose (MS). Kapitel 1.2 thematisiert Impfungen im MS-Kontext. Kapitel 1.3 behandelt die SARS-CoV-2-Pandemie und entsprechende Impfungen bei PwMS, gefolgt von Kapitel 1.4 zur Impfbereitschaft.

1.1 Multiple Sklerose (MS)

MS ist die häufigste chronisch immunvermittelte Erkrankung des zentralen Nervensystems (ZNS), die bei jungen Erwachsenen zu bleibenden Funktionseinschränkungen führen kann [1,2]. Weltweit sind über 2,9 Millionen Menschen an MS erkrankt [1]. Eine Zunahme der Prävalenz ist in Entwicklungsländern sowie bei Kindern zu verzeichnen [1,3]. Frauen sind bis zu dreimal so häufig von MS betroffen wie Männer [1,2]. Die Ätiologie der MS ist nicht vollständig geklärt. Neben individuellen genetischen Faktoren spielen Lebensstil und Umweltfaktoren für das Erkrankungsrisiko eine Rolle. Dazu gehören beispielsweise ein Mangel an Vitamin D, Rauchen sowie Fettleibigkeit im Jugendalter [4–6]. Infektionserreger, insbesondere das Epstein-Barr-Virus (EBV), werden als ein wesentlicher Aspekt im multifaktoriellen Szenario betrachtet [7–9].

Die charakteristischen pathologischen Kennzeichen der MS sind periventrikuläre entzündliche Läsionen, die zu Demyelinisierung, Axonschäden und Synapsenverlust mit konsekutiver Astrogliose führen [10]. Jedoch können auch Läsionen kortikal, juxtakortikal, infratentoriell, am Sehnerv und/oder spinal auftreten [11–13]. Neben fokalen Läsionen rückt zunehmend eine chronische niedriggradige Entzündung (*chronic low-grade*

inflammation) bei MS in den Fokus der Forschung und wird verstärkt als Ziel therapeutischer Ansätze diskutiert [14–16].

Die klinische Manifestation der MS ist heterogen und variiert je nach Lokalisation der ZNS-Läsionen. Symptome umfassen u. a. motorische, sensorische, visuelle sowie kognitive Störungen, Fatigue, Schmerzen und vegetative Dysfunktion [17,18]. Die Eckpfeiler der MS-Diagnose sind der Nachweis der räumlichen und zeitlichen Dissemination von ZNS-Läsionen unter Ausschluss von Differentialdiagnosen [19].

Die MS wird in verschiedene Verlaufsformen unterteilt [20]. Mit 85-90% ist die *Relapsing-Remitting* MS (RRMS, schubförmig remittierende MS) initial die häufigste Form [11], sie ist charakterisiert durch akute Krankheitsschübe mit meist fokalen neurologischen Defiziten, gefolgt von einer vollständigen oder teilweisen Remission. In einigen Fällen geht der RRMS ein *Clinically Isolated Syndrome* (CIS, klinisch isoliertes Syndrom) voraus, das als erste Episode neurologischer Symptome gilt und in vielen Fällen in den Folgejahren zur MS-Diagnose führt [20]. Im weiteren Verlauf der Erkrankung entwickeln etwa 50% der RRMS-Patienten innerhalb von 20 Jahren eine *Secondary Progressive MS* (SPMS, sekundär progrediente MS) die durch eine fortschreitende irreversible Progression der neurologischen Behinderung, teils mit aufgesetzten Schüben, gekennzeichnet ist [21]. Die *Primary Progressive* MS (PPMS, primär progrediente MS) ist durch einen kontinuierlich fortschreitenden Krankheitsverlauf charakterisiert, bei dem keine Schübe auftreten. Etwa 10-15% der PwMS leiden an PPMS [11].

Die derzeitigen Behandlungsmethoden zielen darauf ab, die entzündliche Krankheitsaktivität zu reduzieren, Coping-Strategien zu fördern sowie akute Schübe zu behandeln und Symptome zu lindern. Für die sekundärprophylaktische Behandlung sind verschiedene krankheitsmodifizierende Medikamente (*Disease-Modifying Drugs*, DMDs) zugelassen [2,22–24]. Darüber hinaus werden verschiedene symptomatische Therapien eingesetzt, um die einzelnen Symptome zu lindern [17,25].

Das Infektionsrisiko ist bei Menschen mit PwMS etwa 50 % höher als in der Allgemeinbevölkerung [26,27]. Die Einnahme von DMDs führt zu einer Modulation der Immunantwort, die mit einem Anstieg des Infektionsrisikos verbunden sein kann [28,29]. Eine Studie aus den USA zeigte, dass die Inzidenzrate für tödliche Infektionen bei PwMS um 0,7% höher liegt als bei Personen ohne MS [30]. Zudem stellen Infektionserkrankungen die häufigste Todesursache bei PwMS dar [31]. Weiterhin gibt es Hinweise darauf, dass Infektionen bei MS einen Schub auslösen können [32,33].

1.2 MS und Impfungen

Die Immunisierung dient dem Schutz vor Infektionskrankheiten und erfolgt aktiv durch Stimulation der körpereigenen Bildung spezifischer Antikörper durch B-Zellen und Aktivierung von T-Zellen mit langfristigem Schutz oder passiv durch Verabreichung fertiger Antikörper mit kurzfristiger Wirkung. Die Ständige Impfkommission (STIKO) unterscheidet zwischen Standardimpfungen und Reiseimpfungen. Im Rahmen des Impfmanagement wird zudem zwischen Grundimmunisierungen zur Entwicklung eines Basisschutzes und Auffrischungsimpfungen zur Verlängerung dieses Schutzes unterschieden [34]. Impfstoffe unterscheiden sich hinsichtlich ihres Wirkprinzips: Lebendimpfstoffe enthalten attenuierte Erreger, Totimpfstoffe bestehen aus inaktivierten Pathogenen. *Messenger Ribonucleic Acid*- (mRNA)-Impfstoffe übertragen genetische Information zur Antigenproduktion, während Vektorimpfstoffe hierfür nicht humanpathogene Trägerviren nutzen. Toxoid-Impfstoffe enthalten entgiftete bakterielle Toxine [35]. Die vorliegende Arbeit fokussiert sich auf Standardimpfungen und SARS-CoV-2-Impfungen bei PwMS.

Trotz einiger Bedenken von Patienten und Ärzten hinsichtlich einer möglichen Verschlechterung der MS [36] sind Impfungen ein wichtiger Bestandteil des Therapiemanagements [23,37]. Vereinzelt wurden nach Impfungen neurologische Störungen oder demyelinisierende Läsionen berichtet [38–42], jedoch zeigten größere Untersuchungen zufolge keinen gesicherten Zusammenhang zwischen Impfungen und MS-Erkrankungsrisiko [43–45]. Lediglich Studien zum Gelbfieber-Lebendimpfstoff zeigen widersprüchliche Ergebnisse hinsichtlich einer

möglichen Erhöhung der Schubrate [46–48]. Nach aktuellem Wissensstand beeinflussen Impfstoffe wie die gegen Hepatitis B, humane Papillomaviren (HPV) oder Frühsommer-Meningoenzephalitis (FSME) nicht die MS-Progression [49–51]. Neuere Studien unterstreichen die positiven Effekte von Impfungen für PwMS [36,52].

Internationale Leitlinien, darunter von *European Commitee for Treatment and Research in Multiple Sclerosis* (ECTRIMS) und *European Academy of Neurology* (EAN), betonen die Bedeutung von Impfungen und empfehlen eine angepasste Durchführung [53]. Die STIKO empfiehlt in Deutschland Standardimpfungen für PwMS mit einer individuellen Risiko-Nutzen-Abwägung [54].

Bestimmte DMDs wie Sphingosine-1-Phosphat-Rezeptor-(S1P)-Modulatoren (z. B. Fingoliomd) und Anti-CD20-Antikörper (z. B. Ocrelizumab) verringern die Antikörper- und T-Zell-Antworten [23,37]. Impfungen sollten möglichst vor Therapiebeginn erfolgen; Lebendimpfstoffe mindestens vier, bei Therapie mit Ocrelizumab oder Alemtuzumab mindestens sechs Wochen zuvor verabreicht werden [53].

1.3 SARS-CoV-2-Pandemie und Impfstrategien bei MS

Das hochansteckende Ribonukleinsäure-Virus SARS-CoV-2 verursacht die Infektionserkrankung *Coronavirus Disease 2019* (COVID-19), die mit Symptomen wie Fieber, Husten und neurologischen Komplikationen einhergehen kann [55,56]. Bis April 2025 wurden weltweit über 770 Millionen Fälle und 7 Millionen Todesfälle gemeldet [57]. PwMS haben per se kein erhöhtes Risiko für eine SARS-CoV-2-Infektion, jedoch können Faktoren wie Alter, DMD-Therapie, Adipositas, Komorbiditäten und der Grad der Behinderung gemessen an der *Expanded Disability Status Scale* (EDSS) [58] den Verlauf verschlimmern [59,60]. Daher spielten die neu entwickelten SARS-CoV-2-Impfstoffe eine zentrale Rolle in der Prophylaxe vor schweren Krankheitsverläufen sowie Bekämpfung und Eindämmung der SARS-CoV-2-Pandemie [61,62]. Zum Ende des Datenerhebungszeitraums der vorliegenden Arbeit (Januar 2022) war in Deutschland die Verwendung von vier Impfstoffen gegen SARS-CoV-2 durch die Europäische Arzneimittelagentur (EMA) zugelassen und von der

STIKO empfohlen worden [63,64]. Diese Impfstoffe waren zum einem die mRNA- basierten Impfstoffe Tozinameran (BNT162b2, Comirnaty®) und Elasomeran (mRNA-1273, Spikevax®), zum anderen die beiden vektorbasierten Impfstoffe AZD1222 (Vaxzevria®) und Ad26.COV2.S (Jcovden®) [65].

Für Erwachsene mit Grunderkrankungen wird von der STIKO eine Grundimmunisierung mit drei SARS-CoV-2-Impfungen empfohlen, gefolgt von einer jährlichen Auffrischungsimpfung [66]. Bei PwMS variieren die Immunantworten auf SARS-CoV-2-Impfstoffe abhängig von der krankheitsmodifizierenden Therapie. Unter S1P-Modulatoren (z. B. Fingolimod) und B-Zell-depletierenden Therapien (z. B. Ocrelizumab) sind die humoralen Immunantworten reduziert; insbesondere Fingolimod beeinträchtigt zusätzlich die zelluläre Immunantwort. mRNA-Impfstoffe induzieren im Vergleich zu inaktivierten Virusimpfstoffen höhere Serokonversionsraten, zeigen jedoch unabhängig vom Antikörperstatus eine vergleichbare Langzeitwirksamkeit gegen COVID-19 [67]. Diese Befunde unterstreichen die Relevanz therapiespezifischer Impfstrategien bei MS [67–69].

1.4 Impfbereitschaft

Die Impfbereitschaft in der Allgemeinbevölkerung wird maßgeblich durch Bildung, Wissen über Impfstoffe, das Vertrauen in deren Sicherheit sowie persönliche Erfahrungen mit früheren Impfungen beeinflusst. Zudem spielen Persönlichkeitsmerkmale eine Rolle. So stehen Menschen mit hohen Werten in der Persönlichkeitsdemension Verträglichkeit Impfungen eher positiv gegenüber [70]. Bei chronisch Erkrankten ist die Impfbereitschaft oft ambivalenter. Einerseits kann die höhere Wahrnehmung eines Infektionsrisikos die Impfbereitschaft steigern [71]. Andererseits bestehen häufig Bedenken hinsichtlich möglicher Nebenwirkungen oder Wechselwirkungen mit bestehenden Erkrankungen und Therapien, was zu einer skeptischeren Haltung führen kann [72–74] Besonders bei autoimmunen oder immunmodulierenden Erkrankungen, gibt es vermehrt Unsicherheiten bezüglich des Einflusses der Impfung auf den Krankheitsverlauf [75,76]. Die Durchimpfungsrate bleibt häufig hinter

den STIKO-Zielwerten zurück, wie etwa bei der Influenzaimpfung chronisch erkrankter Patienten deutlich wurde [77].

Bisher fehlten Studien zu Faktoren, die mit der Impfbereitschaft bei PwMS assoziiert sind, sowie im speziellen zur Veränderung der Impfbereitschaft im Rahmen der COVID-19-Pandemie bei PwMS. Die Relevanz der vorliegenden Daten liegt darin, ein besseres Verständnis über die Determinanten der Impfbereitschaft bei PwMS zu schaffen. Dieses Wissen ist entscheidend, um gezielte Strategien zur individuellen Förderung der Impfbereitschaft zu entwickeln und so die Impfquote in dieser vulnerablen Patientengruppe nachhaltig zu verbessern.

2 Fragestellungen

Impfungen sind essenziell zur Prävention von Infektionserkrankungen, insbesondere für Patienten mit Autoimmunerkrankungen wie MS, da Infektionen für sie ein erhöhtes Risiko darstellen können. Sie sind ein zentraler Bestandteil des Therapiemanagements für PwMS. Ziel dieser Arbeit war es, den Impfstatus von PwMS zu erheben und Faktoren zu identifizieren, die mit einer positiven oder ablehnenden Haltung gegenüber Impfungen assoziiert sind.

Während der initialen Datenerhebung kam es zum Ausbruch der SARS-CoV-2-Pandemie. Im Zuge dessen wurde ergänzend untersucht, wie sich die Einstellung zu den Impfungen im Verlauf der Pandemie und von der Entwicklung bis zum Markteintritt der SARS-CoV-2-Impfstoffe verändert hat. Dabei wurden insbesondere Persönlichkeitsmerkmale von PwMS untersucht, die mit der Impfbereitschaft assoziiert sein können.

Die Ergebnisse dieser Studien wurden in drei Originalarbeiten publiziert und sind in dieser kumulativen Dissertationsschrift zusammengefasst. Die untersuchten Fragestellungen lauteten wie folgt:

Publikation 1: General vaccination willingness and current vaccination status in relation to clinical and psychological variables in patients with multiple sclerosis

1. Wie stellt sich der Impfstatus bzgl. Mumps, Masern, Röteln, Tetanus und Influenza bei PwMS dar?
2. Gibt es Unterschiede in den klinischen und soziodemografischen Merkmalen zwischen Patienten mit vollständigen und unvollständigen Impfstatus?
3. Inwieweit gibt es Assoziationen zwischen der Impfakzeptanz zu empfohlenen Standardimpfungen in Bezug auf Persönlichkeitsmerkmale oder psychopathologische Symptome wie Angst und Depression?

Publikation 2: Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic

1. Wie stellt sich die Impfbereitschaft zu den SARS-CoV-2-Impfstoffen bei PwMS im zeitlichen Verlauf dar?
2. Wie ändert sich die Impfakzeptanz zu empfohlenen Standardimpfungen während der SARS-CoV-2-Pandemie?
3. Welche soziodemografischen, klinischen, psychopathologischen Faktoren sowie Persönlichkeitsmerkmale sind assoziiert mit der Impfbereitschaft für empfohlene Standardimpfungen und speziell für SARS-CoV-2-Impfungen während der Pandemie?

Publikation 3: Vaccination status and self-reported side effects after SARS-CoV-2 vaccination in relation to psychological and clinical variables in patients with multiple sclerosis

1. Ist die präpandemische Einstellung von PwMS zu empfohlenen Standardimpfungen mit dem SARS-CoV-2-Impfstatus während der Pandemie assoziiert?
2. Welche Gründe sind die häufigsten für oder gegen eine tatsächliche SARS-CoV-2-Impfung bei PwMS?
3. Welche soziodemografischen, klinischen und psychologischen Patientencharakteristika sind mit der Anzahl erhaltener SARS-CoV-2-Impfungen und mit aufgetretenen Impfreaktionen assoziiert?

3 Methodik

3.1 Studienpopulation

Die Kohorte bestand initial aus 461 PwMS oder einem CIS, die nach ausführlicher Aufklärung zur freiwilligen Teilnahme an der Studie gefragt wurden. Diese Patienten wurden aus der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock sowie der Abteilung für Neurologie des Ökumenischen Hainich Klinikums Mühlhausen rekrutiert. Für diese Studie lag ein positives Votum von der Ethikkommission der Universität Rostock (Genehmigungsnummer A 2019-0048) und der Ärztekammer Thüringen vor. Die Studie wurde in Übereinstimmung mit der Deklaration von Helsinki durchgeführt.

Einschlusskriterien umfassten ein Mindestalter von 18 Jahren sowie eine diagnostizierte MS oder ein CIS gemäß den revidierten McDonald-Kriterien [19]. Insgesamt wurden 57 PwMS aufgrund kognitiver Einschränkungen oder mangelnder zeitlicher bzw. persönlicher Bereitschaft von der Teilnahme ausgeschlossen. In die Basiserhebung wurden somit 404 PwMs eingeschlossen.

3.2 Datenerhebung

Es handelt sich um eine longitudinale Studie zur Beobachtung der Entwicklung von Impfverhalten und -einstellungen, beginnend mit einer Basisbefragung zwischen Juni 2019 und Juni 2020, die durch ein standardisiertes Interview in der MS-Sprechstunde oder während eines stationären Aufenthalts durchgeführt wurde (Abbildung 1). Zudem erfolgte eine Durchsicht des Impfausweises, eine klinische Untersuchung sowie die Auswertung der vorliegenden Patientenakte. Hierbei wurden soziodemografische Daten, wie Alter, Geschlecht, Bildung, Beruf und Familienstand, sowie klinische Daten in Form von MS-Krankheitsverlauf, Behinderungsgrad nach EDSS [58], Einnahme von DMDs und anderen Medikamenten, Komorbiditäten sowie medizinischer Versorgung (ambulant oder stationär) erfasst. Der Fokus lag auf der Tetanusimpfung als häufigste Impfung, der Influenzaimpfung als gängigste saisonale Impfung sowie der Masern-, Mumps und Röteln- (MMR)-Impfung aufgrund der bestehenden Impfpflicht in öffentlichen Einrichtungen (Kindergarten, Schulen). Überdies

erfolgte in der Basisbefragung die Erfassung impfbezogener Daten, wie der Impfeinstellung zu den in Deutschland empfohlenen Standardimpfungen [78]. Außerdem wurden Persönlichkeitsmerkmale der Patienten mittels *NEO Five-Factor Inventory* (NEO-FFI) und *Temperament and Character Inventory-Revised* (TCI-R) ermittelt (Abbildung1).

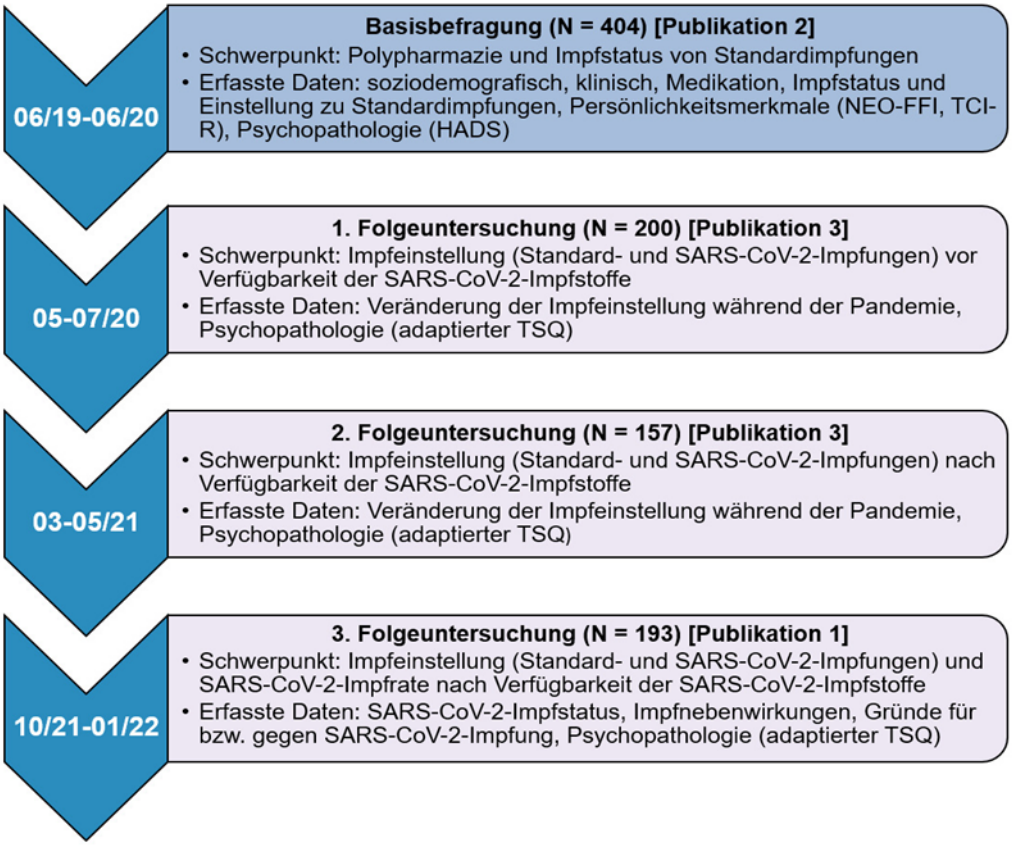

Abbildung 1. Datenerhebung. HADS: Hospital Anxiety and Depression Scale; N: Anzahl; NEO-FFI: NEO Five-Factor Inventory; SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2; TCI-R: Temperament and Character Inventory-Revised; TSQ: Trauma Screening Questionnaire

Der NEO-FFI besteht aus 60 Items, die in fünf Persönlichkeitsfaktoren (Neurotizismus, Extraversion, Offenheit, Verträglichkeit und Gewissenhaftigkeit) unterteilt sind [57]. Diese Items können anhand eines fünfstufigen Antwortmodells (1 = stimme überhaupt nicht zu bis 5 = stimme voll zu) beantwortet werden [79]. Der TCI-R besteht aus 240 Items, welche in sieben Dimensionen von Persönlichkeitsmerkmalen (Neugierverhalten, Schadensvermeidung, Belohnungsabhängigkeit, Beharrungsvermögen, Selbstlenkungsfähigkeit, Kooperativität und Selbsttranszendenz) unterteilt sind. Hierbei handelt es sich um ein Wahr/Falsch-Antwortmodell [80].

Psychopathologische Symptome von Angst und Depression wurden durch die *Hospital Anxiety and Depression Scale* (HADS) erfasst [81]. Hierbei handelt es sich um einen Selbstauskunftsfragebogen, bestehend aus 14 Fragen zum Schweregrad von Angst- und Depressionssymptomen, welche in einer 4-stufigen Likert-Skala beantwortet werden [59]. Die Einteilung der berechneten Scores für Angst und Depression erfolgt in unauffällig (0-7), grenzwertig (8-10) und auffällig (11-21) [82].

In den Folgebefragungen wurden die Impfeinstellung vor (Mai bis Juli 2020, N=200) und nach (März bis Mai 2021, N=157) der Verfügbarkeit von SARS-CoV-2-Impfstoffen, die tatsächliche SARS-CoV-2-Impfrate sowie Impfnebenwirkungen und Gründe der Patienten für bzw. gegen eine SARS-CoV-2-Impfung (Oktober 2021 bis Januar 2022, N=193) untersucht. Die Teilnehmerzahlen der einzelnen Folgebefragungen stellen eine Teilmenge der 404 Patienten aus der Basisbefragung dar, da nicht alle ursprünglich befragten Patienten erneut rekrutiert werden konnten (Abbildung 1).

Im Rahmen der dritten Folgebefragung wurde eine höhere Anzahl an Patienten befragt als in der vorherigen zweiten Folgebefragung (N=193 vs. N=157). Dies ist darauf zurückzuführen, dass für die Teilnahme an der dritten Folgebefragung lediglich die Teilnahme an der Basisbefragung erforderlich war. Die dritte Folgebefragung wurde durch Fragebögen per Post oder Telefoninterviews durchgeführt. Dabei wurden alle SARS-CoV-2-Impfstoffe, die bis zum Ende des Erhebungszeitraumes in Deutschland zugelassen waren, mit einbezogen (mRNA-Impfstoffe: Tozinameran und Elasomeran; vektorbasierte Impfstoffe: Ad26.COV2.S und AZD122). Die Impfungen wurden in Erst-, Zweit- und Drittimpfung unterteilt und die Patienten gaben zu jeder Impfung die wahrgenommenen Nebenwirkungen an, welche in lokale (Schwellung, Rötung oder Schmerzen an der Injektionsstelle) und systemische Nebenwirkungen (Brustschmerzen, Müdigkeit, Fieber und Schüttelfrost, Herzklopfen, Kopfschmerzen, Kurzatmigkeit, Muskel- und Gelenkschmerzen, Schwindel, Unwohlsein oder andere unerwünschte Wirkungen) unterschieden wurden. Eine Impfreaktion bezeichnet eine normale, vorübergehende Immunantwort, während eine Impfnebenwirkung eine seltene, unerwünschte Reaktion ist, die unter Umständen ärztliche Behandlung erfordert [83].

In allen Folgebefragungen füllten die Patienten einen adaptierten *Trauma Screening Questionnaire* (TSQ) aus, der zur Beurteilung der belastenden Auswirkungen der SARS-CoV-2-Pandemie entwickelt wurde [84]. Die Formulierung der 10 Fragen des TSQs bezog sich dementsprechend auf die SARS-CoV-2-Pandemie und ein fünfstufiges Antwortmodell (0 = überhaupt nicht bis 4 = sehr stark) wurde gewählt.

3.3 Statistische Analyse

Die Datendokumentation erfolgte mithilfe von Microsoft Excel 2019. Für die statistische Analyse wurden SPSS (Version 25 und 27) und R (Version 4.1.2) eingesetzt. Aufgrund der geringen Anzahl an CIS-Patienten wurden diese in der Analyse mit den RRMS-Patienten zusammengefasst. Die zusammenfassende Darstellung der intervallskalierten Daten erfolgte durch Mittelwerte und Standardabweichungen bzw. Mediane und Wertebereiche. Ordinal- oder nominalskalierte Daten wurden als Prozentsätze innerhalb der Kategorien angegeben. Zur Untersuchung der Assoziationen zwischen soziodemografischen und klinischen Merkmalen sowie dem Impfstatus und dem Auftreten von Nebenwirkungen nach SARS-CoV-2-Impfungen wurde eine binäre logistische Regression angewendet. Um den Zusammenhang zwischen einem vollständigen Impfstatus (Tetanus, Influenza, MMR) und den Variablen Alter und EDSS-Score zu prüfen, kamen lineare Regressionsanalysen zum Einsatz. Für die Analyse von Zusammenhängen zwischen intervallskalierten und ordinalen oder nominalen Daten wurde eine *analysis of variance* (ANOVA) durchgeführt. Die Korrelation von Variablen wurde mithilfe der Spearman-Rangkorrelationsanalyse berechnet. Unterschiede zwischen Patientensubgruppen wurden mittels t-Test, exaktem Fisher-Test und Chi-Quadrat-Test identifiziert. In der vorliegenden Dissertationsschrift wurden EDSS-Score-Mittelwerte auf eine Nachkommastelle gerundet. Ein p-Wert von $<0,05$ galt als signifikant.

4 Kurzzusammenfassung der Publikationen

In den folgenden Kurzzusammenfassungen wurde der Fokus auf die Hauptergebnisse der Studien gelegt. Aufgrund der zeitlichen Abfolge werden diese Studien in dieser Reihenfolge genannt. Detaillierte Informationen können den jeweiligen Originalarbeiten entnommen werden (Kapitel 8).

4.1 Publikation 1: General vaccination willingness and current vaccination status in relation to clinical and psychological variables in patients with multiple sclerosis

Ziel dieser Arbeit war es, Faktoren zu identifizieren, welche mit dem Impfstatus von PwMS assoziiert sind [85]. Angesichts der begrenzten Datenlage, insbesondere zum Impfstatus von PwMS in Bezug auf Influenza-, MMR- und Tetanusimpfungen, blieb bislang unklar, welche soziodemografischen, klinischen und psychopathologischen Faktoren sowie Persönlichkeitsmerkmale mit dem Status dieser Impfungen in dieser Patientengruppe assoziiert sind.

Im Rahmen der Studie wurden 404 PwMS zwischen Juni 2019 und Juni 2020 untersucht. Psychopathologische Daten und Persönlichkeitsmerkmale wurden mithilfe der Tests NEO-FFI, HADS und TCI-R erfasst. Klinische und soziodemografische Daten sowie der Impfstatus wurden durch Einsicht in Impfausweise und Patientenakten sowie strukturierte Interviews erhoben.

Die PwMS waren im Durchschnitt 47,9 ± 13,3 Jahre alt, bei einer mittleren Krankheitsdauer von 12,5 ± 9,3 Jahren und einem medianen EDSS-Wert von 3,0. An der Basisbefragung beteiligten sich 276 Frauen und 128 Männer. Von 327 Patienten mit vorliegenden Tetanusimpfdaten gaben 244 (74,6%) an, den allgemeinen Impfempfehlungen folgen zu wollen, wovon wiederum 201 (82,4%) einen vollständigen Tetanusimpfstatus hatten. Unter den 83 PwMS, die keine Bereitschaft zeigten, den allgemeinen Impfempfehlungen zu folgen, wiesen 59 (71,1%) einen vollständigen Tetanusimpfstatus auf. Es bestand keine signifikante Assoziation zwischen

dem Tetanusimpfstatus und dem EDSS-Score (p=0,756), des Angst-Score (HADS-A) (p=0,667) oder depressiver Symptomatik (p=0,848). Unter den 244 Patienten, die ihre Bereitschaft zu den empfohlenen Standardimpfungen äußerten, wiesen 21,3% einen vollständigen Influenzaimpfstatus auf, wohingegen nur 9,8% der Patienten, die nicht bereit waren, sich den empfohlenen Impfungen zu unterziehen, gegen Influenza geimpft waren. Patienten mit einem vollständigen Influenzaimpfstatus hatten ein höheres Durchschnittslebensalter (54,2 vs. 45,8 Jahre) und einen höheren mittleren EDSS-Score (3,8 vs. 3,1) als Patienten mit einem unvollständigen Influenzaimpfstatus. Patienten mit vollständig dokumentiertem Influenzaimpfstatus wiesen signifikant höhere Werte in den NEO-FFI-Persönlichkeitsmerkmalen Extraversion (p=0,031) und Offenheit (p=0,045) auf. Zudem zeigten sie erhöhte Werte im TCI-R-Test für Schadensvermeidung (p=0,029) sowie im HADS-A-Test für Angstzustände (p=0,036). Patienten mit einem vollständigen MMR-Impfstatus hatten einen niedrigeren mittleren EDSS-Score (2,0) als Patienten mit einem unvollständigen MMR-Impfstatus (3,3). Zudem waren PwMS mit vollständigem MMR-Impfstatus im Mittel jünger als Patienten ohne vollständigen MMR-Impfstatus (32,2 vs. 49,3 Jahre). Unabhängig von einer spezifischen Impfung war eine allgemeine Impfbereitschaft mit signifikant höheren Werten in den TCI-Dimensionen Neugierverhalten (p=0,027) und Beharrungsvermögen (p=0,019) sowie mit höheren Scores in den NEO-FFI-Kategorien Extraversion (p<0.001), Verträglichkeit (p=0,030), Gewissenhaftigkeit (p=0,006) und Neurotizismus (p=0,023) assoziiert.

Die Mehrheit der in dieser Arbeit analysierten PwMS zeigte eine positive Einstellung zu Standardimpfungen. Mit 74,6% lag die Tetanusimpfquote über der der deutschen Allgemeinbevölkerung (53,3%) [88]. Dies könnte auf die häufige Überwachung dieser Impfung in medizinischen Einrichtungen und die Beratung durch Neurologen zurückzuführen sein. Die Durchimpfungsrate bei der Influenzaimpfung entsprach internationalen Studien zu PwMS, wonach sie in Spanien zwischen 20,4%-41,5% [86] und in Lateinamerika bei 45,4% liegt [87]. Allgemein und auch in der vorliegenden Studie zeigte sich ein Anstieg der Influenzaimpfrate mit

zunehmendem Alter [88]. Dies lässt sich auf die Empfehlung der STIKO zurückführen, die eine jährliche Influenzaimpfung für Personen ab 60 Jahren vorsieht [35]. Die relativ niedrigere Influenzaimpfrate bei PwMS ist ungeklärt und könnte erstens auf jährlich wechselnde Impfstoffe, zweitens Angst vor Nebenwirkungen und drittens auf die Unsicherheit bezüglich der Wirksamkeit zurückzuführen sein. Eine Studie zeigte jedoch eine gute Immunogenität des Influenzaimpfstoffs bei PwMS [89]. In der vorliegenden Arbeit konnte gezeigt werden, dass es einen Zusammenhang zwischen einem vollständigen MMR-Impfstatus und dem Grad der Behinderung bei PwMS gibt. Dies könnte jedoch altersbedingt sein, da jüngere Patienten, die häufiger einen vollständigen MMR-Impfstatus aufwiesen, im Durchschnitt einen niedrigeren EDSS-Score hatten. Bei PwMS ist Impfskepsis relativ verbreitet (10–20%) [73]. Diese Skepsis beruht u. a. auf der Annahme, dass Impfungen das Risiko für MS-Schübe oder Krankheitsprogression erhöhen könnten [36, 37]. Deshalb sollten Unsicherheiten abgebaut werden um das Vertrauen in die Sicherheit der Standardimpfungen bei PwMS stärken.

4.2 Publikation 2: Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic

Ziel dieser longitudinalen bizentrischen Studie war die Entwicklung der Impfbereitschaft gegenüber empfohlenen Standardimpfungen sowie die traumatische Belastung der PwMS durch die SARS-CoV-2-Pandemie anhand eines angepassten TSQ zu untersuchen [90]. Bisher lagen keine Daten zur Veränderung der Impfbereitschaft von PwMS während der SARS-CoV-2-Pandemie vor, insbesondere im Hinblick auf ihre Haltung gegenüber SARS-CoV-2-Impfstoffen. Dies gilt insbesondere vor dem Hintergrund einer häufig bestehenden Polypharmazie sowie der Anwendung immunmodulatorischer Therapien. Die Einstellung zu Standardimpfungen wie MMR, Influenza und Tetanus sowie die damit assoziierten Faktoren waren bislang unerforscht.

Die Datenerhebung erfolgte in zwei Befragungszeiträumen: Die erste Folgeuntersuchung fand von Mai bis Juli 2020 mit 200 Teilnehmern statt,

gefolgt von der zweiten Folgeuntersuchung zwischen März und Mai 2021 mit 157 Teilnehmern.

In der Basisbefragung vor Beginn der SARS-CoV-2-Pandmie gaben 73,5% der 404 PwMS an, den staatlichen Impfempfehlungen der STIKO folgen zu wollen. In der ersten Folgeuntersuchung äußerten 7% der PwMS, dass sich ihre generelle Impfeinstellung durch die Diskussion um die COVID-19-Pandemie verändert hat und dass sich eine kritische Haltung entwickelt oder verstärkt hat. Hingegen befürworten 54% der Patienten ein Impfprogramm, während 39% eine unveränderte Impfhaltung zu Standardimpfungen vertraten. In der zweiten Folgeuntersuchung äußerten 102 der 157 Patienten, die staatlichen Empfehlungen für Standardimpfungen zu akzeptieren, 14 äußerten, dass sie eine ablehnende Haltung gegenüber Impfungen entwickelt haben und 41 bestätigten, dass sich ihre Einstellung zu Impfungen nicht geändert hat.

Bezüglich der SARS-CoV-2-Impfung gaben in der ersten Folgeuntersuchung 120 der 200 Patienten an, sich impfen zu lassen, wenn verfügbar, während 46 die Impfung ablehnten und 34 unentschieden waren. In der zweiten Folgeuntersuchung berichteten 96 PwMS, sich impfen lassen zu wollen, 33 lehnten die Impfung ab und 28 waren unentschieden. Patienten, die zu Studienbeginn eine Zurückhaltung bzgl. offizieller Standardimpfungen zeigten, entwickelten aufgrund der öffentlichen Diskussionen über die SARS-CoV-2-Pandemie häufiger eine negative Einstellung zu empfohlenen Standardimpfungen (16% vs. 3%). Zudem änderten sie ihre Meinung seltener zu einer positiven Haltung (36% vs. 60%) als Patienten, die bereits in der Basisbefragung impfbereit waren.

Eine positive Einstellung zu Standardimpfungen korrelierte mit der Bereitschaft zur SARS-CoV-2-Impfung (p=0,006). In der zweiten Nachuntersuchung waren mehr Männer (73%) als Frauen (54%) zur SARS-CoV-2-Impfung bereit. Der HADS-D-Score korrelierte negativ mit der Änderung der Einstellung zu Standardimpfungen infolge der öffentlichen Pandemiediskussion (p<0,05). Patienten mit höheren Depressionswerten zeigten eine geringere Einstellungsänderung. Im NEO-FFI-Test standen höhere Neurotizismuswerte mit einer ablehnenderen Haltung zu

Standardimpfungen in Zusammenhang (p<0,05). Ebenso zeigten Patienten, die höhere Werte in Gewissenhaftigkeit hatten, eher eine Antihaltung zu Standardimpfungen in der zweiten Folgeuntersuchung (p=0,009). Im Gegensatz korrelierten hohe TCI-Werte in Selbstbestimmung (p=0,018) und Kooperativität (p=0,018) in der zweiten Folgeuntersuchung mit einer positiven Änderung der Impfeinstellung.

In der ersten Folgeuntersuchung während der frühen Phase der SARS-CoV-2-Pandemie zeigte die Studienpopulation eine relativ hohe Impfakzeptanz von 60% für eine SARS-CoV-2-Impfung, ähnlich wie in einer US-Querschnittsumfrage, in der 66% der PwMS eine solche Impfung befürworteten [75]. In der zweiten Folgeuntersuchung lag der Anteil der Patienten, die sich gegen SARS-CoV-2 impfen lassen wollten, bei 61%. Insbesondere bei den 17% bzw. 18% der Patienten, die sich noch ambivalent gegenüber dieser Impfung zeigten, ist es wichtig, ihre Bedenken zu identifizieren und auszuräumen. Eine Impfzurückhaltung kann verschiedene Gründe haben. Soziodemografische Faktoren wie Alter und Geschlecht können die Impfbereitschaft beeinflussen. In der vorliegenden Studie zeigten sich Frauen gegenüber SARS-CoV-2-Impfungen zögerlicher als Männer, was mit einer systematischen Analyse von 65 Studien übereinstimmt, laut der Männer und höher gebildete Personen eine höhere Impfakzeptanz aufweisen [91]. Ältere Patienten der Studienkohorte wiesen im Vergleich zu jüngeren Patienten eine höhere Akzeptanz sowohl für empfohlene Standardimpfungen als auch für die SARS-CoV-2-Impfung auf. Ähnliches zeigt sich in einer Untersuchung bei PwMS für Influenza- und SARS-CoV-2-Impfungen [92]. Dies könnte auf die STIKO-Empfehlungen [35] sowie ein erhöhtes wahrgenommenes Infektionsrisiko in dieser Altersgruppe zurückzuführen sein. Die Wahrnehmung des Erkrankungsrisikos und die Angst vor einer SARS-CoV-2-Infektion erwiesen sich in einer Studie als Prädiktoren für die Impfakzeptanz bei PwMS [93]. Der negative Zusammenhang von Persönlichkeitsmerkmalen wie Neurotizismus wurde in einer aktuellen Untersuchung von Poier et al. bestätigt [94].

Zur Erhöhung der individuellen Impfbereitschaft sind zielgerichtete Aufklärungsmaßnahmen erforderlich, die Bedenken sowie

Persönlichkeitsmerkmale und psychische Faktoren wie Angst und Depression von PwMS berücksichtigen.

4.3 Publikation 3: Vaccination status and self-reported side effects after SARS-CoV-2 vaccination in relation to psychological and clinical variables in patients with multiple sclerosis

In dieser Studie wurde der SARS-CoV-2-Impfstatus bei 193 PwMS erhoben [95]. Es lagen bis dato keine Daten zur Einstellung von PwMS gegenüber empfohlenen Standardimpfungen vor der Pandemie und deren Zusammenhang mit dem SARS-CoV-2-Impfstatus während der COVID-19-Pandemie vor. Unklar war bisher, inwieweit eine positive präpandemische Impfhaltung oder andere Faktoren (wie Alter oder Behinderungsgrad) mit einer höheren SARS-CoV-2-Impfbereitschaft assoziiert sind.

In dieser Arbeit wurden daher Assoziationen zwischen der individuellen Einstellung zu Standardimpfungen, soziodemografischen und klinischen Variablen und psychopathologischen Merkmalen sowie selbstberichteten Nebenwirkungen nach der SARS-CoV-2-Impfung analysiert. Die Befragung erfolgte zwischen Oktober 2021 und Januar 2022 mittels Fragebogen.

Von den 193 untersuchten PwMS erklärten 146 (75,6%) vor der SARS-CoV-2-Pandemie, den offiziellen Empfehlungen für Standardimpfungen zu folgen. Unter den 163 (84,5%) Patienten mit mindestens einer SARS-CoV-2-Impfung war der Hauptgrund für diese der Schutz vor einer schweren Erkrankung (90,1%). Eine zweite Impfung erhielten 151 (78,2%) der PwMS und eine dritte Impfung 25 Patienten (13,0%). Der Hauptgrund für die 30 PwMS ohne SARS-CoV-2-Impfung gegen ebendiese war die Sorge vor möglichen (langfristigen) Impfreaktionen (82,1%). Die PwMS, die bereits vor der SARS-CoV-2-Pandemie eine positive Einstellung zu Standardimpfungen hatten, waren signifikant häufiger einmal oder zweimal gegen SARS-CoV-2 geimpft (1.Impfung Odds Ratio (OR)=3,447, p=0,003; 2. Impfung: OR=3,155, p=0,002). PwMS mit einem grenzwertigen HADS-D-Score waren seltener gegen SARS-CoV-2 geimpft (OR=3,91, p=0,047). Zudem zeigte sich, dass Patienten mit längerer MS-Krankheitsdauer mit

höherer Wahrscheinlichkeit eine dritte SARS-CoV-2-Impfung erhielten (OR=1,051, *p*=0,031).

Etwa die Hälfte der geimpften Patienten berichtete von Impfreaktionen (52,8%). Nach der ersten Impfung gaben 39,9% der Patienten Impfreaktionen an. Dabei waren die drei häufigsten: Müdigkeit (20,2%), Muskel- und Gelenkschmerzen (12,9%) und Kopfschmerzen (11,0%) (unabhängig vom verabreichten Impfstoff). Das Auftreten von Impfreaktionen war u. a. mit folgenden Variablen assoziiert: jüngeres Alter, höhere Bildung, niedrigerer EDSS-Score, kürzere Krankheitsdauer und schubförmige Verlaufsform der MS. So hatten SPMS-Patienten nach der zweiten Impfung seltener Muskel- und Gelenkschmerzen (OR=0,116, *p*=0,036) sowie Müdigkeit (OR=0,260, *p*=0,038) als CIS- bzw. RRMS-Patienten und die Dauer der MS-Erkrankung war positiv mit selbstberichtetem Herzklopfen nach der ersten SARS-CoV-2-Impfung assoziiert (OR=1,110, *p*=0,041).

Die Studienpopulation wies mit einer SARS-CoV-2-Impfrate von 84,5% (Stand: Januar 2022) eine relativ hohe Akzeptanz gegenüber den neuen SARS-CoV-2-Impfstoffen auf. Diese lag in einem ähnlichen Bereich wie die Durchimpfungsrate der deutschen Allgemeinbevölkerung, die im Juni 2024 bei 78,1% (mindestens eine SARS-CoV-2-Impfung) lag [96]. Hauptgründe für die Impfung waren der Schutz vor einem schweren Krankheitsverlauf sowie der Schutz von Familie und sozialem Umfeld, was auch in anderen Studien bestätigt wurde [97,98]. In einer größeren Studie aus Deutschland und dem Vereinigten Königreich mit 2346 PwMS wurden Schmerzen an der Injektionsstelle (46,6%), Müdigkeit (32,9%) und Kopfschmerzen (22,0%) als häufigste Nebenwirkungen nach der ersten SARS-CoV-2-Impfung berichtet [99]. In der vorliegenden Arbeit war Müdigkeit die häufigste systemische Nebenwirkung. Insgesamt unterschied sich das Nebenwirkungsprofil nicht von dem der Allgemeinbevölkerung [99,100].

5 Integrative Diskussion

Eine Forschungslücke bestand in der fehlenden longitudinalen Erfassung der Impfakzeptanz bei PwMS vor und speziell während der SARS-CoV-2-Pandemie. Ziel der vorliegenden Arbeit war es, Faktoren zu identifizieren, die mit der Impfbereitschaft bei PwMS in Verbindung stehen, und die Entwicklung der Impfbereitschaft zu beleuchten. In dieser Arbeit wurde die Einstellung von 404 PwMS zu Standardimpfungen sowie ihre Impfbereitschaft und ihr Impfstatus hinsichtlich SARS-CoV-2-Impfstoffen analysiert.

Die vorliegende Untersuchung (Kapitel 4.1) ergab eine relativ niedrige Durchimpfungsrate hinsichtlich der MMR-Impfung von 23,8%. Es wurde zudem ermittelt, dass die PwMS mit vollständigem MMR-Impfstatus einen geringeren Behinderungsgrad aufwiesen als die nicht vollständig geimpfte Patienten (Kapitel 4.1). Hierbei ist zu bedenken, dass PwMS mit einem niedrigen EDSS-Score in der Regel jünger sind als ältere Patienten. Jüngere Menschen sind jedoch eher gegen MMR geimpft, da die erste STIKO-Empfehlung für die Masernimpfung in der BRD erst 1974 veröffentlicht wurde, während in der DDR bereits ab 1970 eine Impfpflicht bestand [101,102]. Eine vergleichbare Erhebung der MMR-Impfquote von PwMS gibt es in Deutschland nicht. In einer irischen Studie betrug die MMR-Durchimpfungsrate bei PwMS 51,4% [73]. Vorherige Untersuchungen haben gezeigt, dass eine MMR-Infektion sowie auch eine MMR-Impfung nicht mit einem erhöhten Risiko, eine MS zu entwickeln, einhergehen [52,103]. In Bezug auf die Tetanusimpfung konnte kein erhöhtes Risiko für die Entwicklung einer MS festgestellt werden [38,52]. Eine aktuelle Beobachtungsstudie aus sechs MS-Zentren in Deutschland ergab, dass nur etwa die Hälfte der PwMS die empfohlenen Standardimpfungen erhalten hatte – seltener als in einer gesunden Vergleichsgruppe [104]. Trotz dieser Lücken im Impfschutz zeigte sich bei den Betroffenen eine hohe Impfbereitschaft, während impfkritische Haltungen nur vereinzelt auftraten [104].

In der vorliegenden Studie (Kapitel 4.3) erhielten nur 15,5% der PwMS keine SARS-CoV-2-Impfung bis zum Untersuchungsende (01/2022), was

auf eine relativ hohe Impfakzeptanz hinweist. Es wurde in dieser Arbeit zudem festgestellt, dass ältere PwMS eine höhere Impfbereitschaft sowohl für die SARS-CoV-2- als auch für die Influenzaimpfung aufweisen als jüngere Patienten. Diese Ergebnisse ähneln einer aktuellen iranischen Studie, in der die Impfverweigerungsrate bei PwMS bei 10,5% lag [105]. Eine systematische Übersichtsarbeit, die auch Studien zu Patienten mit anderen chronischen Erkrankungen einbezog, stellte ebenfalls heraus, dass ein höheres Alter mit einer verstärkten Inanspruchnahme der Influenzaimpfung assoziiert ist [106]. Aktuell wird für die SARS-CoV-2-Auffrischungsimpfung eine jährliche Empfehlung für Personen über 60 Jahren ausgesprochen [35]. Für Patienten mit chronischen Erkrankungen sind jedoch Influenza- und SARS-CoV-2-Impfungen in jedem Alter empfohlen [35].

In der vorliegenden Studie (Kapitel 4.3) hatten Patienten, die vor der Pandemie Standardimpfungen akzeptierten, mit einer signifikant höheren Wahrscheinlichkeit die erste (OR=3,447, p=0,003) und zweite SARS-CoV-2-Impfung (OR=3,155, p=0,002) erhalten. Männliche PwMS wiesen mit 73% eine höhere SARS-CoV-2-Impfbereitschaft auf als weibliche mit 54% (Kapitel 4.2). Bezüglich des tatsächlichen SARS-CoV-2-Impfstatus konnte jedoch kein signifikanter Geschlechtsunterschied festgestellt werden (erste Impfung: p=0,176; zweite Impfung: p=0,171; dritte Impfung: p=0,959). Ähnlich zeigte eine israelische Untersuchung, dass jüngere Frauen mit einer Impfbereitschaft von nur 12,0–13,6% deutlich skeptischer gegenüber einer SARS-CoV-2-Impfung waren als Männer (23,1–27,3%) [107]. Im Gegensatz dazu ergab eine retrospektive Analyse, dass Frauen häufiger gegen Influenza geimpft sind als Männer (62,8% vs. 53,2%) [108]. Patienten, die vor der Pandemie Standardimpfungen akzeptierten, hatten eine signifikant höhere Wahrscheinlichkeit, die erste (OR=3,447, p=0,003) und zweite SARS-CoV-2-Impfung (OR=3,155, p=0,002) zu erhalten. Eine US-Studie stellte zudem dar, dass eine frühere Influenzaimpfung sowie Faktoren wie höhere Bildung und ein besserer ökonomischer Status mit einer erhöhten Impfakzeptanz für SARS-CoV-2 und Influenza bei PwMS verbunden sind [87]. Wu et al. zeigten, dass vermehrte körperliche Aktivität mit einer höheren Akzeptanz der Influenzaimpfung assoziiert ist, während

Raucher sich seltener impfen lassen [109]. Dies deutet darauf hin, dass Patienten mit größerer Gesundheitsfürsorge eher zu Impfungen bereit sind [110]. Yap et al. präsentierten, dass PwMS eher zur SARS-CoV-2-Impfung als zu Pneumokokken- und Influenzaimpfungen bereit sind [73]. Die Autoren vermuteten, dass diese Impfstoffe als weniger notwendig wahrgenommen werden [73].

In der untersuchten Patientenkohorte war der Hauptgrund für die SARS-CoV-2-Impfung der Schutz vor einer schweren Erkrankung (90,1%). Dagegen wurde das Risiko möglicher Impfreaktionen (82,1%) als häufigster Ablehnungsgrund genannt (Kapitel 4.3). Ähnlich äußerten in der Studie von Yap et al. 40% der 105 befragten PwMS Zweifel an der Wirksamkeit und Sicherheit der SARS-CoV-2-Impfstoffe [73]. Eine aktuelle Studie bestätigt dieses Ergebnis bei PwMS [111] und entspricht zudem den Ergebnissen vergleichbarer Untersuchungen in der Allgemeinbevölkerung [112]. Zudem zeigten sich in anderen Untersuchungen weitere Gründe, welche die individuelle Impfbereitschaft der Allgemeinbevölkerung beeinflussen können, u. a. das Misstrauen gegenüber der Wissenschaft [99], der Glaube an alternative Medizin [113] sowie Verunsicherung durch Verschwörungstheorien [114]. Eine Informationsflut über SARS-CoV-2 wurde mit einer negativen Einstellung zur Impfakzeptanz in Verbindung gebracht, da sie eine Ermüdung und Desensibilisierung hervorrufen kann [115,116]. Umgekehrt fördert ein hohes Vertrauen in staatliche Institutionen und wissenschaftlich fundierte Informationsquellen sowie ein größeres Vertrauen in das Gesundheitssystem die Bereitschaft für SARS-CoV-2-Impfen [117].

Persönlichkeitsmerkmale beeinflussen das Gesundheitsverhalten und damit die individuelle Impfbereitschaft. In der vorliegenden Arbeit waren Extraversion (p=0,031) und Offenheit (p=0,045) mit einem vollständigen Influenzaimpfstatus assoziiert (Kapitel 4.1), während höhere Neurotizismuswerte (p<0,005) mit einer zunehmend ablehnenden Einstellung gegenüber Standardimpfungen im Laufe der SARS-CoV-2-Pandemie assoziiert waren (Kapitel 4.2). Eine aktuelle Meta-Analyse von Bleidorn et al. bestätigt diese Befunde: Hohe Werte in Extraversion (r=0,02) und Verträglichkeit (r=0,06) gingen mit einer positiven Impfeinstellung

einher, während höhere Neurotizismuswerte (r=-0,01) mit einer negativen Impfeinstellung verbunden waren [118]. Die Persönlichkeitszüge Verträglichkeit und Gewissenhaftigkeit (NEO-FFI) werden häufig mit präventivem Gesundheitsverhalten in Verbindung gebracht [119,120]. Personen mit höheren Gewissenhaftigkeitswerten im NEO-FFI-Test wurden in einer Befragung der US-amerikanischen Allgemeinbevölkerung häufiger mit der Einhaltung verstärkter Vorsichtsmaßnahmen gegen SARS-CoV-2 in Verbindung gebracht als solche mit niedrigeren Werten [121]. Im Gegensatz dazu steht eine Untersuchung von Reagu et al., in der 5340 Personen mit unterschiedlichstem soziodemografischem Hintergrund befragt wurden, welche zeigte, dass Personen mit hohen Gewissenhaftigkeitswerten sich weniger häufig gegen SARS-CoV-2 impfen ließen [122]. Ein möglicher Grund hierfür könnte sein, dass diese Personen eigene Nachforschungen anstellen statt den Empfehlungen der Gesundheitsbehörden zu folgen [122]. Gewissenhafte Personen könnten zudem glauben, durch Disziplin und gesunde Verhaltensweisen auf Impfungen verzichten zu können [123].

In der vorliegenden Arbeit (Kapitel 4.3) wurde gezeigt, dass PwMS mit grenzwertigen Depressions-Scores seltener gegen SARS-CoV-2 geimpft waren (OR=0,39). Zum aktuellen Zeitpunkt existiert keine vergleichbare Literatur zu diesem Ergebnis bei PwMS. Eine deutsche Querschnittstudie mit 795 chronisch Kranken fand keinen Zusammenhang zwischen Depression und der Influenzaimpfbereitschaft [124]. Es wurde jedoch eine Verbindung zwischen bestehender Depression und geringerem Vertrauen in die SARS-CoV-2-Impfstoffe vermutet [125].

Von 47 der 163 gegen SARS-CoV-2 geimpften PwMS wurden lokale Impfreaktionen nach der Impfung berichtet (Kapitel 4.3). Zu den häufigsten systemischen Impfreaktionen zählten Muskel- und Gelenkschmerzen, Kopfschmerzen sowie Müdigkeit, die jeweils initial bei mehr als 10% der geimpften Patienten auftraten. Eine Studie von Achiron et al. zeigte ähnliche Ergebnisse: 16% der 555 untersuchten PwMS berichteten nach der ersten SARS-CoV-2-Impfung über lokale Reaktionen an der Injektionsstelle, insbesondere Schmerzen [126]. Diese Ergebnisse entsprechen den Befunden der Zulassungsstudie zu Tozinameran, in der 21.720 Teilnehmer untersucht wurden [127]. Dabei wurden bei Teilnehmern im Alter von über

55 Jahren nach der ersten Dosis folgende Impfreaktionen gemeldet: Schmerzen an der Injektionsstelle (71%), Rötung (5%) und Schwellung (7%) [127].

Die vorliegende Arbeit weist mehrere Limitationen auf, die die Generalisierbarkeit und Validität der Ergebnisse einschränken könnten. Die geringe Teilnehmerzahl, das Fehlen einer Kontrollgruppe aus der Allgemeinbevölkerung und die Datenerhebung an nur zwei MS-Zentren in Nord- und Mitteldeutschland begrenzen die Repräsentativität der erhobenen Daten. Wichtige Aspekte wie Gründe gegen Standardimpfungen wurden nicht erfasst. Zudem gab es keinen festen Zeitrahmen für die Erhebung von Impfnebenwirkungen, was Erinnerungsverzerrungen begünstigen könnte. Selbstauskünfte der Patienten könnten zusätzlich zu Verzerrungen geführt haben. Die Ergebnisse spiegeln den Datenerhebungszeitraum wider und sind nicht direkt auf den aktuellen Stand übertragbar.

Trotz dieser Einschränkungen bietet die Studie wertvolle Erkenntnisse, die für zukünftige Forschungsarbeiten von Bedeutung sind. Weitere Studien, die eine breitere Teilnehmerbasis aus verschiedenen Regionen und einbezogene Daten von niedergelassenen Neurologen sowie internationalen Quellen berücksichtigen, könnten tiefere und umfassendere Einsichten in das Impfverhalten von PwMS liefern. Ein vielversprechender Forschungsansatz wäre die Untersuchung der Entwicklung der Impfbereitschaft hinsichtlich der empfohlenen Auffrischungsimpfungen gegen SARS-CoV-2 und der jährlichen Influenzaimpfungen. Darüber hinaus könnte die Analyse der Veränderung der allgemeinen Impfbereitschaft bei PwMS nach der SARS-CoV-2-Pandemie einen wertvollen Beitrag zur weiteren Optimierung von Impfstrategien leisten.

6 Zusammenfassung

MS ist die häufigste immunvermittelte Erkrankung des zentralen Nervensystems. PwMS haben ein etwa 50% höheres Infektionsrisiko als die Allgemeinbevölkerung, wobei Infektionen die häufigste Todesursache darstellen. Impfungen sollten daher ein essenzieller Bestandteil des Behandlungsmanagement bei PwMS sein. Ziel dieser longitudinalen Studie war es, die Entwicklung der Impfbereitschaft gegenüber empfohlenen Standardimpfungen und der Impfung gegen SARS-CoV-2 sowie mögliche Einflussfaktoren (soziodemografisch, klinisch, psychopathologisch, Persönlichkeitsmerkmale) zu untersuchen.

Die Datenerhebung erfolgte an zwei klinischen Zentren über vier Befragungsphasen: eine Basiserhebung (06/2019–06/2020) und drei Folgebefragungen bis Januar 2022. Insgesamt nahmen 404 PwMS an der Basisbefragung teil. Die Datenerhebung basierte auf standardisierten Interviews, Impfausweiskontrollen und Einsicht in die Patientenakten.

In der Basisbefragung zeigte sich eine hohe Impfquote für Tetanus (79,5%), während die Raten für Influenza- und MMR-Impfungen niedriger ausfielen (28,8% bzw. 18,4%). Eine vollständige Influenzaimpfung war mit höherem Lebensalter, höherem EDSS-Wert, sowie mit den Persönlichkeitsmerkmalen Extraversion, Offenheit und erhöhter Schadensvermeidung assoziiert. Ein vollständiger MMR-Impfstatus korrelierte mit jüngerem Alter und niedrigerem EDSS-Wert. Patienten mit allgemeiner Impfbereitschaft wiesen signifikant höhere Werte in Extraversion, Gewissenhaftigkeit, Verträglichkeit, Neurotizismus, Neugierverhalten und Beharrungsvermögen auf.

In der ersten und zweiten Folgeuntersuchung wurde die Entwicklung der Impfeinstellung während der SARS-CoV-2-Pandemie untersucht. Dabei zeigten sich insbesondere bei impfkritischen Personen häufiger negative Veränderungen der Einstellung. Umgekehrt entwickelten PwMS mit hoher Selbstbestimmung und Kooperativität eher eine positive Impfeinstellung. Eine hohe Impfbereitschaft zu Standardimpfungen ging zudem mit einer größeren Offenheit gegenüber der SARS-CoV-2-Impfung einher. Die Bereitschaft zur SARS-CoV-2-Impfung war bei Männern und älteren

Patienten deutlich ausgeprägter. Höhere Depressionswerte, erfasst mittels der HADS-D-Skala, standen in Zusammenhang mit einer geringeren Veränderung der Impfeinstellung.

In der dritten Folgeuntersuchung wurden Impfstatus, Impfgründe und Nebenwirkungen der SARS-CoV-2-Impfung bei 193 PwMS analysiert. 84,5% der PwMS waren mindestens einmal gegen SARS-CoV-2 geimpft, wobei der Schutz vor schwerer Erkrankung der Hauptgrund war. Eine positive präpandemische Impfeinstellung war signifikant mit der Inanspruchnahme einer SARS-CoV-2-Impfung verbunden. Häufig berichtete Impfreaktionen waren Müdigkeit, Muskel- und Gelenkschmerzen sowie Kopfschmerzen. Jüngeres Alter, höhere Bildung und geringere Behinderung waren mit häufigerem Auftreten von Nebenwirkungen assoziiert.

Persönlichkeitsmerkmale sowie psychische und krankheitsbezogene Faktoren sind relevante Prädiktoren für das Impfverhalten bei PwMS. Eine individualisierte Impfberatung unter Berücksichtigung dieser Variablen kann die Impfquote in dieser vulnerablen Gruppe verbessern. Die vorliegende Arbeit stellt eine prospektive, longitudinale, bizentrische Studie zur Impfbereitschaft bei PwMS dar und liefert damit wichtige Erkenntnisse für die Optimierung der Impfstrategie in diesem Patientenkollektiv.

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8 Publikationen

8.1 Publikation 1

General vaccination willingness and current vaccination status in relation to clinical and psychological variables in patients with multiple sclerosis

Autoren: Barbara Streckenbach, Julia Baldt, Felicita Heidler, Niklas Frahm, Silvan Elias Langhorst, Pegah Mashhadiakbar, **Katja Burian**, Uwe Klaus Zettl, Jörg Richter

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General vaccination willingness and current vaccination status in relation to clinical and psychological variables in patients with multiple sclerosis

Barbara Streckenbach [a,b,*], Julia Baldt [a,b], Felicita Heidler [b], Niklas Frahm [a], Silvan Elias Langhorst [a], Pegah Mashhadiakbar [a], Katja Burian [a,b], Uwe Klaus Zettl [a,1], Jörg Richter [b,c,d,1]

[a] Department of Neurology, Neuroimmunology Section, University of Rostock, Gehlsheimer Straße 20, 18147 Rostock, Germany
[b] Ecumenic Hainich Hospital gGmbH, Pfafferode 102, 99974 Mühlhausen, Germany
[c] University of Hull, Faculty of Health Sciences, Cottingham Rd, Hull HU6 7RX, UK
[d] Durham Law School, Durham University, The Palatine Centre, Stockton Road, Durham, DH1 3LE, UK

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ABSTRACT

Background: Infections can have a signi cant impact on morbidity and mortality in multiple sclerosis (MS) patients. Therefore, vaccinations are of immense importance. If vaccination willingness is to be increased, possible influencing factors should be identi ed. The aim of the present study was to investigate the status of active immunisation in MS patients in association with sociodemographic, clinical-neurological, psychopathological and personality variables using the NEO-Five Factor Inventory, the Temperament and Character Inventory-Revised and the Hospital Anxiety and Depression Scale.

Method: Four hundred and four MS patients from two German neurological hospitals were examined for their vaccination attitudes, in detail, the general willingness to vaccinate and the current vaccination status of mumps, measles and rubella (MMR) as well as tetanus and influenza. We also looked at the current level of disability in relation to the current vaccination status, as well as possible associated personality and psychopathological variables.

Results: Patients with a complete MMR vaccination status were signi cantly younger and those with a complete influenza vaccination status were signi cantly older than those with related incomplete vaccination status. Tetanus vaccination status completeness did not differ depending on age and did not show substantial association with personality scores. However, influenza vaccination completeness was associated with differences in personality and psychopathological variables; extraversion, openness, novelty seeking, harm avoidance and anxiety. A reported general vaccination willingness was signi cantly correlated with the current completeness of tetanus and influenza vaccinations. Novelty seeking, persistence, extraversion, agreeableness, conscientiousness and neuroticism were found associated with an increased vaccination willingness. Anxiety and depression were not related to general vaccination willingness.

Conclusions: No speci c personality trait could be de ned on its own in relation to general vaccination willingness or complete vaccination status. Younger patients should be made more aware of influenza vaccination. Reasons for rather low vaccination rates need to be further investigated.

1. Introduction

Multiple sclerosis (MS) is the most common chronic, immune-mediated disease of the central nervous system, associated with demyelination, axon and synapse loss and subsequent astrogliosis. Transient and persistent clinical de cits can develop at a young age. These can be very different symptoms, e.g. visual disturbances, sensory or motor de cits, but also ataxia, bladder and rectal disorders or symptoms of fatigue. [1,2]. About 2.8 million people worldwide are affected by MS. In Germany, there are about 250,000 MS

* Corresponding author at: Department of Neurology, Neuroimmunology Section, University of Rostock, Gehlsheimer Str. 20, 18147 Rostock (Germany) Ph.: +49381 494 9517.
E-mail addresses: babswehr@web.de (B. Streckenbach), Julia.baldt@outlook.de (J. Baldt), f.heidler@oehk.de (F. Heidler), niklas-frahm@gmx.de (N. Frahm), silvan.langhorst@uni-rostock.de (S.E. Langhorst), pegah.mashhadiakbar@uni-rostock.de (P. Mashhadiakbar), katja.burian@gmx.de (K. Burian), uwe.zettl@med.uni-rostock.de (U.K. Zettl), jrichterj@web.de (J. Richter).
[1] These authors contributed equally.

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patients; the prevalence is given as 300 per 100,000 inhabitants [3,4]. Women are affected about three times as often as men [5,6]. A clinical isolated syndrome (CIS) can be the first clinical manifestation of a potential MS. MS has different courses: relapsing-remitting (RRMS), primary progressive (PPMS) and secondary progressive MS (SPMS), with RRMS being the most common course in about 74% of patients [7,8]. The aetiology of MS is still not comprehensively understood. It is assumed that both genetic factors and environmental influences (e.g., smoking, infection with Epstein-Barr-Virus) could contribute to the manifestation of MS [9,10].

MS as a disease in itself, but also the use of immunomodulatory drugs (for the treatment of MS) pose a considerable risk of infection. At the same time, infectious diseases are a given risk factor for increased mortality in MS patients [11,12]. Consistent reduction of potential sources of infection is a major goal [1,13], and vaccination plays a central role in the treatment and management of MS [14]. There has been a great deal of uncertainty among both physicians and patients about the risk–benefit ratio of vaccination in MS [15].

There have been reports of various neurological disorders after vaccination, such as encephalomyelitis after active influenza vaccination [16] and similar disorders after mumps, measles and rubella vaccination [17] in patients with and without MS. Disease progression or new-onset demyelinating lesions have been observed after a hepatitis B vaccination [18,19]. However, no increased risk of CNS manifestations was found for any of these vaccinations in various case-control studies with MS patients and healthy ones [20] or with regard to other autoimmune diseases [21]. Recent research provided clear evidence for the positive impact of vaccinations against infectious diseases in MS patients without evidence of MS activation [15,22] suggesting the importance of recommended vaccinations such as the standard vaccinations against mumps, measles and rubella; or tetanus as examples of vaccinations that have been recommended by the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute (STIKO) for everyone regardless of age or pre-existing conditions. Indication vaccinations are given to groups of people with an increased risk of infection and associated consequences such as previous illnesses or pregnancy [23]. Vaccinations can prevent or reduce the occurrence of MS relapses and the risk of hospitalization [24]. Nevertheless, the actual vaccination status of the general population, especially of patients with chronically inflammatory diseases, was found incomplete and significantly deviating from the recommendations. The vaccination coverage of various vaccinations remained far behind the recommendations, meaning that they were not up to date. Furthermore, a discrepancy between the indicated willingness to get vaccinated and the vaccination status was found [25].

The aim of the present study was to investigate, on the one hand, the status of active immunisation of mumps, measles and rubella (MMR), tetanus and influenza vaccination in MS patients. On the other hand, the willingness to get vaccinated, mainly indicated by the completeness of the vaccination status among MS patients should be analysed for associations with sociodemographic, clinical-neurological, psychopathological and personality variables. By the current study, we focussed on the general attitudes of MS patients towards vaccination related to the actual implementation, on the degree of disability of the patients in relation to the completeness of certain vaccinations and what role psychopathological symptoms or personality characteristics might play in relation to the general willingness to get vaccinated. Since personality characteristics are assumed to be associated with vaccination willingness, also the association between these two constructs. Personality characteristics vary widely between individuals but represent relatively stable emotional, cognitive, and behavioural phenomena [26]. An US study found that high scores on agreeableness, conscientiousness and emotional stability tended to indicate that vaccination was seen as beneficial. Individuals with high conscientiousness scores were also more likely to support compulsory vaccination at school. This study demonstrated the importance of personality related to attitudes towards vaccination [27].

2. Methods

2.1. Study population and design

In total, 404 MS patients were included in this cross-sectional, multi-centre study (outpatients as well as inpatients) conducted at the Department of Neurology of Rostock's University Medical Centre (Germany) and at the Neurological Department of the Ecumenical Hainich Hospital in Mühlhausen (Germany). The complete study procedure is shown in Fig. 1.

The data collection started in June 2019 and ended in June 2020. Outpatients were asked to participate in the study during regular MS outpatient appointments and inpatients during their inpatient period. The patients were included after detailed information was given and after they signed an informed consent form. Inclusion criteria were a minimum age of 18 years and a diagnosis of either CIS or MS according to the revised McDonald criteria [28]. The study was approved by the Ethics Committee of the University of Rostock (approval number A 2019–0048) and the Physicians' Chamber of Thuringia and was conducted in accordance with the Declaration of Helsinki [29].

2.2. Data acquisition and measurement

Sociodemographic data (e.g. age, gender, marital status, job, education level), clinical-neurological data (including the disease course and the degree of disability according to Kurtzke's expanded disability status scale [EDSS] [30] with a possible range from 0 = no disability due to any MS symptom and 10 = death due to MS), medication data and data on general attitudes as well as the knowledge concerning vaccination was gathered by patient record reviews and a structured patient interview. Interview questions referred to the last time the topic of vaccination was discussed, if the patients experienced complications after any vaccination, if the patients knew that there are governmental vaccination recommendations and if they were willing to get the officially recommended vaccinations. Finally, patients were asked to complete questionnaires assessing personality characteristics. The most commonly applied personality questionnaire is the NEO-Five Factor Inventory (NEO-FFI) [31,32]. Descriptions of characteristics of individuals with high and low scores on NEO-FFI factors are presented in Table 1.

The NEO-FFI consists of 60 items, split into the five factors to be answered by a five-point Likert type answer model (1 = strongly disagree to 5 = strongly agree). As the psychometric properties of the NEO-FFI were investigated in a sample of 419 MS patients and the internal consistency, factorial validity and congruence between self-report and other-report were satisfactory [33], we decided to use it in our study.

The Temperament and Character Inventory-Revised (TCI-R) [34] was also used. **Temperament** characteristics were defined as automatic emotional responses to various experiences and are relatively stable over time, **character** refers to individual differences in values and norms and is measured by 3 dimensions. Descriptions of characteristics of individuals with high and low scores on the seven TCI dimensions are presented in Table 2.

The items are to be answered on an alternative true/false answer-model in the German version of the TCI-R [35]. The inter-

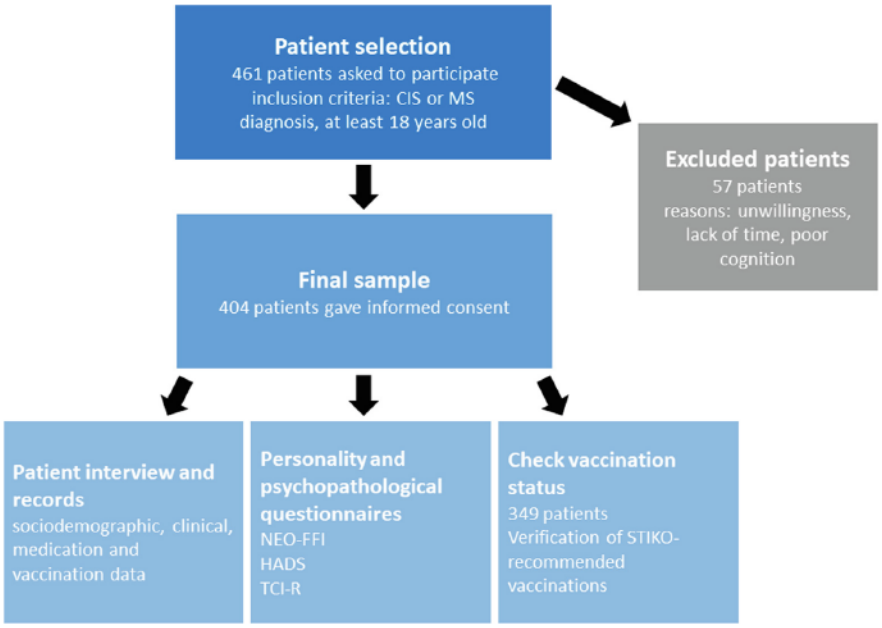

Fig. 1. Study design. CIS, clinically isolated syndrome; MS, multiple sclerosis; HADS, Hospital Anxiety and Depression Scale; NEO-FFI, NEO-Five Factor Inventory; TCI-R, Temperament and Character Inventory-Revised; STIKO, German Standing Committee on Vaccination.

Table 1
Description of characteristics of individuals with high and low scores on NEO-FFI factors.

Factors	Meaning of low scores	Meaning of high scores
Neuroticism	emotionally stable, calm, balanced, carefree	emotionally unstable, embarrassed, nervous, fearful, tendency to unrealistic ideas
Extraversion	reserved, independent, balanced, less obedient	con dent, active, sociable, cheerful, optimistic
Openness	tendency to conventional behaviour and conservative attitudes, emotionally rather subdued	imaginative, inquisitive, keen to experiment, intellectual
Conscientiousness	rather careless, indifferent and ckle	determined, ambitious, hard-working, persevering, reliable
Agreeableness	rather self-centred and distrustful of others, uncooperative	interpersonal trust, cooperativeness, compliance, need for harmony

NEO-FFI, NEO-Five Factor Inventory.

nal consistencies (Cronbach's alpha) of the scales are reported to range between 0.54 and 0.83 (mean 0.63) in a sample of 509 healthy German subjects. Richter et al. reported retest reliabilities (54-day interval) in 126 psychiatric patients of 0.51 to 0.74 (mean 0.63). There are also studies on factorial validity as well as convergent and discriminant validity [36].

In addition, a screening test was administered to assess the severity of depression and anxiety, the Hospital Anxiety and Depression Scale (HADS) with a total of 14 questions to be answered on a four-point Likert type scale, developed by Zigmond and Snaith [37,38]. The internal consistency (Cronbach's alpha) was 0.68–0.93 with a mean of 0.83 for anxiety (HADS-A) and 0.67–0.90 with a mean of 0.82 for depression (HADS-D). The validity is described as good content validity, good convergent validity in the sense of correlations with parallel anxiety and depression tests (between 0.49 and 0.83). Factorial analyses clearly demonstrated the dichotomous structure indicating good construct validity [39].

Finally, the patients were asked to provide their vaccination cards (i.e., both the old one from the German Democratic Republic

Table 2
Temperament and Character dimensions of the TCI-R.

Factors	Meaning of low scores	Meaning of high scores
Temperament dimensions		
Novelty seeking	Rigidity, thoughtfulness, frugality	Explorative behaviour, impulsiveness, untidiness
Harm avoidance	Pessimism, fear of uncertainty, shyness	Optimism, con dence, sociability, vitality
Reward dependence	Emotional and social coolness, aloofness	Good nature, warmth, sensitivity
Persistence	Laziness, unreliability, unpredictability	Diligence, hairiness
Character dimensions		
Self-centeredness	Disorganized, irresponsible, unreliable behaviour	Reliable, mature, purposeful behaviour
Cooperativeness	Intolerant, unfriendly, rather vindictive behaviour	Friendly, considerate, tolerant behaviour
Self-transcendence	Proud, intolerant, uncreative, arrogant behaviour	Humble, selfless, patient behaviour

TCI-R, Temperament and Character Inventory-Revised.

and the current one of the Federal Republic of Germany). In total, 349 MS patients could be included in the study. 55 of the 404 patients were excluded due to missing or non-existent vaccination cards. Assumptions about the actual vaccination status by the patients expressed during the interview could be compared with the vaccinations status documented in the vaccination cards.

2.3. Statistics

Statistical calculations were performed using SPSS, Version 25. Based on MS course type, patients with CIS and RRMS were combined into one group since 21 CIS patients would have been too few as one group and, clinically, a transition from CIS to RRMS occur very often. Interval-scaled data were presented by means and standard deviations. The independent sample Student's *t*-test was used to calculate differences between groups. Nominal and ordinal scaled patient data were presented by percentages within the categories. Possible correlations between ordinal or nominal scaled data were calculated using chi-square test or contingency coef cients, respectively. Multiple linear regressions were performed to show associations between completeness of vaccination status for tetanus, influenza and MMR and the variables age and EDSS score. The selection of variables included in the multiple regression was based on correlations between all theoretically meaningful included variables. Only variables with a signi cant correlation coef cient were subsequently included in the regression analysis. The criterion of $p < 0.050$ was used as two-tailed signi cance level.

3. Results

The mean age of the patients was 47.9 ± 13.3 years, the mean disease duration was 12.5 ± 9.3 years, and the median EDSS score was 3.0 implying that the average disabled patient was evaluated by either suffering a moderate disability in one functional system or a light disability in two functional systems. CIS or RRMS was diagnosed in 280 patients (69.3%), 93 patients (23%) were diagnosed with SPMS, and 31 patients (7.7%) had PPMS. The sociodemographic, clinical and psychological characterisation of the study population strati ed by sex is presented in Table 3.

The number of patients with available vaccination data for the individual vaccinations mumps-measles-rubella, tetanus and influenza are presented in Fig. 2.

The following questions were supposed to be answered by the study:

3.1. Do MS patients differ in their attitudes towards vaccinations with regard to willingness for recommended vaccinations and the objective evidence of vaccination status provided by vaccination cards, related to tetanus and influenza?

Of the 327 patients with available tetanus vaccination data, 244 patients (74.6%) reported willingness for compliance with generally recommended vaccinations. Of those patients willing to follow recommended vaccinations (N = 244), 201 patients (82.4%) had a complete tetanus vaccination status (χ^2 (1) = 4.85, p = 0.028). In the patients, not willing to accept recommended vaccinations (N = 83), 59 patients (71.1%) had a complete tetanus vaccination status (see Fig. 3). Information on current influenza vaccination status was found for 326 patients. Of those patients with given willingness for generally recommended vaccinations (N = 244), 52 patients (21.3%) currently had a complete influenza vaccination status (χ^2 (1) = 5.46, p = 0.019). In the group with no willingness for generally recommended vaccinations (N = 82), eight patients (9.8%) were currently vaccinated against influenza (see Fig. 3).

3.2. Is there an association between the completeness of the vaccination status and the disability status of MS patients?

3.2.1. Related to mumps, measles and rubella vaccination in childhood:

In patients with complete MMR vaccination status, the mean EDSS was 1.95 ± 1.42 and signi cantly lower than in patients with an incomplete vaccination status (3.33 ± 2.10; t (242) = -4.66, d = 0.71, p < 0.001) indicating an association between a complete

Table 3
Comparison of sex regarding sociodemographic, clinical and psychological aspects.

	F	M	*t*-test (df)	95% CI lower,upper	d	p
N	276	128				
Age[a]	47.3 ± 13.7	49.3 ± 12.2	−1.40 (402)	−4.77, 0.79	−0.15	0.161
EDSS score[b]	3.0	3.5	1.33 (402)	−0.74, 0.14	−0.14	0.185
Disease duration[a]	12.7 ± 9.2	12 ± 9.6	0.63 (402)	−1.34, 2.59	0.07	0.532
CIS/RRMS[c]	204 (73.9%)	76 (59.4%)	χ^2 = 15.84 (2)			**<0.001**
SPMS[c]	60 (21.7%)	33 (25.8%)				
PPMS[c]	12 (4.3%)	19 (14.8%)				
Vaccination card available[c]	243	106				
HADS-A[a]	7.4 ± 3.8	6.5 ± 3.6	2.06 (372)	0.04, 1.66	0.23	**0.040**
HADS-D[a]	5.4 ± 3.7	6.3 ± 4.0	2.14 (371)	1.71, −0.07	−0.24	**0.033**
Extraversion[a]	31.6 ± 8.5	30.96 ± 9.3	0.67 (371)	−1.25, 2.56	0.07	0.501
Agreeableness[a]	34.9 ± 5.9	32.95 ± 5.4	3.04 (371)	0.68, 3.18	0.34	**0.003**
Neuroticism[a]	28.7 ± 11.2	26.4 ± 11.8	0.63 (371)	−0.24, 4.72	0.20	0.076
Conscientiousness[a]	41.1 ± 8.5	38.6 ± 7.96	2.7 (371)	0.68, 4.30	0.30	**0.007**
Openness[a]	29.7 ± 5.8	29.8 ± 5.5	−0.24 (371)	−1.39, 1.08	−0.03	0.809
Novelty seeking[a]	15.0 ± 4.4	15.2 ± 5.3	−0.22 (316)	−1.24, 0.99	−0.03	0.827
Harm avoidance[a]	18.9 ± 6.4	16.9 ± 6.8	2.54 (314)	0.45, 3.57	0.31	**0.012**
Reward dependence[a]	19.0 ± 5.1	16.5 ± 5.3	4.19 (317)	1.36, 3.77	0.51	**<0.001**
Persistence[a]	19.6 ± 5.5	18.8 ± 6.6	1.06 (317)	−0.64, 2.15	0.13	0.290
Self-directedness[a]	29.3 ± 6.5	28.6 ± 7.0	0.84 (317)	−0.90, 2.26	0.10	0.400
Cooperativeness[a]	27.5 ± 4.2	26.3 ± 4.5	2.37 (317)	0.21, 2.26	0.29	**0.019**
Self-transcendence[a]	7.2 ± 4.0	6.8 ± 4.1	0.74 (317)	0.60, 1.32	0.09	0.461

a, mean ± standard deviation; b, median; c, number of patients (%); CI, con dence interval; t, t value; χ^2, chi square value; p, p value; N, number of patients; CIS, clinically isolated syndrome; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; MS, multiple sclerosis; d, effect size; df, number of degrees of freedom; EDSS, expanded disability status scale; F, female; M, male; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

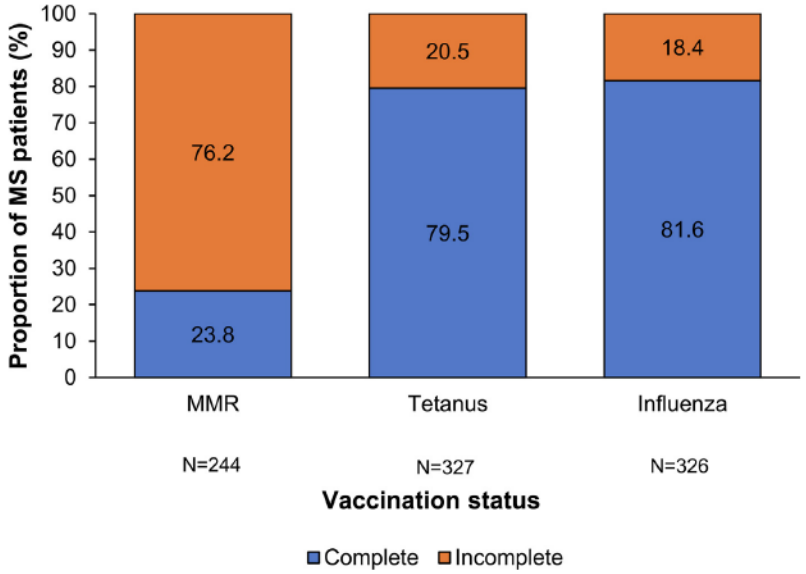

Fig. 2. Vaccination status for relevant vaccinations. Out of 349 patients with available vaccination cards, only 69.9% (N = 244) had information on MMR vaccination status, 93.7% (N = 327) had information on tetanus vaccination status and 93.4% (N = 326) had information on influenza vaccination status. Patients with available vaccination data are subdivided depending on the completeness of the current vaccination (according to STIKO recommendations). STIKO, German Standing Committee on Vaccination; MMR, mumps, measles and rubella; MS, multiple sclerosis.

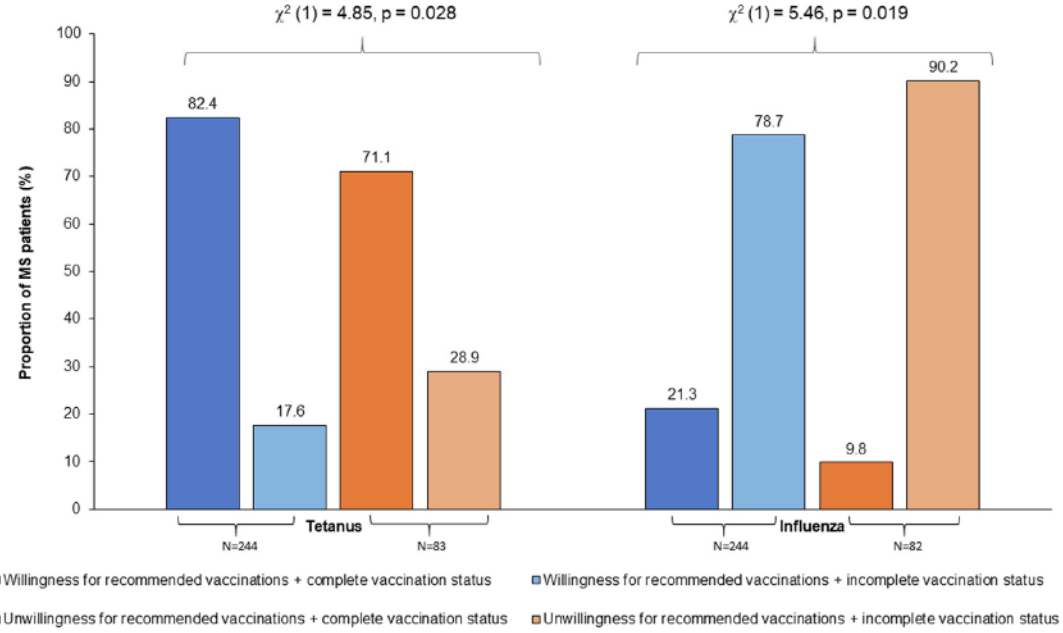

Fig. 3. Vaccination rates for tetanus and influenza in relation to willingness for generally recommended vaccinations. Proportion of patients with in/complete vaccination status of tetanus and influenza are shown depending on the willingness to receive standard vaccinations recommended by STIKO. Of patients with available vaccination data on tetanus (N = 327), 244 reported willingness and 83 patients reported unwillingness for recommended standard vaccinations. Of patients with available vaccination data on influenza (N = 326), 244 reported willingness and 82 patients reported unwillingness for recommended standard vaccinations. For both, tetanus and influenza, vaccination status completeness was signi cantly associated with willingness for recommended standard vaccinations. MS, multiple sclerosis; χ^2, chi square value; p, p value; N, number of patients; STIKO, German Standing Committee on Vaccination.

MMR immunization (given in childhood) and the degree of disability. Furthermore, age and complete MMR-vaccination status were highly signi cantly associated: completely MMR-immunized MS patients were younger than patients with an incomplete vaccination status (32.19 ± 7.99 years versus 49.32 ± 11.45 years; (t (242) = -10.61, d = -1.59, p < 0.001). In a multiple regression

analysis, the variance in completeness of MMR vaccination status was signi cantly explained by the variation in age (standardized β = -0.74; t = -7,62; p < 0.001; CI −0.03/-0.02), EDSS score (standardized β = -0.56; t = -2.62; p = 0.009; CI −0.18/-0.03), and the interaction term of age and EDSS (standardized β = 0.64; t = 2.51; p = 0.013; CI 0.00/0.01) to about 33% (F change (3/239) = 41.45; p < 0.001).

3.2.2. Related to tetanus vaccination:

The mean EDSS score did not differ between the 260 MS patients (79,5%) with a complete tetanus vaccination status and those 67 MS patients (20,5%) without complete tetanus vaccination (t (325) = -0.31, d = -0.04, p = 0.756). The variation of completeness of tetanus vaccination could only be signi cantly explained to 2 % implying a very low effect size of this result suggesting that both factors age and EDSS score are rather independent of tetanus vaccination completeness.

3.3. Is there a relationship between current psychopathological syndromes (anxiety, depression) or personality characteristics and the completeness of vaccination?

3.3.1. Related to tetanus vaccination

For the anxiety score, no statistically signi cant difference regarding the vaccination status could be found: complete tetanus vaccination (N = 253) vs. incomplete tetanus vaccination (N = 62) (7.01 ± 3.54 vs. 6.79 ± 3.97, t (313) = -0.43, d = -0.06, p = 0.667). Furthermore, MS patients with a complete tetanus vaccination (N = 252) did not differ from patients with incomplete tetanus vaccination on depressive symptoms (N = 62) (5.48 ± 3.76 vs. 5.58 ± 4.05; t (312) = 0.19, d = 0.03, p = 0.848). No signi cant difference in any of the personality factors and dimensions (NEO-FFI, TCI-R) depending on tetanus vaccination completeness could be found (p > 0.05).

3.3.2. Related to current influenza vaccination

Patients with a currently complete influenza vaccination status (N = 60) were signi cantly older (54.2 ± 12.7 years) than patients with an incomplete influenza vaccination status (N = 266: 45.8 ± 12.7 years; t (324) = -4.63, d = -0.66, p < 0.01). Similarly, patients with a complete influenza vaccination status had a signi cant higher EDSS score (3.75 ± 2.06) than those with an incomplete one (3.14 ± 2.07; t (324) = -2.08, d = -0.297, p = 0.039). In the multiple regression analysis with completeness of influenza vaccination as dependent variable, a signi cant model could be found explaining 5 % by the variance in age, EDSS score and its interaction with age being the only variable substantially contributing indicated by a signi cant β score (standardized β = 0.29; t = 2.75; p = 0.006; CI 0.002/0.015). Related to personality, signi cant differences between patients with and without complete influenza vaccination status could be found for the factors extraversion (t (311) = 2.17, d = 0.12, p = 0.031), openness (t (311) = 2.02, d = 0.29, p = 0.045), novelty seeking (t (273) = 2.45, d = 0.39, p = 0.015), harm avoidance (t (270) = -2.2, d = -0.35, p = 0.029) and for anxiety (HADS-A) (t(312) = -2.11, d = -0.31, p = 0.036). Patients with complete influenza vaccination status had signi cant higher scores on these factors than the unvaccinated group.

3.4. Are there differences in anxiety, depression or personality characteristics (NEO-FFI scales and TCI domains) with regard to the willingness to comply with recommended vaccinations?

Patients, who reported a willingness to receive standard vaccinations, had higher scores in novelty seeking (t (316) = -2.22, d = 0.17, p = 0.027) and persistence (t (317) = -2.36, d = 0.31, p = 0.019). Regarding the NEO-FFI, a general willingness to get vaccinated was associated with higher scores in extraversion (t (371) = -3.71, d = 0.44, p=<0. 001), agreeableness (t (371) = -2.18, d = 0.26, p = 0.030), conscientiousness (t (371) = -2.76, d = 0.33, p = 0.006) and neuroticism (t (371) = -2.29, d = 0.27, p = 0.023) compared to those not willing to follow the recommendations.

4. Discussion

The present study had several objectives. Firstly, the general willingness to vaccinate was investigated and this was also seen in relation to the current vaccination status regarding mumps, measles and rubella, tetanus and influenza. Furthermore, sociodemographic and clinical data, especially the current level of disability, were considered. Psychopathological and personality variables were also examined as possible influencing determinants with regard to the willingness to vaccinate using the NEO-FFI, TCI-R and HADS.

The clinical characterisation of the sample was similar to the data from the German MS registry.[8].

The shown association between a complete **MMR** vaccination status and the patient's degree of disability could support the assumption that fully vaccinated patients might bene t from a slower MS progression. Although this effect may be due to the fact that younger patients, who usually also have lower disability levels compared to older patients, are more likely to have a complete MMR vaccination. At least, no increased risk of developing MS after MMR vaccination was detected in other studies [40,41]. **Tetanus** vaccination completeness was not found substantially related to the degree of disability. This may be due to the fact that tetanus vaccination is probably the most frequently controlled vaccination and should not show a signi cant difference with respect to age. Similar to MMR vaccination, the literature does not report an increased risk for developing MS or MS relapse activity related to tetanus vaccination [42]. Older MS patients were signi cantly more likely to have been vaccinated against **influenza.** The STIKO recommends annual influenza vaccination for every individual over 60 years [43]. It is also recommended for pregnant people and for people with chronic diseases such as MS, as infection with the influenza virus itself could lead to a relapse or disease progression [23]. Similarly, the World Health Organisation (WHO) recommends influenza vaccination for young children, pregnant women, the chronically ill and the elderly, as they have an increased risk of severe disease progression [44].Young MS patients may not be as familiar with influenza vaccination, and physicians may pay more attention to older patients just because they are at higher risk and more often also have previous illnesses. Related to influenza vaccination completeness, a lower EDSS score is probably associated with younger age rather than the fact that the unvaccinated group has a lower EDSS score. This could support our assumption that vaccinated patients have a higher EDSS simply because it is more often the older patients who are vaccinated. Influenza vaccination may be more dependent on personal initiative, possibly influenced by personality factors. With regard to complete influenza vaccination status, patients seem to be more self-con dent, optimistic, cheerful and sociable, inquisitive, imaginative and experimental. Patients who are generally more open to change seem to get vaccinated more often. And this also seems to apply to patients with high anxiety. Some patients may decide to vaccinate out of openness, others may decide to vaccinate because of increased fearfulness. To our best knowledge, a comparative literature on this subject does not exist yet. Con dent patients are more likely to get vaccinated. A possibility to increase influenza vaccination rates among MS patients could be to inform more

reluctant and insecure patients more comprehensively and more often about the vaccination, related risks (possible worsening of the MS disease course) and especially bene ts (avoidance of the influenza infection itself). Tetanus vaccination completeness was not substantially related to any of the assessed personality characteristics. This might be due to the fact that a tetanus vaccination booster is recommended every 10 years as well as in case of uncertainty about existing vaccination protection at given risk [43]. So, the tetanus vaccination status is well monitored and recommended across all age groups in Germany, whereas the influenza vaccination is recommended especially for people > 60 years and for chronically ill people or people with other reasons for an increased risk of infection [23]. Communicating knowledge about the diseases and their consequences could also lead to a change in risk perception. However, no long-term behavioural changes were observed here, so that direct implementation may also be necessary if the intention is to vaccinate after being informed about possible risks [45].

The general willingness to get vaccinated seems to be possibly influenced by various personality characteristics. This could be demonstrated in our study for tetanus and influenza. In particular, a higher willingness to get vaccinated was reported by patients with explorative, impulsive but also perseverative behaviour. When MS patients are characterised by highly nervous or emotionally unstable behaviour and less self-con dence or by high self-con dence, optimism, sense of duty and tolerance, this was associated with an increased willingness to get vaccinated. This implies that there are several personality characteristics interacting by varying impact in determining willingness for getting vaccinated. In a sample of healthy German students, fear seemed to affect the overall willingness to get vaccinated against influenza. Fear of the disease itself increased the willingness to get vaccinated, while fear of vaccination decreased it [46]. The sense of responsibility towards the community, in the sense of herd immunity, also seems to have an influence on vaccination behaviour [47].The vaccination behaviour in general seems to depend on other psychological factors as well, described in the 5C model including the factors con dence, complacency (perception of risk), constraints (barriers), calculation (extent of information seeking), and collective responsibility (willingness to protect the community) [48]. To increase willingness to get vaccinated, doubts of the patients should be accepted and met in discussions on the basis of convincing scienti c evidence. Studies suggest an adequate immune response of MS patients to influenza vaccination supporting its usefulness for protecting MS patients [49].

The study has strengths and limitations. Although we were able to include a larger group of MS patients than in many other studies, the sample size of some subgroups was rather small in the analysis of group differences. However, this is a cross-sectional study and does not allow any conclusions to be drawn about causal relationships; in the absence of long-term data, associations can be assumed. However, according to our best knowledge our study represents the rst analysis on vaccination combined with personality characteristics in MS patients. Since we did not explicitely address the reasons for the lack of willingness to get vaccinated, this should be investigated in a next step to enable practitioners to effectively counselling MS patients on need for vaccinations. If fear and scepticism play an overriding role, education and an open approach to this topic can be useful. The perception of vaccination as a moral obligation leads to higher vaccination rates [50]. Physicians, especially general practitioners or other specialists in private practice, should draw attention to the bene ts of being vaccinated. This also requires vaccinators to have con dence in the safety of the vaccines. This, along with the introduction of reminder systems and easier access to the vaccines, could be ways to increase vaccination rates [51].

5. Conclusion

Certain personality characteristics may be related to the general willingness to get vaccinated and the actual implementation of vaccinations. Psychopathological symptoms such as anxiety or depression do not seem to be signi cantly linked to general willingness to get vaccinated. Tetanus as a standard vaccination does not suggest a connection with personality characteristics in our study. This could be due to the fact that doctors generally pay a lot of attention to the completeness of this vaccination among patients. Completeness of MMR and influenza vaccinations seems to depend somewhat on age. Influenza vaccination could be influenced by different personality characteristics. Further training for physicians should be provided on influenza vaccination to enable them effectively and convincingly to work with MS patients, in particular. The reasons for lack of vaccination willingness should be discussed with the respective patients, including doubts and concerns. It would be important to keep raising awareness of this issue and its importance through public campaigns. Vaccinations are and remain the most effective way to prevent serious infections and possible consequences for patients with MS.

6. Contributions

Conception and design of the study: BS, JB, FH, JR, NF, UZ; collection of data or analysis and interpretation of data: BS, JB, SL, PM, FH, JR, KB, NF, UZ; editing of the article or critical revision for important intellectual content: BS, FH, JR, KB, NF, UZ; nal approval of the version to be submitted: BS, JB, SL, PM, NF, FH, KB, JR, UZ.

All authors attest that they meet the ICMJE criteria for authorship.

Declaration of Competing Interest

The authors declare that they have no known competing nancial interests or personal relationships that could have appeared to influence the work reported in this paper.

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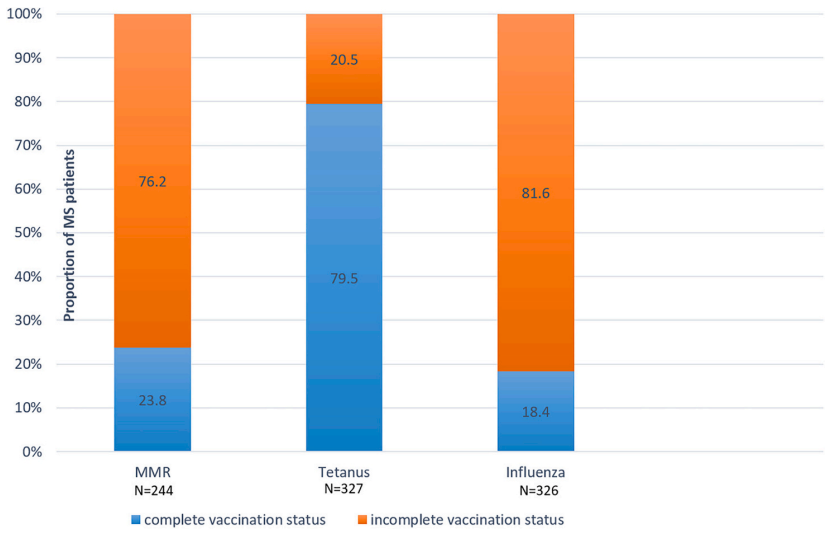
Corrigendum to "General vaccination willingness and current vaccination status in relation to clinical and psychological variables in patients with multiple sclerosis" [Vaccine 40 (23) (2022 May 20) 3236–3243]

Barbara Streckenbach [a,b,*], Julia Baldt [a], Felicita Heidler [b], Niklas Frahm [a], Silvan Elias Langhorst [a], Pegah Mashhadiakbar [a], Katja Burian [a], Uwe Klaus Zettl [a], Jörg Richter [b,c]

[a] Department of Neurology, Neuroimmunology Section, University of Rostock, Gehlsheimer Straße 20, 18147 Rostock, Germany
[b] Ecumenic Hainich Hospital gGmbH, Pfafferode 102, 99974 Mühlhausen, Germany
[c] University of Hull, Faculty of Health Sciences, Cottingham Rd, Hull HU6 7RX, UK; Durham Law School, Durham University, The Palatine Centre, Stockton Road, Durham, DH1 3LE, UK

The authors regret <Unfortunately, we noticed an error in a graphic very late. It concerns the completeness of the MMR, tetanus and influenza vaccinations in Fig. 2. The columns for the influenza vaccination have been swapped. I am enclosing a corrected version.

We sincerely apologise for this error.>
The authors would like to apologise for any inconvenience caused.



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* Corresponding author at: Department of Neurology, Neuroimmunology Section, University of Rostock, Gehlsheimer Straße 20, 18147 Rostock, Germany.
E-mail addresses: babswehr@web.de (B. Streckenbach), f.heidler@oehk.de (F. Heidler), silvan.langhorst@uni-rostock.de (S.E. Langhorst), pegah.mashhadiakbar@uni-rostock.de (P. Mashhadiakbar), uwe.zettl@med.uni-rostock.de (U.K. Zettl).

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8.2 Publikation 2

Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic

Autoren: Felicita Heidler, Julia Baldt, Niklas Frahm, Silvan Elias Langhorst, Pegah Mashhadiakbar, Barbara Streckenbach, **Katja Burian**, Uwe Klaus Zettl, Jörg Richter

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Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic

Felicita Heidler[1,5], Julia Baldt[2], Niklas Frahm[2✉], Silvan Elias Langhorst[2], Pegah Mashhadiakbar[2], Barbara Streckenbach[2], Katja Burian[2], Uwe Klaus Zettl[2,5] & Jörg Richter[1,3,4,5]

Vaccination is a key strategy for controlling the SARS-CoV-2 pandemic. Acceptance of SARS-CoV-2 vaccines by chronically ill patients, such as multiple sclerosis (MS) patients, plays an important role in prevention of complicated disease course. This longitudinal, prospective, multi-centre-study of German MS-patients aimed to detect socio-demographic, clinical, or psychological determinants of attitudes towards standard vaccines, SARS-CoV-2 vaccines, and governmental measures before/during the pandemic. Exactly 404 MS-patients were investigated by standardized questionnaires and structured interviews on socio-demographic, clinical-neurological, and psychological characteristics, vaccination status, and vaccination from June 2019. Data on SARS-CoV-2 vaccination willingness were collected in two follow-up assessments (1st: June to July 2020, before SARS-CoV-2 vaccine availability, N = 200; 2nd: March to May 2021, after SARS-CoV-2 vaccine availability, N = 157). Age, sex, MS course type, depression, and personality characteristics (Extraversion, Novelty seeking, Self-directedness, and Cooperativeness) were significantly associated with vaccination willingness. Although the majority of MS-patients showed SARS-CoV-2 vaccination willingness at both follow-ups (1st: 60%, 2nd: 61%), a substantial proportion had concerns and were undecided or opposed to vaccination. Socio-demographic variables like age and sex, psychopathological status, and various personality characteristics might influence vaccination willingness and should be considered when discussing with MS-patients about SARS-CoV-2 vaccination.

Since the beginning of the SARS-CoV-2 pandemic in 2020, there are more than 600 million confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, including 6.5 million deaths[1]. Vaccination represents the most important intervention in the pandemic management[2–4]. Therefore, it is essential to achieve a major vaccination acceptance among the population[5–8]. The willingness to get a SARS-CoV-2 vaccine is considerably varying in the general population. For instance, the vaccination willingness was 55.8% among English residents regarding a future vaccine[9] and 69% in U.S. American residents[10]. In January 2021, 60.1% of the 552 Thuringian participants of a German COVID-19 Snapshot Monitoring (COSMO) study indicated the willingness to receive the SARS-CoV-2 vaccination, while 12.0% were undecided and 27.9% did not or less tend to vaccination[11]. In another German study from January 2021, 1779 adults from the general population were online-surveyed shortly after the first SARS-CoV-2 vaccines were approved. The majority of study participants (78%) stated that they would like to become vaccinated or would rather become vaccinated, while 11% were undecided and 11% stated no or rather no willingness to be vaccinated[12]. This study revealed a positive association of anxiety due to COVID-19 as well as health-related fears with the acceptance of SARS-CoV-2 vaccines[12].

[1]Department of Neurology, Ecumenic Hainich Hospital gGmbH, Pfafferode 102, 99974 Mühlhausen, Germany. [2]Department of Neurology, Neuroimmunology Section, University Medical Centre of Rostock, Gehlsheimer Str. 20, 18147 Rostock, Germany. [3]Faculty of Health Sciences, University of Hull, Hull, UK. [4]Durham Law School, Durham University, Durham, UK. [5]These authors contributed equally: Felicita Heidler, Uwe Klaus Zettl and Jörg Richter. ✉email: niklas-frahm@gmx.de

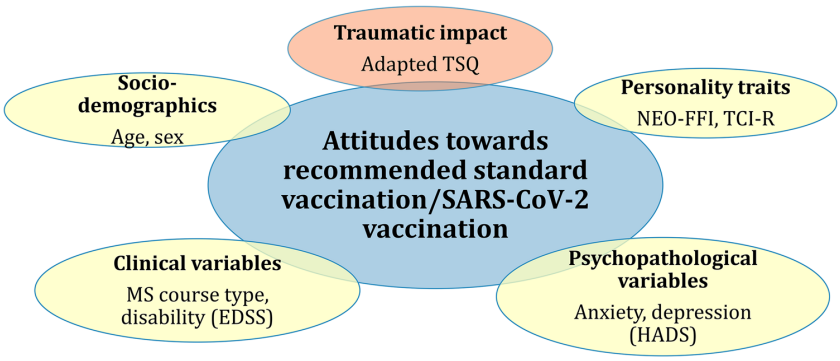

Figure 1. Variables to be analysed for associations with vaccination willingness in general and regarding SARS-CoV-2. *EDSS* Expanded Disability Status Scale, *HADS* Hospital Anxiety and Depression Scale, *MS* Multiple sclerosis, *NEO-FFI* NEO Five Factor Inventory; *TCI-R* Temperament and Character Inventory Revised, *TSQ* Trauma Screening Questionnaire.

A high level of SARS-CoV-2 vaccination willingness is especially important for people suffering from autoimmune diseases (AI). These patients have a higher susceptibility to infection which can be further increased by immunomodulatory treatments[13–15]. The overall estimated prevalence of AIs varied between 3 and 5%[16]. Multiple Sclerosis (MS) is the most common AI of the central nervous system in young adults with a wide range of neurological deficits such as hyposensibility, dysaesthesia, optic neuritis, paresis, spasticity, gastrointestinal as well as bladder disturbances, fatigue, depression, and neuropsychological deficits[17–22]. The general flu jab rate among German MS-patients was 19% before the SARS-CoV-2 pandemic[23]. A survey among MS-patients living in the U.S.A. between April and May 2020 reported a vaccination willingness regarding SARS-CoV-2 vaccines of 66.0%[24]. The willingness to receive a SARS-CoV-2 vaccination among Portuguese MS-patients was over 80.9% (35.2% definitely willing and 45.7% probably willing) in December 2020/January 2021[25].

There are several factors which might influence the vaccination willingness of MS-patients during the SARS-CoV-2 pandemic. On the one hand, the increased infection risk of immunocompromised patients and the perceived effectiveness of vaccines, especially of SARS-CoV-2 vaccines, could shape attitudes in favour of a willingness to get vaccinated[24–28]. On the other hand, many MS-patients worry about worsening disease progression and increased disease activity after general vaccination, which might lower vaccination willingness[29]. Another issue that might play an important role in vaccination behaviour of MS-patients in the pandemic and that could lead to a vaccination hesitancy is the safety of the new vector and mRNA vaccines against SARS-CoV-2[9,10,30]. For example, the use of the SARS-CoV-2 vaccine ChAdOx1 nCoV-19 (AZD1222) from Oxford-AstraZeneca (Vaxzevria®) was suspended in some European countries due to the occurrence of thromboembolic events in vaccinated people[31]. Such developments can easily cause insecurity, fear, and distrust in governmental recommendations. All these considerations raise the question if MS-patients' willingness to get vaccinated is solely based on weighing facts and data, or if personality traits also play a decisive role, since personality characteristics represent relatively stable behavioural, emotional, and cognitive phenomena[32].

It is very important to understand factors that influence the willingness to get vaccinated against SARS-CoV-2. A successful vaccination program has enormous importance on world health and economic status[30]. Therefore, the aim of the present study is to: (1) assess willingness to get a SARS-CoV-2 vaccine and attitudes towards recommended standard vaccinations before as well as during SARS CoV-2 pandemic among German MS-patients; (2) determine socio-demographic, clinical, psychosocial, and personality traits as patient characteristics which might be associated with the general and the SARS-CoV-2 vaccination willingness.

Methods

Study design. Four hundred and four individuals aged ≥ 18 years diagnosed with clinically isolated syndrome (CIS) or MS according to the revised McDonald criteria[33] have been included in a cross-sectional multicentre study on polypharmacy and vaccination status after signing an informed consent starting in June 2019. Detailed description of the sample is incuded in the study by Heidler et al.[34]. The consecutive convenient sample was recruited at the department of neurology of Rostock's University Medical Centre and at the neurological department of the Ecumenical Hainich Hospital in Mühlhausen/Thuringia (Germany). The patients have initially been recruited on the occasion of regular visits at the institutional MS outpatient clinics or during an inpatient stay. In total, 404 patients participated in the baseline survey (of 462 patients asked to participate). Because of the occurrence of the SARS-CoV-2 pandemic, this investigation was extended by two follow-up investigations on attitudes towards general as well as SARS-CoV-2 vaccination and on the perceived impact of federal SARS-CoV-2 safety measures in Germany in a subsample (1st follow-up: June to July 2020 before a vaccine against SARS-CoV-2 was available—N = 200, 2nd follow-up assessment: March 2021 to May 2021 after vaccines against SARS-CoV-2 were available—N = 157), see Fig. 1. There was neither any substantial dropout of participants from the baseline to the first follow-up nor to the second follow-up indicated by non-significant

differences between the investigated groups on age, sex, Expanded Disability Status Scale (EDSS) score, Hospital Anxiety and Depression Scale (HADS) scores, MS course type, number of comorbid illnesses, and willingness to accept governmentally recommended vaccinations. Thus, there was no systematic loss of participants.

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.

Data acquisition. The MS-related clinical, socio-demographic (e.g. age, sex, education and occupation), and basic vaccination-related data as well as psychopathological scores and personality data were obtained in 2019 (baseline) by a structured interview (Supplementary Document S1), a review of clinical patient records, and a clinical examination. Patients were asked to provide their vaccination card for a check of vaccination completeness based on the current recommendations by the German Standing Committee on Vaccination (STIKO) of the Robert-Koch-Institute, the German national institute for investigation and prevention of infectious diseases, and responsible for health monitoring[35]. Data on the MS course type, EDSS score[36], disease duration, and medication was collected as well as patients' assumption about their vaccination status and their attitudes towards vaccination in general (completed by 404 patients). Psychopathological syndrome severity was measured by the HADS (completed by 373 patients) and personality characteristics were assessed, measured by the Neo Five Factor Inventory (NEO-FFI), based on the Big-5 model of personality (completed by 373 patients), and by the Temperament and Character Inventory-revised (TCI-R, German version) derived from Cloninger's psychobiological model of personality presented as paper-and-pencil tests[37] (completed by 233 patients). The consequences of the pandemic and the related governmental measures were assessed by an adapted trauma questionnaire (social, psychological, and physical burden; Trauma Symptom Questionnaire [TSQ])[38], attitudes towards standard vaccination and willingness and possibly their changes to get vaccinated against SARS-CoV-2 were collected twice during the pandemic (1st and 2nd follow-up, completed by all patients participating in the respective follow-ups).

HADS. The HADS consists of 14 symptom-items (seven each measuring anxiety or depression) to be answered based on a four-point answer model (0–3). A clear two-factor structure was found in a factor analysis; and substantial correlations with the Beck Depression Inventory, the State-Trait Anxiety Inventory and domain scores of the Short-Form Health Survey indicated its high concurrent validity in a Spanish study of its construct validity[39]. A test–retest correlation of high effect size ($r = 0.85$) as well as high Cronbach's alpha coefficients of 0.86 for both of the psychopathological syndrome scores suggested its high reliability.

NEO-FFI. The NEO-FFI consists of 60 items, split into the five personality factors Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness to be answered by a five—point Likert type answer model (1 = strongly disagree to 5 = strongly agree). It was tested for validity and reliability in a sample of 419 MS-patients with satisfactory internal consistency, factorial validity, and congruence between self-disclosure and third-party disclosures[40]. Cronbach's alpha coefficients between 0.66 for Openness and 0.84 for Neuroticism or 0.71 for Oenness, Agreeableness and Conscientiousness, and 0.85 for Neuroticism were established in big samples of psychosomatic outpatients and of individuals from the general public, respectively, in Germany[41].

TCI-R. The TCI-R consists of 240 items divided into the seven domains described in Cloninger's personality model (Harm Avoidance, Novelty Seeking, Reward Dependence, Persistence, Self-Directedness, Cooperativeness, and Self-Transcendence) to be answered by a true–false answer model in its German version[37]. Cronbach's alpha coefficients for the domains ranged from 0.54 to 0.83 in a general population sample, and retest reliability ranged between 0.51 and 0.74 in psychiatric patients.

Adapted TSQ. To analyse the impact of SARS-CoV-2 pandemic (in terms of fear, burden, or changes in attitudes towards vaccination), a short questionnaire was created and presented in a telephone interview. To assess the burden caused by the SARS-CoV-2 pandemic itself and the related information in the media as well as limiting social measures, the TSQ was adapted[38]. 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 five-point scale with 0 = not at all to 4 = very much. The TSQ consists of ten symptom items (five arousal and five re-experiencing items) to assess post-traumatic stress disorder symptoms, and it is recommended to screen survivors of traumatic stress. A sum-score was calculated as indicator for burden caused by the introduced measures to limit the infection rate within the country and by living with the danger to become infected as well as suffer from a severe SARS-CoV-2 disease comorbid to the given MS.

Statistics. Interval scaled patient data were presented by mean score and standard deviation. Ordinal or nominal scaled data are reported by percentages within the categories. Spearman Rho correlation coefficients were used to determine relationships between interval scaled data. Associations between interval scaled data and ordinal (e.g., intensity of burden) or nominal scaled data were calculated by one-way analysis of variance (ANOVA) with related post-hoc tests depending on equality of variances (equal variances: Tuckey'-b; unequal variances: Games-Howell), or by point-biserial correlation coefficients in case of a nominal scaled variable with just two categories related to an interval scaled variable. Relationships between ordinally scaled or nominally scaled data were defined by chi-squared tests or contingency coefficients, respectively. The cut-off indicating significant results was set to $p = 0.050$.

	Baseline
N (all three assessments)	157
Age (years)	49.0 ± 12.5
Disease duration (years)	12.1 ± 8.9
EDSS score	3.6 ± 2.4
Education (years)	10.5 ± 1.2
Intensity physical burden	2.5 ± 1.2
Intensity psychological burden	2.6 ± 1.2
Intensity social burden	2.4 ± 1.3
MS course type	
CIS	3.8%
RRMS	64.1%
SPMS	24.4%
PPMS	7.7%
Number of comorbid diseases	1.9 ± 1.7
DMD-treated	59.9%
Trauma score	17.6 ± 6.3

Table 1. Patient characteristics at baseline. *CIS* clinically isolated syndrome, *DMD* disease modifying drug, *EDSS* expanded disability status scale, *MS* multiple sclerosis, *N* number of patients *PPMS* primary progressive MS, RRMS relapsing–remitting MS, *SPMS* secondary progressive MS.

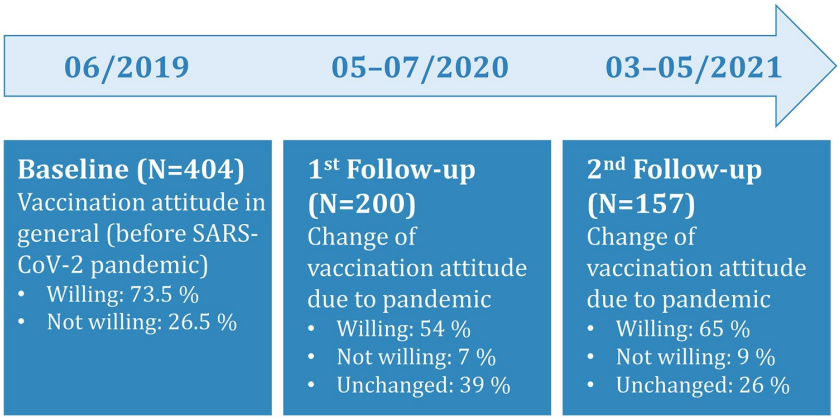

Figure 2. Development of general vaccination attitude before and during the course of the SARS-CoV-2 pandemic. *N* number of patients, *SARS-CoV-2* Severe acute respiratory syndrome coronavirus 2.

Since the study clearly was of an explorative nature, the alpha level was not controlled for multiple testing. All calculations were run using SPSS, version 25.

Results

Study population at baseline. Basic socio-demographic data and clinical information of the subsample of MS-patients included in all three assessments are presented in Table 1.

Indicators for attitudes towards vaccination in general. Over 70% of the 404 MS-patients analysed at baseline (from June 2019) indicated that they would be willing to follow the governmentally recommended vaccination program (73.5%), see Fig. 2.

Due to the discussion about the SARS-CoV-2 pandemic, 54% of the 200 patients of the 1st follow-up (June 2020 to July 2020) reported that their willingness to accept the governmentally recommended vaccination program would have been changed to agreement or that they have always been in favour of such a program. However, 7% developed or already had an anti-attitude, and 39% reported no impact of the discussions on their attitudes towards the recommended vaccinations. Regarding the SARS-CoV-2 vaccination willingness, 60% indicated that they probably or with certainty will accept a vaccination when a recommended vaccine will be available, while 23% said no or it would be unlikely, and 17% did not know yet.

	2nd follow-up (2021)		
1st follow-up (2020)	A	B	C
A	50/56	20/19	30/25
B	7/14	36/43	57/43
C	6/9	21/13	73/78

Table 2. Associations between 1st and 2nd follow-up (percentage – general vaccination attitudes/willingness for SARS-CoV-2 vaccination). A—Always anti or developed general negative attitudes towards vaccinations recommended/certainly not or unlikely taking SARS-CoV-2 vaccine; B—Unchanged attitudes towards recommended vaccinations/not known yet towards a SARS-CoV-2 vaccine; C—Always pro or developed positive attitudes towards recommended vaccinations/probably or with certainty taking the SARS-CoV-2 vaccine. Meaning of percentages in a field—example field A/A: 50% of those MS-patients with a negative attitude towards general vaccination recommendations during the 1st follow-up had also a negative attitude during the 2nd follow-up; 56% of those with a negative attitude towards a SARS-CoV-2 vaccination during the 1st follow-up had still a negative attitude at the 2nd follow-up.

At the 2nd follow-up in February/March 2021, when several SARS-CoV-2 vaccines were already approved and governmentally recommended, 65% of the 157 repeatedly investigated MS-patients indicated that their willingness to accept the governmentally recommended vaccination program would have been changed to agreement or that they always have been in favour of such a program due to the discussions about the SARS-CoV-2 pandemic. Only 9% developed or always had an anti-attitude, and 26% reported no impact of the discussions on their attitudes towards the recommended vaccinations. Regarding the SARS-CoV-2 vaccination, 61% of the patients expressed that they probably or with certainty will accept a vaccination, while 21% would not or unlikely accept such a vaccination, and 18% did not know yet.

Association of attitude towards recommended standard vaccinations and SARS-CoV-2 vaccination. The indicated willingness to take recommended vaccinations at baseline was significantly associated to the attitude change regarding the public discussions about the SARS-CoV-2 pandemic at the 1st follow-up assessment (c^2 [4] = 15.39; p = 0.004), but not with the attitude change between the 1st and the 2nd follow-up assessment (c^2 [4] = 5.41; p = 0.247). During the 1st follow-up assessment, those who did not accept the recommended vaccinations at baseline (N = 107) more often developed a negative attitude towards vaccination in general due to SARS-CoV-2 discussions (16% vs. 3%), more often reported no attitude change (48% vs. 37%), and less frequently changed to a positive attitude or always have been in favour for the recommended vaccination program (36% vs. 60%) compared to MS-patients accepting recommended vaccinations at baseline.

The indicated willingness to take recommended vaccinations at baseline was significantly associated to the expressed willingness to take a SARS-CoV-2 vaccine when it would be available and recommended at the 1st follow-up assessment (c^2 (4) = 14.59; p = 0.006), but not with the willingness to take a SARS-CoV-2 vaccine after its availability in February and March 2021 (2nd follow-up: c^2 (4) = 5.36; p = 0.253). Significantly more willing than unwilling patients regarding the recommended standard vaccinations at baseline indicated that they would get vaccinated against SARS-CoV-2 (67% vs. 42%) at 1st follow-up, whereas standard-vaccination-unwilling patients were more likely not to get vaccinated against SARS-CoV-2 (38% vs. 17%). In both groups, there were patients who were undecided regarding their attitude towards SARS-CoV-2 vaccination at the time of the 1st follow-up (standard-vaccination willing vs. -unwilling: 16% vs. 10%).

There was a significant association in the attitude change regarding standard vaccinations due to the SARS-CoV-2 discussions (c^2 (16) = 69.12; p < 0.001) as well as for the willingness for taking a SARS-CoV-2 vaccine (c^2 (16) = 79.59; p < 0.001) between the 1st and 2nd follow-up assessment (see Table 2).

Determinants of attitude change towards standard vaccination and the willingness for SARS-CoV-2 vaccination. *Socio-demographic patient characteristics (age and sex).* Age significantly positively correlated with a change in the general attitudes towards recommended vaccinations at both follow-up assessments (1st follow-up: Spearman rho = 0.21, p = 0.003; 2nd follow-up: Spearman rho = 0.19, p = 0.017) as well as with willingness to get vaccinated against SARS-CoV-2 (1st follow-up: Spearman rho = 0.27, p < 0.001; 2nd follow-up: Spearman rho = 0.19, p = 0.017), but did not with the willingness to follow recommended vaccinations at baseline (r_{pbis} = −0.09, p = 0.190).

Substantial sex differences occurred only for the willingness to get vaccinated against SARS-CoV-2 at the 2nd follow-up in 2021 (c^2 (1) = 14.66; p = 0.005), with more female than male patients still have been undecided (26% vs. 4%), and more male than female patients were willing to take the vaccine probably or with certainty (73% vs. 54%).

Clinical patient characteristics. Considering MS course type, there were two significant associations with the willingness to get vaccinated against SARS-CoV-2 during the 1st follow-up (c2 [12] = 23.13; p = 0.027): significantly fewer CIS patients compared with the other disease courses were willing to be probably or definitely vaccinated against SARS-CoV-2 (36.5% [CIS] vs. 61.0 [relapsing–remitting MS – RRMS]/61.0% [secondary progressive MS – SPMS]/73.0% [primary progressive MS – PPMS]), and significantly fewer PPMS-patients compared with the other MS types reported being unlikely or certain not to get a SARS-CoV-2 vaccine (7.0% [PPMS] vs.

	A	B	C	N
CIS	36.5/0.0	27.0/33.3	36.5/67.0	11/6
RRMS	23.0/25.0	16.0/20.0	61.0/55.0	128/100
SPMS	22.0/14.0	17.0/13.0	61.0/73.0	40/38
PPMS	7.0/27.0	20.0/9.0	73.0/64.0	15/11

Table 3. Association between MS course type and willingness to take SARS-CoV-2 vaccine (percentage within course type groups at 1st follow-up/2nd follow-up). A—Certainly not or unlikely taking a SARS-CoV-2 vaccine; B—Not known yet; C—Probably or with certainty taking a SARS-CoV-2 vaccine; *CIS* clinically isolated syndrome, *MS* multiple sclerosis, *PPMS* Primary progressive MS, *N* total number of patients, *RRMS* relapsing–remitting MS, *SPMS* Secondary progressive MS. Meaning of percentages in a field – example field RRMS/A: 23.0% of RRMS-patients at the 1st follow-up and 25.0% at the 2nd follow-up were certainly not or unlikely taking a SARS-CoV-2 vaccine.

22.0% [SPMS]/23.0% [RRMS]/36.5% [CIS]), see Table 3. Even though age and MS course type were found substantially interrelated (Kendall's tau-b = 0.30; $p < 0.001$), age was substantially more associated with the willingness to take an anti-SARS-CoV2 vaccine (Kendall's tau-b = 0.15; $p = 0.017$) than the MS-course type (Kendall's tau-b = 0.07; $p = 0.360$) indicating that age and possibly the related personality maturity are of higher impact than MS-course type. There were no significant associations between the SARS-CoV-2 vaccination willingness or the attitude change regarding recommended standard vaccinations with EDSS, number of comorbidities, number of drugs taken, or number of DMD switches at any examination period.

Anxiety and depression. Anxiety severity (HADS-A score) at baseline was not substantially related to any of the attitudes towards SARS-CoV-2 vaccination indicators at any of the follow-up assessments. Depression severity (HADS-D score) significantly negatively correlated with the general attitude change towards recommended standard vaccinations due to the public SARS-CoV-2 pandemic discussion (1st follow-up: Spearman rho = −0.14, $p = 0.049$; 2nd follow-up: Spearman rho = −0.29, $p < 0.001$) with the more severely depressed the MS-patients were at baseline, the less the attitude change at both follow-up assessments. The trauma-score was substantially positively associated with the willingness to take a SARS-CoV-2 vaccine within the 1st follow-up in 2020 (1st Spearman rho = 0.15, $p = 0.039$) with the higher the trauma score was the more the patients were willing to get vaccinated against SARS-CoV-2 virus, while it was significantly negatively related to the attitude change towards general vaccination within the 2nd follow-up with low effect size (2_{nd} Spearman rho = −0.24, $p = 0.003$).

Personality characteristics. The willingness to comply with the governmentally recommended vaccinations at baseline was significantly correlated with the Extraversion score ($r_{pbis} = 0.20$; $p = 0.007$) and the Novelty Seeking score ($r_{pbis} = 0.18$; $p = 0.017$), with those accepting the recommendations scoring higher in both variables, see Fig. 3. The higher the Neuroticism score (1st follow-up: Spearman rho = −0.14, $p = 0.049$; 2nd follow-up: Spearman rho = −0.40, $p < 0.001$) and the Conscientiousness score (1st Spearman rho = −0.04, $p = 0.594$; 2nd Spearman rho = −0.21, $p = 0.009$) of the NEO-FFI, the more dismissive was the change of attitudes towards vaccination in general at both follow-up assessments. Furthermore, the higher the MS-patients scored for Self-Directedness (1st follow-up: Spearman rho = 0.07, $p = 0.343$; 2nd Spearman rho = 0.20, $p = 0.018$) and for Cooperativeness (1st follow-up: Spearman rho = 0.10, $p = 0.194$; 2nd follow-up: Spearman rho = 0.20, $p = 0.018$) at baseline (TCI-R), the more they favourably changed their attitudes towards vaccination in general at both follow-up assessments.

All other scores for personality characteristics did not significantly correlate with any attitude or willingness for getting a SARS-CoV-2 vaccine.

Discussion

The present longitudinal, prospective multi-centre-study investigated German MS-patients' attitudes towards a SARS-CoV-2 vaccination and governmental measures before and after the 1st SARS-CoV-2 pandemic wave and within the 3rd wave in Germany based on socio-demographic, clinical, and personality variables. A high reported acceptance to comply with governmentally recommended vaccinations from the STIKO of 75% was found in the baseline investigation before the SARS-CoV-2 pandemic started.

The 1st follow-up was carried-out during or shortly after the 1st wave of the SARS-CoV-2 pandemic (June 2020). No vaccine against SARS-CoV-2 was available at this time. This 1st follow-up showed a major acceptance of a vaccination against SARS-CoV-2: 60.5% of the patients were willing to get a vaccine, 17.0% were undecided, and 22.5% were against it[34]. Although the majority of MS-patients analysed in the present study showed willingness to get vaccinated against SARS-CoV-2 at both follow-ups (1st: 60%, 2nd: 61%), a substantial proportion had concerns and were undecided or opposed to vaccination. This is lower than in MS-patients in the U.S.A. with 66.0–70.1%[24,42]. A higher rate of vaccination endorsement (80.9%) was found in a small Portuguese study[25]. In a comparable survey period to our first follow-up (June to July 2020), 70% of participants of a real time survey as a part of the German Socio-Economic Panel were willing to become vaccinated against SARS-CoV-2[43]. These results match another online survey from April 2020 in which 73.9% of 7664 participants from seven European countries (United Kingdom, Germany, Netherlands, Portugal, France, Denmark and Italy) reported that they

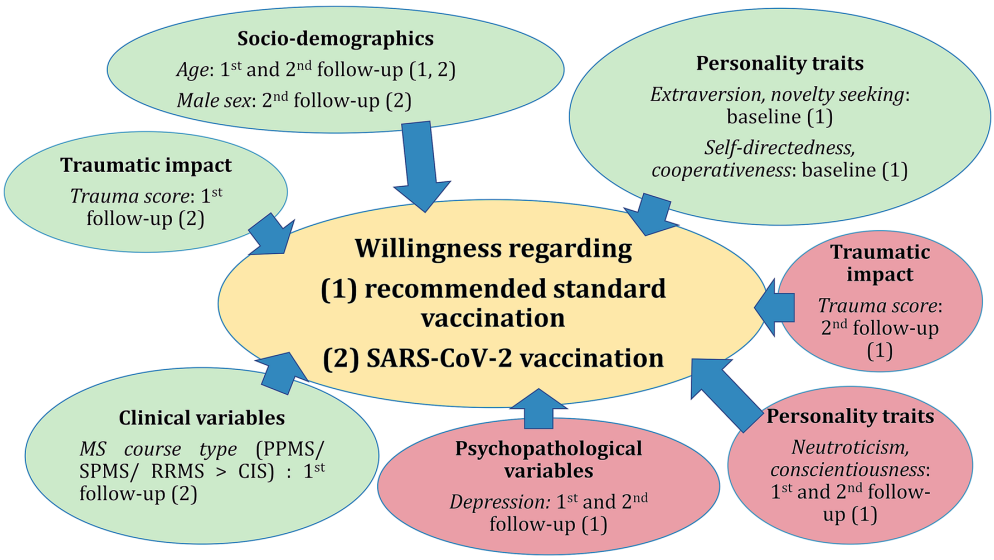

Figure 3. Patient characteristics associated with the willingness regarding recommended standard vaccinations and SARS-CoV-2 vaccinations. The coloured elements show the significant positive (green) or negative (red) associations of socio-demographic, clinical variables, personality traits, psychopathological variables, as well as traumatic impact with the willingness regarding (1) recommended standard vaccinations and (2) SARS-CoV-2 vaccination during the baseline investigation and the two follow-ups. *CIS* Clinically isolated syndrome, *MS* Multiple Sclerosis, *PPMS* Primary progressive MS, *RRMS* Relapsing remitting MS, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SPMS* Secondary progressive MS.

would be in favour of getting vaccinated against SARS-CoV-2, while 18.9% were undecided and 7.2% were unwilling to get vaccinated[30]. Consequently, the vaccination willingness in our surveyed MS patients at the time of the 1st follow-up was about 10% lower than in the general population.

A general vaccination hesitancy can have many causes[44]. The perceived absence of feeling danger can be due to various thoughts. Perceiving a lack of usefulness of the vaccination as well as the feeling that the situation is not serious may be one subjective assumption. The personal risk may be considered as low, which can cause a lower vaccination willingness. A high awareness for risk perception like, the vaccine has not been tested adequately or has been tested too quickly after insufficient research, can lead to a refusal of a vaccination. The media documentation of the economic goals of vaccine manufacturers can contribute to patient uncertainty[45,46]. The fear of affecting the personal health negatively by a vaccine can additionally cause a refusal of vaccination, in terms of being enabled to father healthy children any longer; to unfavourably impact on a chronic illness; or to expose the body to a foreign, unfamiliar substance at all[44]. The lack of knowledge or belief that being vaccinated protects others as well as a low social pressure are important factors as well as the conviction that others also refuse the vaccination. The general interaction with the health care system like the frequency of consulting physicians or getting direct recommendations could be additional decisive factors. However, our findings suggest the substantial role of general, pre-pandemic attitudes towards recommended vaccinations regarding the willingness to get vaccinated against SARS-CoV-2. The results pointed to a high stability of vaccination willingness independent on the course of the pandemic and on the discussion of this topic in the media.

An important socio-demographic variable associated with SARS-CoV-2 vaccination willingness was age. The older the patients, the higher their acceptance to get a SARS-CoV-2 vaccine, which was also found in other studies in the general U.S.-population[47]. A higher perception of risks, due to a longer time of experience, could be one reason. Several other socio-demographic and clinical characteristics like sex, number of comorbid illnesses (like in an Indian study[48]), medication, or a high disability level had no substantial impact on vaccination willingness in our study. However, a sex difference was found in a study from Israel concerning vaccination attitudes in the younger population, in contrast to our data. Females were much more sceptical regarding an immediate vaccination against SARS-CoV-2 than males in the Israeli study (vaccination willingness: 12.0–13.6% vs. 23.1–27.3%)[49].

In our study, several psychological factors were found as important influences on a decision about getting vaccinated. Attitudes towards vaccination and future vaccination behaviour correlated with factors regarding mental health and personality characteristics. These included comorbidity with depression, traumatic burden, and increased Neuroticism. Poor evidence is available regarding the plights of MS-patients during the SARS-CoV-2 pandemic. In three studies, participants from pre-pandemic investigations were re-assessed to determine, what type of stress changed disorders within studied intervals. Mixed results suggested little or no change in anxiety or depression[50]. Another investigation revealed a negative correlation to vaccination readiness in depression[51]. Even though a close association between mental health and chronic diseases was reported in several studies, we could only determine this for depression[52,53]. The more depressed the MS-patients were, the lower the indicated change

of attitudes towards the generally recommended vaccinations due the pandemic and the discussion in the media at both follow-up investigations of our study. Furthermore, the more intensively traumatized by the pandemic, the governmental measures against the pandemic and the related discussion in the media, the MS-patients were open to accept a SARS-CoV-2 vaccine at the 1st follow-up, but not at the 2nd follow-up. When individuals have been traumatized by the pandemic, it might have been a meaningful consequence to do everything to avoid an infection and to do, what is possible, to avoid a serious course of COVID-19. A vaccination currently seems to be the only recommended opportunity. The difference of the associations between the two follow-ups might be caused by the long-lasting course of the pandemic and by the increasingly upcoming negative arguments on the conduct of the studies, the decreasing vaccine efficacy over time and the various side-effect potential as well as management of the several vaccines in the media[54–60].

Furthermore, the more outgoing, energetic, and assertive (high on Extraversion) and the more exploratory, curious, and enthusiastic (high on Novelty Seeking; Cloninger et al.[37]) the MS-patients were, the more likely they reported their willingness to accept recommended vaccinations at the baseline investigation. The more organized and the more diligently working toward achieving goals (high on Conscientiousness) and the more anxious, angrily hostile, depressed, and vulnerable (high on Neuroticism) the MS-patients were, the less they changed their attitudes towards recommended vaccinations due to the pandemic at both follow-up assessments. This indicates that different personality characteristics can cause stability of attitudes. On the one hand, stability could be due to goal directed behaviour and, on the other hand, anxiety, depressed mood and vulnerability could lead to an avoidance of change. However, the more responsible, reliable, and goal-oriented (high on Self-Directedness) and the more empathic, supportive, and principled (high on Cooperativeness) the MS-patients were, the more their attitudes towards governmentally recommended vaccinations changed in the direction of acceptance due to the pandemic between baseline assessment and both follow-up assessments. According to our data, highly mature individuals seem to accept and follow recommended vaccinations more often than less mature individuals.

The generalizability of our findings is somewhat limited by the included sample size, the drop-out rate of participants from baseline to the 2nd follow-up (however without a systematic loss to follow-up) and the lack of a control group of people without MS. The validity of the data might be limited since the follow-up data exclusively were patient-reported. However, it represents one of the rare studies to explore SARS-CoV-2 and general vaccination willingness among MS-patients, and, according to our best knowledge, it is so far the only one with two follow-up assessments. Furthermore, this represents the 1st investigation recognising associations between personality characteristics and psychopathological background variables with willingness of vaccination against SARS-CoV-2.

In summary, our present study suggested that about two thirds of German MS-patients analysed were willing to receive a SARS-CoV-2 vaccine. Important variables associated with vaccination willingness, reported in a previous study[34] were socio-demographic variables such as higher age and personality characteristics such as Novelty Seeking as well as Extraversion. Changes to pro-vaccination attitudes during the follow-ups were seen in individuals with higher scores in Self-Directedness and Cooperativeness. Factors that were continuously negatively correlated to the acceptance of a vaccination against SARS-CoV-2 were depression, Neuroticism, and Conscientiousness. Personality characteristics and their impact on vaccination settings were investigated the 1st time.

Our study underlines the importance of the factors related to SARS-CoV-2 vaccination acceptance, which can be used for personalized discussions with vaccine-insecure MS-patients. Besides concerns about vaccination in general and objections against the novel type of nucleic acid-based vaccines against SARS-Cov-2, certain personality characteristics as well as psychopathological conditions, depression in particular, should be considered by doctors when talking to MS-patients about getting vaccinated. It is a big challenge to reach much higher vaccination rates than currently achievable. In this context, the question for future studies is whether the availability and approval of other types of vaccines against SARS-CoV-2, such as inactivated vaccines (e.g. Novavax [NVX-CoV 2373] or Valneva [VLA 2001]), will fundamentally change the willingness to become vaccinated.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions
F.H. substantially contributed to the conception, to the study design and to the 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, to the study design and to the data interpretation. They critically revised the completed final draft for important intellectual content. J.B., B.S., P.M., K.B., 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, to the study design and to the 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.

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to N.F.

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8.3 Publikation 3

Vaccination status and self-reported side effects after SARS-CoV-2 vaccination in relation to psychological and clinical variables in patients with multiple sclerosis

Autoren: **Katja Burian**, Felicita Heidler, Niklas Frahm, Michael Hecker, Silvan Elias Langhorst, Pegah Mashhadiakbar, Barbara Streckenbach, Julia Baldt, Janina Meißner, Jörg Richter, Uwe Klaus Zettl

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Vaccination status and self-reported side effects after SARS-CoV-2 vaccination in relation to psychological and clinical variables in patients with multiple sclerosis

Katja Burian[1,2]✉, Felicita Heidler[2], Niklas Frahm[1], Michael Hecker[1], Silvan Elias Langhorst[1], Pegah Mashhadiakbar[1], Barbara Streckenbach[1,2], Julia Baldt[1,2], Janina Meißner[1,2], Jörg Richter[2,3,4] & Uwe Klaus Zettl[1]

The recent SARS-CoV-2 pandemic and the vaccination campaign posed a challenge to patients with autoimmune disease, such as multiple sclerosis (MS). We aimed for investigating whether psychological/sociodemographic/clinical characteristics of MS patients are associated with SARS-CoV-2 vaccination status and self-reported vaccination side effects (SEs). We have asked patients with MS about their willingness to receive recommended standard vaccinations pre-pandemically since June 2019. Between 10/2021 and 01/2022, we surveyed 193 of these MS patients about their current SARS-CoV-2 vaccination status, their perception of vaccination-related SEs, and reasons for and against SARS-CoV-2 vaccination. 75.6% of the patients declared their willingness to receive standard vaccinations before the pandemic. 84.5%, 78.2%, and 13.0% of the patients had received the first, second, and third SARS-CoV-2 vaccination, respectively, until the follow-up survey. The most common reason for not getting vaccinated against SARS-CoV-2 was concern about possible side effects (82.1%), followed by the belief that the vaccines had not been adequately tested (64.3%). Vaccination-related SEs were reported by 52.8% of the patients. Younger age, higher education, lower degree of disability, relapsing disease course, shorter disease duration, not receiving a disease-modifying therapy and higher anxiety and depression levels were associated with the occurrence of certain vaccination-related SEs. Concerns about novel vaccines are widespread among MS patients and necessitate targeted education of the patients, especially to those with more severe psychopathological symptoms (anxiety or depression) and those who are generally skeptical of vaccination.

Keywords SARS-CoV-2, Multiple sclerosis, Vaccination willingness, Vaccination status, Vaccination hesitancy, Side effects

Multiple sclerosis (MS) is the most common immune-mediated disease of the central nervous system that can lead to permanent disability[1]. There are worldwide around 2.8 million people affected by this disease. In Germany, approximately 280,000 people suffer from MS[2,3]. The etiology of MS has not been comprehensively clarified yet. In addition to genetic predisposition, the risk of MS is influenced by environmental and lifestyle factors such as

[1]Neuroimmunology Section, Department of Neurology, Rostock University Medical Center, Gehlsheimer Straße 20, 18147 Rostock, Germany. [2]Department of Neurology, Ecumenic Hainich Hospital gGmbH, Pfafferode 102, 99974 Mühlhausen, Germany. [3]Faculty of Health Sciences, University of Hull, Cottingham Rd, Hull HU6 7RX, UK. [4]Durham Law School, The Palatine Centre, Durham University, Stockton Rd, Durham DH1 3LE, UK. ✉email: katja.burian@gmx.de

vitamin D deficiency, nicotine abuse, obesity, and infection with Epstein-Barr virus[4–6]. MS is characterized by heterogeneous symptoms[7,8].

Immunosuppressive as well as immunomodulatory disease-modifying therapies (DMTs) are widely used to treat MS. However, the use of certain DMTs, particularly B-cell-depleting therapies, is associated with an increased risk of infection. The highly contagious RNA virus severe acute respiratory syndrome type 2 (SARS-CoV-2) can cause the coronavirus 2019 (COVID-19) disease. Severe courses of this disease can go along with a severe acute respiratory distress syndrome, which is associated with increased mortality and thus requires intensive medical treatment[9]. Therefore, the SARS-CoV-2 pandemic starting in 2020 and the risk of infection with SARS-CoV-2 posed a challenge to patients with MS[10–12].

COVID-19 can include a variety of symptoms such as fever, sore throat, cough, chest and muscle pain, dyspnea, confusion, anosmia, ageusia, and headache[13]. The disease can progress to a life-threatening respiratory insufficiency also affecting the heart, kidney, liver, or the nervous system[14,15]. Treatment with DMTs in MS is associated with an increased risk of severe SARS-CoV-2 infection[16,17]. Studies have shown that an important risk factor for COVID-19 infection is the use of B-cell-depleting drugs[18]. It was shown that the frequency of having a severe clinical course of COVID-19 infection was 2–3 times higher with anti-CD20 therapy than with other DMTs[19]. A French study also showed that older age, male sex, obesity and a higher degree of disability are independent risk factors for SARS-CoV-2 infection[20]. More specifically, patients with an Expanded Disability Status Scale (EDSS) score higher than 6 had a sevenfold higher risk of suffering from a serious course of COVID-19[20]. The study also indicated that there is a 60% higher risk of having a severe course of COVID-19 for every 10 years of increasing age[20].

The newly developed vaccines against SARS-CoV-2 played a central role in the global strategy to control the pandemic[21,22]. In Germany, four vaccines against SARS-CoV-2 had been approved by the European Medicines Agency (EMA) and recommended by the German Standing Committee on Vaccination (STIKO) of the Robert Koch Institute (RKI) at the time of this study: the mRNA-based vaccines tozinameran (BNT162b2, Comirnaty®) and elasomeran (mRNA-1273, Spikevax®), which contain specific mRNA molecules that encode protein antigens (Zhang et al. 2019), and the two vector-based vaccines AZD1222 (Vaxzevria®) and Ad26.COV2.S (Jcovden®)[23].

Various sociodemographic and clinical factors as well as psychologic characteristics can impact the willingness or unwillingness to become vaccinated against SARS-CoV-2[24]. Risk perception and fear of infectious diseases also appear to be important predictors of vaccination acceptance[25]. A major reason for people to become vaccinated was to protect themselves and others from a severe COVID-19 course, but there were also concerns regarding the safety of the vaccines[26]. The occurrence of severe thrombotic events due to vaccination with AZD1222 in a number of cases led to further uncertainty in the population[27]. Although studies showed that SARS-CoV-2 vaccines are safe in patients with MS, with no increased risk of worsening of the disease or relapse[28,29], the rapid development of vaccines and the lack of information and experience about (long-term) side effects of the vaccines administered were reasons leading to skepticism among patients with MS[30], but also in the general population[31]. On the one hand, some patients with autoimmune diseases, such as MS, have initially raised concerns that disease progression may be exacerbated by vaccination[32]. On the other hand, MS patients have an increased risk of morbidity and mortality due to infections[33,34]. Even though numerous studies have disproved vaccinations as a trigger for MS or increased disease activity[35,36], some MS patients have lasting concerns about being vaccinated[28].

The aim of the present study was, on the one hand, to investigate whether a high general willingness to be vaccinated prior to the pandemic was associated with subsequent actual SARS-CoV-2 vaccination in patients with MS. On the other hand, we determined the reasons for or against SARS-CoV-2 vaccination with the new nucleic acid-based vaccines and how the patients' attitudes towards recommended standard vaccinations have developed during the pandemic. We also investigated the associations between psychological, sociodemographic, and clinical characteristics and the number of SARS-CoV-2 vaccinations received as well as the vaccination-related adverse events perceived.

Methods

Patient enrollment and consent

The data had been collected at two centers (Department of Neurology at the Rostock University Medical Center and Ecumenical Hainich Hospital Mühlhausen, Germany). Inclusion criteria for participants were an age ≥ 18 years and a confirmed diagnosis of a clinically isolated syndrome (CIS) or MS according to the revised McDonald criteria[37]. Written informed consent to participate in this study was obtained from all patients. Exclusion criteria were unwillingness to participate and diagnoses other than CIS or MS. The study was approved by the ethics committees of the University of Rostock (permit number A 2019-0048) and the State Medical Association of Thuringia and conducted in accordance with the Declaration of Helsinki and the European data protection regulations.

Data collection

At baseline, sociodemographic data, e.g., age, sex, and educational level, as well as clinical data, e.g., course of MS, duration of disease, degree of disability according to the EDSS[38], and comorbidities of the patients, have been acquired[24]. Comorbidities were categorized by organ system. These were as follows: cardiovascular, chronic inflammatory, pulmonary, neurological, metabolic, psychiatric, orthopedic, gastrointestinal, dermatological, ophthalmologic, otolaryngologic, urologic or gynecologic diseases, endocrinological, hematological, pain, cancer, and other diseases. The general willingness to receive the recommended vaccinations was surveyed in the form of a questionnaire since June 2019 and thus before the SARS-CoV-2 outbreak. The standard vaccinations (basic immunization and booster vaccinations) are listed in the STIKO vaccination calendar[39]. The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological variables. The HADS is a self-report

questionnaire to assess the severity of depression and anxiety. It consists of 14 questions that are answered on a 4-point Likert scale[40]. The classification of the patients was done according to Marrie et al.[41]: Scores of 0–7 points were considered normal, scores of 8–10 points were considered borderline, and scores of 11–21 were considered abnormal[42]. The data were collected during an ambulatory neurology appointment (outpatients) or during a hospital stay (inpatients). The baseline data were collected in Mühlhausen by JB and BS and in Rostock by PM, SEL and NF. Further details on the baseline data collection can be found in the published articles by Heidler et al.[43] and Streckenbach et al.[44]. Of the original 404 patients in the baseline study, 211 patients did not participate in this follow-up study.

Approximately one year after the first COVID-19 vaccines were authorized in the EU (i.e., between October 2021 and the end of January 2022), we examined the patients about their SARS-CoV-2 vaccination status and vaccination-related adverse events. For the follow-up survey, the patients were asked the same set of questions in the same order in the form of a structured interview. The questionnaire consisted of 30 questions with sub-items. In some cases, more than one answer was possible. The data were collected and analyzed by PM, SEL and NF at the Department of Neurology at the Rostock University Medical Center. At the Ecumenical Hainich Hospital Mühlhausen, this was done by KB, JR and FH. We obtained information on administered vaccinations with the newly developed SARS-CoV-2 vaccines in the patients with MS. All vaccines that were approved in Germany up to the end of the survey period were recorded in the standardized interview: The two mRNA-based vaccines tozinameran and elasomeran and the two viral vector-based vaccines Ad26.COV2.S and AZD122. The protein-based vaccine NVX-CoV2373 (Nuvaxovid®), which was not available until the end of the survey period[45], was not included in this study. The vaccinations were differentiated into first vaccination, second vaccination, and third vaccination. We also asked the changes of patients' attitudes towards vaccination recommendations during the pandemic. Data on the perceived side effects after each SARS-CoV-2 vaccination administered were collected. A distinction was made between local (swelling, redness, or pain at the injection site) and systemic side effects (chest pain, fatigue, fever and chills, palpitations, headache, shortness of breath, muscle and joint pain, dizziness, malaise, or other adverse effects). The period for recording side effects after vaccination was not limited. In addition, the patients were asked about reasons for or against SARS-CoV-2 vaccination (multiple answers were possible) and whether they had experienced MS relapses or MS progression after a SARS-CoV-2 vaccination. In this context, self-reporting was used to ask after which vaccination a disease worsening or relapse occurred without specifying a time frame. It should be noted that due to the study design, the patients were not interviewed after a predetermined period of time following vaccination.

Statistical analysis

The numerical and categorical data were recorded in SPSS. All data were pseudonymized. The statistical analyses were conducted using SPSS (version 27) and R (version 4.1.2). Descriptive statistics have been calculated for the sociodemographic and clinical data as well as for the vaccination data, including self-reported side effects. The chi-squared-test was used to test whether certain side effects occurred more or less frequently after administration of a particular SARS-CoV-2 vaccine as compared to other SARS-CoV-2 vaccines. Fisher's exact test was used to evaluate the association between sex and the occurrence of side effects after SARS-CoV-2 vaccination. Binary logistic regression analyses were performed to assess the relationship of sociodemographic, clinical, and psychological variables as well as the pre-pandemic willingness to receive recommended standard vaccinations with SARS-CoV-2 vaccination status as well as the occurrence of side effects after SARS-CoV-2 vaccination. This yielded odds ratios (ORs) with 95% confidence intervals (CIs). As the number of patients with CIS was small, CIS and relapsing–remitting MS (RRMS) patients were combined for the statistical analysis. A p-value of < 0.05 was set as the criterion for statistical significance.

Results

Vaccination willingness and psychological characteristics of the patients

A total of 193 patients were included in this study (Table 1). The cohort was composed of patients with CIS ($n = 12$), RRMS ($n = 121$), secondary progressive MS (SPMS) ($n = 48$), and primary progressive MS (PPMS) ($n = 12$). The proportion of female patients was 67.9% ($n = 131$). A subset of 150 patients received a DMT for MS (77.7%). The DMTs and comorbidities of the patients are provided in Supplemental Tables S3 and S4.

146 of the patients (75.6%) stated that they intend to have a complete standard vaccination status, i.e., that they are willing to follow the official vaccination recommendations in Germany[39].

On the HADS-A scale, the score was in the normal range for 98 patients, in the borderline range for 50 patients, and in the abnormal range for 39 patients. A normal score was determined on the HADS-D scale for 128 patients. A borderline HADS-D score was obtained for 32 patients and an abnormal score for 26 patients. Seventeen out of the 26 (65.4%) patients with an abnormal HADS-D score also had an abnormal HADS-A score (Table 1).

Reasons for or against SARS-CoV-2 vaccination

Among the patients who received at least one vaccination against SARS-CoV-2, protection against a serious disease was the most common reason (90.1%). The most common reason against SARS-CoV-2 vaccination among the unvaccinated patients was concern about possible side effects (82.1%) (Fig. 1).

Of the 30 patients who were not vaccinated against SARS-CoV-2, eight reported that they had developed or increased a negative attitude toward standard vaccinations because of the coronavirus pandemic. Of the 30 unvaccinated patients, 16 patients (53.3%) had a positive attitude towards recommended standard vaccinations pre-pandemic. Of the 163 patients who were vaccinated at least once against SARS-CoV-2, 130 patients (79.8%) had a positive attitude toward the recommended standard vaccinations. In contrast, a negative attitude toward

Characteristic	
Sex, *n* (%)	
Men	62 (32.1)
Women	131 (67.9)
Age (years), mean ± SD	48.0 ± 12.2
Education (years), mean ± SD	10.3 ± 1.1
Willingness to receive recommended vaccinations (pre-pandemic, *n* (%))	
Yes	146 (75.6)
No	47 (24.4)
Psychological variables[1]	
HADS-A score, *n* (%)	
Normal	98 (52.4)
Borderline	50 (26.7)
Abnormal	39 (20.9)
HADS-D score, *n* (%)	
Normal	128 (68.8)
Borderline	32 (17.2)
Abnormal	26 (14.0)
Disease duration (years), median (range)	9 (0–39)
Disease course, *n* (%)	
CIS/RRMS	133 (68.9)
SPMS	48 (24.9)
PPMS	12 (6.2)
EDSS score, mean ± SD	3.5 ± 2.3
Medical care, *n* (%)	
Inpatient	29 (15.0)
Outpatient	164 (85.0)
Use of DMT, *n* (%)	
Yes	150 (77.7)
No	43 (22.3)
Comorbidities, *n* (%)	
Yes	142 (73.6)
No	51 (26.4)
Prior infection with SARS-CoV-2[2], *n* (%)	
Yes	10 (5.2)
No	183 (94.8)

Table 1. Characteristics of the patients ($N = 193$). *CIS* clinically isolated syndrome, *DMT* disease-modifying therapy approved for the treatment of multiple sclerosis, *EDSS* expanded disability status scale, *HADS-A* subscale of anxiety of the hospital anxiety and depression scale, *HADS-D* subscale of depression of the hospital anxiety and depression scale, *MS* multiple sclerosis, *n* number of patients, *PPMS* primary progressive MS, *RRMS* relapsing–remitting MS, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SD* standard deviation, *SPMS* secondary progressive MS. [1]There were missing values for HADS-A ($n = 6$) and HADS-D ($n = 7$). Only valid data were considered for the analyses. [2]Prior to the survey regarding the SARS-CoV-2 vaccination status.

the recommended standard vaccinations prior to the coronavirus pandemic was reported by only 33 (20.2%) of the 163 patients who had received at least one vaccination against SARS-CoV-2 (Supplemental Table S2).

SARS-CoV-2 vaccination status

Administration of the first, second, and third SARS-CoV-2 vaccine doses was reported by 163 (84.5%), 151 (78.2%) and 25 (13.0%) of the 193 MS patients, respectively (Table 2). There were 138 patients who had received only mRNA-based vaccines, and 13 patients had received only vector-based SARS-CoV-2 vaccines. At the second vaccine administration, 10 patients switched from previously receiving a vector-based vaccine to an mRNA-based vaccine. At the third vaccine administration, 2 patients switched to an mRNA vaccine and thus had a heterologous SARS-CoV-2 vaccination scheme. No patient switched from mRNA-based vaccines to vector-based vaccines. The date of the first SARS-CoV-2 vaccination was between January 2021 and January 2022.

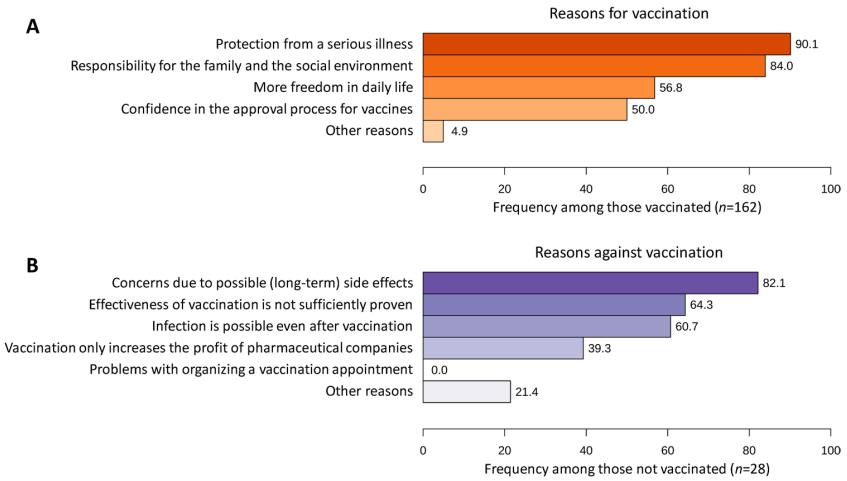

Figure 1. Prevalence of reasons for and against SARS-CoV-2 vaccination. MS patients with and without immunization against SARS-CoV-2 were asked about the reasons for (**A**) and against (**B**) the vaccination, respectively. It was possible to provide more than one reason. Three patients did not provide any information, which resulted in missing values. *MS* multiple sclerosis, *n* number of patients, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2.

SARS-CoV-2 vaccination[1]	1st vaccination	2nd vaccination	3rd vaccination[2]
Vaccination received, *n* (%)			
Yes	163 (84.5)	151 (78.2)	25 (13.0)
No	30 (15.5)	42 (21,8)	167 (87.0)
Type of vaccine received, *n* (%)			
Tozinameran	126 (77.3)	128 (84.8)	21 (84.0)
Elasomeran	12 (7.4)	13 (8.6)	4 (16.0)
AZD1222	18 (11.0)	9 (6.0)	0 (0)
Ad26.COV2.S	7 (4.3)	1 (0.7)	0 (0)

Table 2. SARS-CoV-2 vaccination status of the patients with multiple sclerosis ($N = 193$). *N* number, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2. [1]Vaccinations until the time point of data collection, which ended January 2022 (none of the patients had received more than three COVID-19 vaccinations). [2]One case with missing data was not considered in the frequency tabulations.

Factors associated with SARS-CoV-2 vaccine administration in patients with MS

Patients with a higher willingness to undergo the recommended standard vaccinations prior to the pandemic were significantly more likely to have received the first and second vaccination against SARS-CoV-2 (1st: OR = 3.447, $p = 0.003$; 2nd: OR = 3.155, $p = 0.002$) (Table 3). Conversely, patients with borderline HADS-D scores were significantly less likely to have been vaccinated against SARS-CoV-2. For the borderline and abnormal HADS-A and HADS-D categories, ORs < 1 consistently resulted for the first and second vaccinations, implicating that anxiety and depression were negatively associated with getting vaccinated against SARS-CoV-2 in general. There were no significant associations with sociodemographic data for any vaccination stage. Likewise, the type of MS course and the degree of disability (according to the EDSS) were not significantly associated with SARS-CoV-2 vaccinations. There was also no significant difference between the sexes with regard to the different vaccines administered (first SARS-CoV-2 vaccination: Fisher`s exact test $p = 0.176$, second SARS-CoV-2 vaccination: $p = 0.171$, third SARS-CoV-2 vaccination: $p = 0.959$). Disease duration was the only clinical variable that was significantly associated with receiving the third SARS-CoV-2 vaccination. More specifically, patients with longer disease duration were more likely to have received a third SARS-CoV-2 vaccination (OR = 1.051, $p = 0.031$) (Table 3). The comparison between SARS-CoV-2 vaccinated and unvaccinated patients in terms of individual characteristics can be found in Supplemental Table S2. Regarding DMTs and comorbidities, there was no significant difference between patients who had been vaccinated at least once against SARS-CoV-2 and unvaccinated patients (Supplemental Tables S3 and S4).

Parameter	1st vaccination			2nd vaccination			3rd vaccination		
	OR	95% conf. interv.	*p*-value	OR	95% conf. interv.	*p*-value	OR	95% conf. interv.	*p*-value
Sociodemographic data									
Sex (ref. male)	0.734	0.307–1.756	0.487	1.229	0.599–2.523	0.574	1.598	0.604–4.225	0.345
Age (in years)	1.027	0.994–1.060	0.108	1.018	0.989–1.046	0.223	0.999	0.966–1.034	0.973
Education (in years)	1.071	0.752–1.525	0.703	1.020	0.753–1.383	0.897	1.121	0.785–1.600	0.531
Willingness to receive recom-mended vac-cinations	3.447	1.529–7.769	**0.003**	3.155	1.516–6.568	**0.002**	0.810	0.316–2.079	0.661
Psychological variables									
HADS-A (ref. normal)									
Borderline	0.542	0.223–1.318	0.177	0.659	0.300–1.451	0.301	1.066	0.370–3.074	0.906
Abnormal	0.841	0.295–2.398	0.746	0.994	0.396–2.492	0.989	1.150	0.372–3.556	0.809
HADS-D (ref. normal)									
Borderline	0.391	0.155–0.986	**0.047**	0.463	0.198–1.085	0.076	0.431	0.094–1.972	0.278
Abnormal	0.842	0.258–2.745	0.776	0.809	0.294–2.225	0.681	0.539	0.117–2.491	0.429
Clinical data									
Disease duration (in years)	0.984	0.942–1.027	0.455	1.004	0.965–1.045	0.847	1.051	1.004–1.099	**0.031**
Disease course (ref. CIS/RRMS)									
SPMS	1.098	0.435–2.776	0.843	1.262	0.550–2.898	0.583	1.280	0.491–3.335	0.614
PPMS	0.938	0.192–4.589	0.937	0.874	0.222–3.433	0.847	1.462	0.294–7.284	0.643
EDSS score	0.945	0.796–1.122	0.517	0.988	0.849–1.149	0.875	1.062	0.882–1.279	0.524
Medical care (ref. inpatient)	1.522	0.561–4.126	0.409	1.173	0.463–2.969	0.737	0.924	0.292–2.921	0.893
Use of DMT	1.626	0.683–3.871	0.272	1.548	0.712–3.368	0.270	1.178	0.415–3.349	0.758
Comorbidity (ref. no)	0.656	0.251–1.709	0.388	0.486	0.201–1.177	0.110	1.133	0.425–3.019	0.803
Prior infection with SARS-CoV-2 (ref. no infection)	1.695	0.207–13.892	0.623	0.393	0.106–1.464	0.163	0.731	0.089–6.034	0.771

Table 3. Associations of SARS-CoV-2 vaccination status with patient characteristics and pre-pandemic standard vaccination willingness in patients with MS. *CIS* clinically isolated syndrome, *conf. interv.* confidence interval, *DMT* disease-modifying therapy approved for the treatment of multiple sclerosis, *EDSS* expanded disability status scale, *HADS-A* subscale of anxiety of the hospital anxiety and depression scale, *HADS-D* subscale of depression of the Hospital Anxiety and Depression Scale, *MS* multiple sclerosis, *OR* odds ratio from univariable logistic regression analysis, *PPMS* primary progressive MS, *ref.* reference, *RRMS* relapsing–remitting MS, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SPMS* secondary progressive MS. Significant values are given in bold.

Side effects of SARS-CoV-2 vaccinations

Of the 163 patients who received at least one SARS-CoV-2 vaccination, 52.8% reported an adverse reaction. A subset of 44.2% of the patients reported systemic side effects, and 28.8% of the patients reported local side effects after any vaccination. After administration of the first SARS-CoV-2 vaccination, 39.9% of the patients reported side effects. The most frequently reported systemic side effects after the first vaccination, regardless of the vaccine type administered, were fatigue (20.2%), muscle and joint pain (12.9%), and headache (11.0%). After the second vaccination with elasomeran, fever or chills and chest pain occurred in some patients, unlike after the first administration of elasomeran. Moreover, the rate of fatigue after the second elasomeran administration was 53.8% and thus considerately higher than after the first vaccination with elasomeran. Regarding AZD1222, the most frequently reported adverse events after the first vaccination were headache and fatigue, each affecting 27.8% of the patients. In comparison, for Ad26.COV2.S, the most common side effects were fatigue, headache, and muscle/joint pain. Common side effects of tozinameran were fatigue and injection site reactions. There were only minor differences in the side effect profiles when comparing the four vaccines analyzed. Patients who initially received a vector-based vaccine reported headache significantly more frequently than patients who initially received an mRNA-based vaccine (chi-squared test $p = 0.034$). On the other hand, after the second vaccination against SARS-CoV-2, complaints about fatigue were reported only by patients who received mRNA vaccines ($p = 0.009$) (Fig. 2).

Relapse or worsening of MS after SARS-CoV-2 vaccination

Only few patients ($n = 7$, $n = 5$, $n = 0$ after the first, second, and third vaccination, respectively) self-reported that they had experienced relapse activity or disease worsening after a SARS-CoV-2 vaccination. Among them, six patients reported worsening after the first administration of tozinameran and one patient after the first administration of AZD1222. The five patients who reported disease worsening after the second SARS-CoV-2

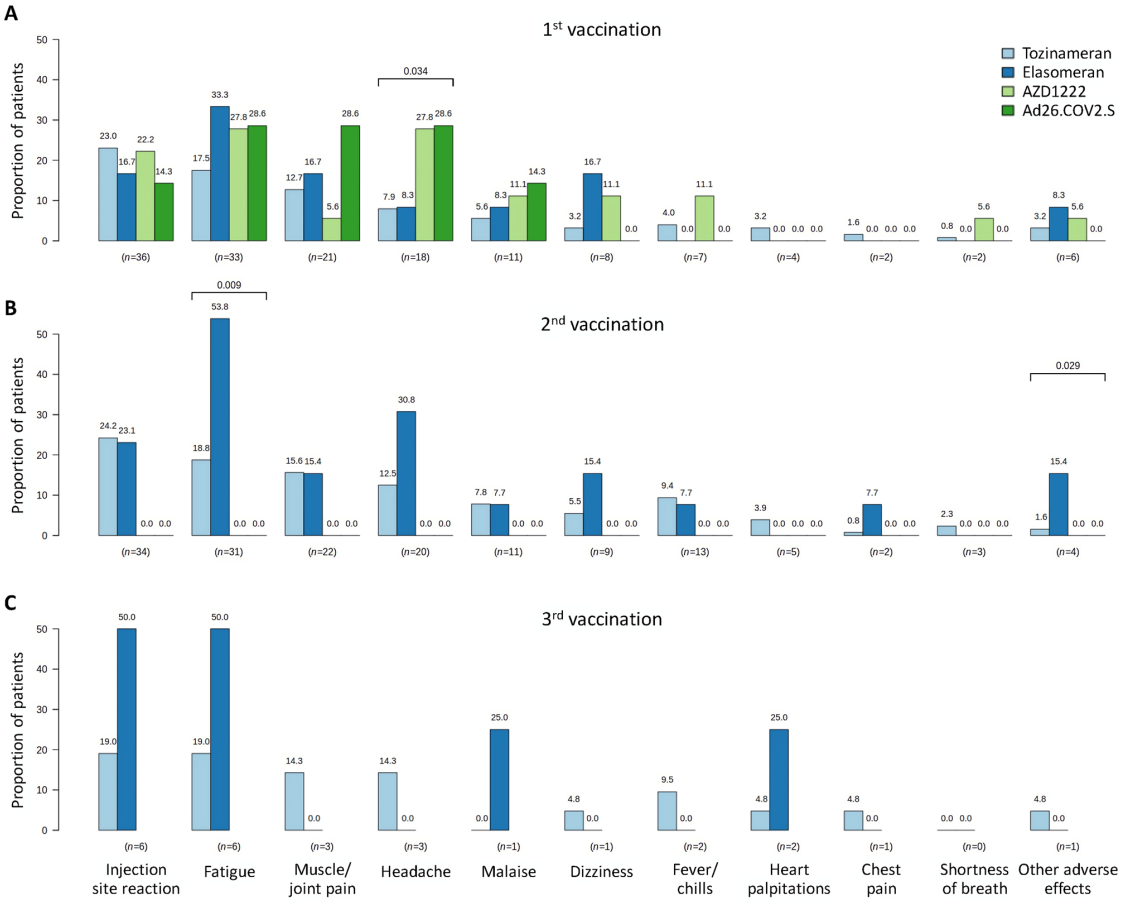

Figure 2. Adverse effects after SARS-CoV-2 vaccination in the patient cohort ($N = 193$). This figure shows the frequency of adverse effects (in descending order) after (**A**) the first ($n = 163$), (**B**) the second ($n = 151$) and (**C**) the third vaccination ($n = 25$). Significant differences between vaccine groups are indicated by brackets with chi-square test p-values (not adjusted for multiple testing) provided above. After the first SARS-CoV-2 vaccination, headache was more often reported by MS patients who received a vector-based vaccine (green bars), whereas fatigue was more often reported by patients who received elasomeran for the second vaccination (dark blue bar). However, it should be noted that the number of cases was sometimes small, in particular with regard to the third vaccination. *MS* multiple sclerosis, *n* number of patients, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2.

vaccination received tozinameran. Of the patients who reported a relapse or worsening of their disease, eight were taking DMTs.

Factors associated with side effects following SARS-CoV-2 vaccine administration in patients with MS

Overall, 61.5% of the women and 35.2% of the men reported side effects after any SARS-CoV-2 vaccination (Fisher's exact test $p = 0.003$). Women were more likely than men to report headache ($p = 0.008$) and muscle/joint pain ($p = 0.023$) after the second vaccination than men.

Further analyses of psychological, sociodemographic, and clinical data in relation to specific adverse events following individual administrations of SARS-CoV-2 vaccines showed nominally statistically significant associations for HADS-A score and HADS-D score, age, education, EDSS score, disease course, disease duration, DMT utilization, and previous SARS-CoV-2 infection (Supplemental Table S1). For example, it was found that patients with abnormal HADS-D scores reported significantly more often that they experienced dizziness after the initial SARS-CoV-2 vaccination (OR = 5.944, $p = 0.018$). Patients who were not willing to receive recommended standard vaccinations at baseline also reported significantly more often dizziness after the first SARS-CoV-2 vaccination (OR = 4.345, $p = 0.046$).

There was an association between younger age and perception of fatigue symptoms after the first SARS-CoV-2 vaccination (OR: 0.969, 95% CI 0.939–1.000, $p = 0.049$). Following the second SARS-CoV-2 vaccination, fever or chills (OR: 0.923, 95% CI 0.876–0.973, $p = 0.003$), headache (OR: 0.954, 95% CI 0.917–0.992, $p = 0.020$), and muscle and joint pain (OR: 0.954, 95% CI 0.918–0.991, $p = 0.015$) occurred more frequently in patients of younger age. MS disease duration was positively associated with self-reported heart palpitations after the first SARS-CoV-2 immunization (OR: 1.110, 95% CI 1.004–1.226, $p = 0.041$), while it was negatively associated with fatigue (OR: 0.944, 95% CI 0.894–0.997, $p = 0.038$), headache (OR: 0.917, 95% CI 0.852–0.988, $p = 0.023$), fever/chills (OR: 0.893, 95% CI 0.806–0.989, $p = 0.031$) as well as muscle and joint pain (OR: 0.915, 95% CI 0.852–0.984, $p = 0.016$) after the second SARS-CoV-2 vaccination. PPMS patients did not show a significant difference in the occurrence of post-vaccination adverse events. Patients with SPMS, however, were less likely to experience muscle and joint pain (OR: 0.116, 95% CI 0.015–0.901, $p = 0.039$) and fatigue (OR: 0.260, 95% CI 0.074–0.918, $p = 0.036$) after the second SARS-CoV-2 vaccination than patients with CIS or RRMS (Supplemental Table S1).

Only one of the 163 patients vaccinated against SARS-CoV-2 reported developing an anti-attitude towards standard vaccinations in the course of the pandemic. This patient experienced fatigue, headache, and malaise following both the first and second SARS-CoV-2 vaccination.

Discussion

Given the increased risk of infection in MS patients treated with DMTs[46–49], the enhancement of immune response against pathogens is an important issue[28,50,51]. In this study, we provide information on the actual SARS-CoV-2 vaccination rate in MS patients approximately one year after the approval of first vaccines and the vaccination side effect profile of the patients in relation to the pre-pandemic willingness to receive recommended standard vaccinations as well as psychological, sociodemographic, and clinical variables.

More than three quarters (84.5%) of the surveyed patients received at least one SARS-CoV-2 vaccination. This is similar to the actual vaccination rate of the general population in Germany (78.0%) reported by the RKI[52]. There was also no apparent difference in the rate of receiving a second vaccination in our study as compared to the general population (78.2% vs. 76.4%). Regarding the frequency of the third vaccination, no adequate comparison with the general population could be made due to the survey period, as most patients (87.0%) had not yet received a third SARS-CoV-2 vaccination at the time of the survey, presumably because a booster vaccination was not yet recommended for most of them as the second vaccination was less than 6 months ago[53].

This study revealed a relatively high actual SARS-CoV-2 vaccination rate compared to 65% of MS patients with willingness to become vaccinated against SARS-CoV-2 in a previous study by Heidler et al.[24]. We were able to show that patients who were willing to receive the recommended standard vaccinations prior to the pandemic were also more often vaccinated against SARS-CoV-2. The positive vaccination attitude seems to be a predictor for the acceptance of the novel SARS-CoV-2 vaccines. Other reasons for this could be extensive education and information campaigns as well as low-threshold offers to become vaccinated. However, political incentives during the SARS-CoV-2 pandemic, such as fewer restrictions in everyday life for vaccinated people, may also have had a positive influence on the decision to become vaccinated. In addition, a prior positive SARS-CoV-2 infection test positively influenced the vaccination setting[54]. We were able to show that a key reason for SARS-CoV-2 vaccination was protection against severe disease. A study by Rzymski et al. revealed that 88% of immunosuppressed patients, representing a group at high risk of severe COVID-19 courses, were willing to receive a booster vaccination against SARS-CoV-2[55]. Furthermore, studies have shown that older age leads to higher vaccination propensity towards SARS-CoV-2 vaccines[56–59]. This has already been shown in other studies for influenza vaccination[60]. It would be reasonable to postulate that patients of older age could be more attentive to their healthcare and that physicians pay more attention to the complete vaccination status of this patient group. A survey in Germany also showed that men and older people were more likely to be vaccinated against SARS-CoV-2[54]. According to RKI data, 90.1% of people over 60 years of age in Germany received a basic immunization against SARS-CoV-2[61]. This could be due to the vaccination recommendation of the STIKO with its phased prioritization plan in Germany: People with old age as well as patients with a particular high risk to suffer from a serious COVID-19 course preferentially received a vaccine against SARS-CoV-2 in the initial phase[62]. Another reason that older patients were more likely to be vaccinated may be that older age is associated with a higher likelihood of comorbidities ($r = 0.32$, $p < 0.001$), which are known to be a risk factor for more severe outcomes[63] and therefore may be linked to a higher vaccination acceptance.

Our data suggest that sex is not an important factor affecting SARS-CoV-2 vaccination coverage. However, studies from other countries such as Australia and Israel indicated that women are more reluctant to receive SARS-CoV-2 vaccines than men[64,65]. The way people are informed about vaccinations might influence the willingness to receive a vaccine and thus also the actual vaccination rate. High exposure to conflicting information from social media as well as low trust in the healthcare system are factors associated with a negative attitude towards acceptance of SARS-CoV-2 vaccination. In addition, an overabundance of information and news can trigger a type of fatigue and desensitization[66,67]. Conversely, a high level of trust in governmental institutions as well as in scientifically based sources of information and better trust in the healthcare system promotes a higher propensity to become vaccinated[68]. This could be a starting point for improving vaccination rates by making information transparently available to the population in a simple and understandable way[58]. Positively influencing factors on vaccination also include higher education levels[69]. Other related factors include how patients perceive their exposure and the exposure of others to COVID-19. Patients with a chronic disease as well as patients who perceived increased risk potential to contract COVID-19 in their personal environment reported a higher willingness to receive SARS-CoV-2 vaccination[70–72]. We found that patients with borderline HADS-D scores were significantly less likely to be vaccinated against SARS-CoV-2. This could be due to the fact that patients who are more depressed have less motivation and drive to get vaccinated. A negative association between vaccination

acceptance and depression was also found in other studies[73,74]. One possible explanation could be that patients with depressive symptoms are more likely to believe misinformation about SARS-CoV-2 vaccinations[75]. In general, patients with mental illness were more likely to have an incomplete vaccination status[76]. Policies like having more freedom in daily life after full immunization are associated with increased vaccination willingness[77]. In our study population, this was also a major reason for getting vaccinated against SARS-CoV-2 (56.8%). The main reason for patients who did not get vaccinated against SARS-CoV-2 was the unforeseeable risk of short-term or long-term side effects (82.1%). This corresponds to other studies, according to which patients with vaccination hesitancy frequently expressed concerns about the efficacy and safety of the SARS-CoV-2 vaccines[78]. Another factor is concern about quality control, rapid development, and the side effect profile of SARS-CoV-2 vaccines[79]. In a survey representative of the general population, the main reasons for hesitating to vaccinate were that vaccines have not been adequately tested, fear of side effects, and a desire to act at one's own discretion[80].

In our study, we also examined the usage frequency of the different SARS-CoV-2 vaccines available. Tozinameran was administered most frequently for basic immunization and booster vaccination. In contrast, the AZD1222 vaccine showed a decline in vaccination coverage from first to third vaccination. For the third vaccination, this agent was no longer used in the patients in our study. The reason for this was presumably a STIKO recommendation and the fact that, due to its side effect profile, the vaccine has only been recommended for certain patient groups in Germany since December 1, 2021. Unusual thrombotic events have been reported in association with the use of AZD1222[81–83].

Furthermore, we analyzed the side effect profile of the SARS-CoV-2 vaccines. A proportion of 28.8% of the patients reported local general reactions after vaccine administration, which included swelling, pain, and redness at the injection site. This result is similar to the study by Archiron et al. in which 555 patients with MS were interviewed regarding their side effects after the first and second SARS-CoV-2 vaccination: 16% reported local pain at the injection site after the first vaccination and 14.2% after the second vaccination[29]. Among systemic reactions reported by our study population, fatigue was the most common symptom. This is also in line with the above-mentioned study by Archiron et al.: 9.2% and 15.9% of MS patients reported fatigue as a side effect after the first and second dose of tozinameran, respectively[29]. In the pivotal efficacy trial, which included 21,720 participants who received tozinameran, fatigue and headache were the most common systemic vaccination reactions (59% and 52%, respectively)[84]. In a recent study involving MS patients from the United Kingdom and Germany, the most common side effects after SARS-CoV-2 vaccination were headache, fatigue, and pain at the injection site[85]. Women were more frequently affected by these side effects than men, which is in line with our study. Regarding the overall occurrence of side effects in our cohort, there were associations with age, sex, EDSS score and the course of the disease. Patients with abnormal HADS scores more often reported muscle and joint pain and dizziness after SARS-CoV-2 vaccination. Patients who were already skeptical of recommended standard vaccinations before the pandemic also reported dizziness after SARS-CoV-2 vaccination more frequently. This raises the question of whether these patients pay more attention to side effects after getting vaccinated against SARS-CoV-2. Furthermore, our results showed a significant association between self-reported palpitations after the first vaccination and years of education. This may suggest that the patients with higher levels of education were more attentive to or better able to remember side effects such as palpitations, which have been previously reported for mRNA vaccines[86,87]. Another consideration for the results is that patients with SPMS tend to be older than patients with CIS or RRMS. It could therefore be hypothesized that the natural aging of the immune system leads to a decrease in the immune response, and therefore patients with SPMS may report less often side effects (fatigue and joint and muscle pain) than patients with CIS or RRMS[88]. However, some of the results were close to $p = 0.05$, which may indicate statistical associations but not necessarily clinically meaningful associations. On the other hand, the associations mostly reached statistical significance after the second SARS-CoV-2 vaccination, but not after the first or third vaccination. These and other inconsistencies in our analysis of associations between patient characteristics and the occurrence of adverse effects after individual SARS-CoV-2 vaccinations may be indicative of false positive findings, and therefore our results should be interpreted with caution. Nevertheless, our data suggest that patients with MS are not at an increased risk of experiencing side effects following SARS-CoV-2 vaccination as compared to the general population.

After any SARS-CoV-2 vaccination, less than 5% of our patients reported an exacerbation of the disease. These data are similar to another study of MS patients from Germany according to which the frequency of reported relapses after SARS-CoV-2 vaccination was 9.3%[89]. In a study by Achiron et al., the rate of patients with an acute relapse was 2.1%[29]. In another study, 1661 MS patients were evaluated after SARS-CoV-2 vaccination[90]. That study showed a slight increase in the annualized relapse rate after the vaccination as compared to the previous year (0.22 vs. 0.17)[90]. In another analysis of 425 MS patients, 136 patients reported adverse events after SARS-CoV-2 vaccination and 36 patients reported new or worsening neurological symptoms[91]. However, most symptoms disappeared after 24 h to 3 days. A recent study showed that mRNA-based SARS-CoV-2 vaccination in MS patients did not result in worsening of the autoimmune disease nor triggered immune-mediated neurological diseases[92].

The lack of a control group from the general population could be interpreted as a limitation of the present study. Furthermore, although we conducted a standardized interview, the validity of our data might be limited by factors such as recall bias and the inherent subjectivity of self-reports. It should be also noted that the patients were interviewed after a variable period of time after the last vaccination (if they had received any). However, the study examined important clinical aspects that were not addressed in the pivotal studies of the SARS-CoV-2 vaccines in patients with autoimmune disease, especially for patients with MS. In addition, the patient cohort was examined regarding their willingness to follow standard vaccination recommendations and the attitude change during the course of the pandemic.

Conclusion

This study has shown that MS patients were relatively likely to get vaccinated against SARS-CoV-2 despite their concerns about getting vaccinated. We showed that patients who had a positive vaccination attitude prior to the pandemic were 3 times more likely to become vaccinated against SARS-CoV-2 in the course of the pandemic. In our studies, the leading reason for vaccination was protection against severe disease. In contrast, the leading reason against SARS-CoV-2 vaccination was the concern about possible side effects. With regard to the psychological characteristics, patients with borderline HADS-D score were less likely to be vaccinated against SARS-CoV-2. We did not find associations between sociodemographic and clinical variables and the likelihood of getting vaccinated against SARS-CoV-2, except for MS disease duration. Approximately half of the patients reported side effects after SARS-CoV-2 vaccination, independently of the type of vaccine administered. The leading side effects were fatigue, muscle and joint pain, headache, and redness at the injection site. Women reported side effects significantly more frequently than men. Younger patient age and shorter disease duration were also associated with an increased likelihood of certain side effects. These data suggest that it would be important to pay special attention to patients who exhibit vaccine skepticism to increase their vaccine acceptance through targeted counseling. An interesting research topic for further investigation is how SARS-CoV-2 vaccination rates evolved in the context of recommended booster vaccinations and after protein-based vaccines became available, particularly in older people and patients with chronic disease such as MS.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions
K.B. contributed to the study design, performed the data analysis, and wrote the manuscript. U.K.Z. and N.F. also contributed to the conception of the study. M.H. and J.R. contributed to the analysis of the data. M.H. prepared

the figures. J.B., F.H., B.S., P.M., J.M., S.E.L., U.K.Z., N.F., and M.H. critically reviewed the draft for important intellectual content and approved the final version as submitted.

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Correspondence and requests for materials should be addressed to K.B.

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9 Anhang

9.1 Abkürzungsverzeichnis

ANOVA ..... *analysis of variance*
CIS..... *clinically isolated syndrome*
COVID-19 ..... *coronavirus disease 2019*
DMD ..... *disease-modifying drug*
EAN ..... *European Academy of Neurology*
ECTRIMS… ..... *European Committee for Treatment and Research in MS*
EDSS..... *Expanded Disability Status Scale*
EMA..... *Europäische Arzneimittelagentur*
FSME..... *Frühsommer-Meningoenzephalitis*
HADS..... *Hospital Anxiety and Depression Scale*
HPV ..... *Humane Papillomaviren*
MMR ..... *Masern-, Mumps und Röteln*
mRNA ..... *messenger ribonucleic acid*
MS ..... *Multiple Sklerose*
NEO-FFI ..... *NEO Five-Factor Inventory*
OR ..... *odds ratio*
PPMS ..... *primary progressive MS*
PwMS ..... *People with Multiple Sclerosis*
RRMS ..... *relapsing remitting MS*
S1P..... *Sphingosine-1-Phosphat-Rezeptor*
SARS-CoV-2..... *severe acute respiratory syndrome coronavirus type 2*
SPMS ..... *secondary progressive MS*
STIKO..... *Ständige Impfkommission*
TCI-R ..... *Temprament* and *Character Inventory-Revised*
TSQ ..... *Trauma Screening Questionnaire*
ZNS ..... *Zentrales Nervensystem*

9.2 Thesen zur Dissertation

1. Die Multiple Sklerose (MS) ist die häufigste chronische immunvermittelte Erkrankung des zentralen Nervensystems, welche bereits bei jungen Erwachsenen zu irreversiblen Behinderungen führen kann.

2. Die Ätiologie der MS ist multifaktoriell und neben genetischen Faktoren beeinflussen Lebensstil und Umweltfaktoren das individuelle Erkrankungsrisiko.

3. Die MS per se und Komorbiditäten sowie die Einnahme von immunmodulatorischen Medikamenten führen zu einem erhöhten Infektionsrisiko der Patienten.

4. Infektionskrankheiten bei MS führen zu einer erhöhten Morbidität und Mortalität. Eine Infektion mit dem *Severe Acute Respiratory Syndrome Coronavirus type 2* (SARS-CoV-2) kann zu einem schweren Atemnotsyndrom führen und intensivmedizinische Betreuung erfordern.

5. Impfungen spielen zur Reduktion des Infektionsrisiko eine wesentliche Rolle. *People with Multiple Sclerosis* (PwMS) sind häufig besorgt, dass Impfungen den Verlauf der MS-Erkrankung negativ beeinflussen könnten.

6. Es mangelte bislang an umfassenden Studien, die Faktoren detektieren, die mit der Impfakzeptanz bzw. Impfskepsis bei PwMS in Zusammenhang stehen können.

7. Ziel dieser Arbeit war es, die Assoziation zwischen soziodemografischen, klinischen und psychopathologischen Faktoren sowie Persönlichkeitsmerkmalen und der Impfbereitschaft von PwMS für empfohlene Standardimpfungen und SARS-CoV-2-Impfungen zu untersuchen, um mögliche Einflussfaktoren auf die

Impfakzeptanz und deren Veränderung im Verlauf der COVID-19-Pandemie besser zu verstehen.

8. Insgesamt 404 volljährige PwMS mit klinisch isoliertem Syndrom oder MS wurden in einer Multicenterstudie (Universitätsmedizin Rostock und Ökumenisches Hainich Klinikum Mühlhausen) in die Untersuchungen eingeschlossen.

9. Die Basisbefragung zu Standardimpfungen fand von Juni 2019 bis Juni 2020 statt. Darauf folgten drei Nachbefragungen: Von Mai bis Juli 2020 wurde die Impfbereitschaft gegen SARS-CoV-2 vor Verfügbarkeit der Impfstoffe erhoben, von März bis Mai 2021 die Impfbereitschaft nach Verfügbarkeit der ersten Impfstoffe erfragt, und von Oktober 2021 bis Januar 2022 der tatsächliche SARS-CoV-2-Impfstatus mittels standardisierter Fragebögen erfasst.

10. Die Datenerhebung der Basisbefragung erfolgte mittels eines standardisierten Interviews sowie durch eine klinische Untersuchung, Einsicht in die Patientenakte und den Impfausweis. Persönlichkeitsmerkmale der Patienten wurden anhand der Fragebögen *NEO Five-Factor Inventory* (NEO-FFI) und *Temperament and Character Inventory-Revised* (TCI-R) evaluiert. Psychopathologische Merkmale wurden mittels *Hospital Anxiety and Depression Scale* (Angstskala: HADS-A, Depressionsskala: HADS-D) erfasst. Zudem wurde ein angepasster *Trauma Screening Questionnaire* (TSQ) verwendet, um die psychische Belastung der Patienten im Zusammenhang mit der SARS-CoV-2-Pandemie zu erfassen.

11. In der ersten Nachbefragung gaben 60% (N=200) der eingeschlossenen PwMS an, sich gegen das SARS-CoV-2-Virus impfen lassen zu wollen. In der zweiten Nachbefragung nach der Verfügbarkeit entsprechender Impfstoffe, gaben von 157 PwMS 61% an, sich gegen SARS-CoV-2 impfen lassen zu wollen.

12. Ein höheres Lebensalter zeigte eine positive Korrelation mit der Bereitschaft, empfohlene Standardimpfungen sowie SARS-CoV-2-Impfungen durchführen zu lassen. Zudem wiesen Patienten mit höheren TSQ-Werten eine gesteigerte Bereitschaft zur SARS-CoV-2-Impfung auf.

13. Von den 193 PwMS, die zur dritten Nachbefragung eingeschlossen werden konnten, erhielt die Mehrheit (84,5%) bis dahin mindestens eine SARS-CoV-2-Impfung. Eine zweite bzw. dritte Impfungen hatten 78,2% bzw. 13% der PwMS erhalten. Der Wirkstoff Tozinameran war der am häufigste verwendete SARS-CoV-2-Impfstoff in der vorliegenden Arbeit.

14. Der Hauptgrund für die Entscheidung für eine SARS-CoV-2-Impfung war für 90,1% der Befragten der Schutz vor einer schweren SARS-CoV-2-Erkrankung. Bei den ungeimpften 30 Patienten war für 82,1% von ihnen die Sorge vor möglichen (langfristigen) Nebenwirkungen der wesentliche Grund, diese Impfung abzulehnen.

15. Patienten, die vor der Pandemie eine positive Einstellung gegenüber empfohlenen Standardimpfungen hatten, waren signifikant häufiger gegen SARS-CoV-2 geimpft als jene, die Standardimpfungen präpandemisch kritisch gegenüberstanden (OR: 3,4). Patienten mit grenzwertigen HADS-D-Scores waren seltener gegen SARS-CoV-2 geimpft als Patienten mit normalen HADS-D-Scores (OR: 0,4).

16. Patienten mit einem vollständigem Influenzaimpfstatus (*n*=60) zur Basisbefragung waren signifikant älter und schwerwiegender behindert als Patienten mit unvollständigem Influenzaimpfstatus (*n*=266). Ebenfalls hatten Patienten mit vollständigen Influenzaimpfstatus höhere Werte in den NEO-FFI- bzw. TCI-R-Dimensionen Extraversion (*p*=0,031), Offenheit (*p*=0,045) und

Schadensvermeidung (p=0,029) sowie im Angstscore (HADS-A: p=0,036).

17. Patienten mit vollständigem Mumps-, Masern- und Röteln (MMR)-Impfstatus (n=58) zur Basisbefragung waren signifikant jünger (p<0,001) und wiesen einen niedrigeren Behinderungsgrad auf als Patienten mit einem unvollständigen MMR-Impfstatus (n=186) (p<0,001).

18. Die Untersuchungen ergaben neue Erkenntnisse hinsichtlich der Faktoren im Zusammenhang mit der Impfakzeptanz bzw. Impfskepsis und hinsichtlich der Entwicklung der Impfeinstellung im Rahmen der SARS-CoV-2-Pandemie bei Patienten mit MS.

19. Durch die Identifizierung von PwMS, die Impfungen kritisch oder unsicher gegenüberstehen, und der Entwicklung von individuellen umfassenden Aufklärungsstrategien unter Einbeziehung von Persönlichkeitsmerkmalen könnte eine Reduzierung der Impfskepsis erreicht werden.

9.3 Selbstständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unerlaubte Hilfe verfasst habe. Ich versichere, nur die angegebenen Quellen und Hilfsmittel benutzt zu haben. Die Regeln guter wissenschaftlicher Praxis wurden beachtet. Die Arbeit hat noch keiner anderen Prüfungsbehörde vorgelegen. KI-basierte Tools (ChatGPT und DeepL) wurden ausschließlich zur sprachlichen Überarbeitung einzelner Formulierungen verwendet, nicht jedoch zur inhaltlichen Erstellung der Arbeit.

Ort, Datum Katja Burian

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9.5 Curriculum vitae

Persönliche Daten	
Name	Katja Burian
Geburtsdatum/ -ort	22.10.1987, Mühlhausen
Familienstand	Verheiratet, 2 Kinder
Ausbildung	
2006	Abitur, Tilesius-Gymnasium Mühlhausen
2006-2007	Freiwilliges soziales Jahr
2007-2010	Ausbildung zur Gesundheits- und Krankenpflegerin, Helios Klinikum Erfurt
2010-2012	Tätigkeit als Gesundheits- und Krankenpflegerin, Universitätsklinikum Köln
2012-2018	Studium der Humanmedizin, Heinrich-Heine-Universität Düsseldorf
2019-2020	Weiterbildungsjahr: Psychiatrie, Ökumenisches Hainich Klinikum Mühlhausen
Seit 2020-	Weiterbildungszeit: Neurologie, Ökumenisches Hainich Klinikum Mühlhausen
Publikationen	
2017	Grajewski RS, Barahmand Pour N, **Burian K**, Caramoy A, Kirchhof B, Cursiefen C, Heindl LM (2017) Analysis of the impact of allergy and atopy on new onset of uveitis. Acta Ophthalmol 95:236-24

2022	Heidler F, Baldt J, Frahm N, Langhorst SE, Mashhadiakbar P, Streckenbach B, **Burian K**, Zettl UK, Richter J (2022) Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic. Sci Rep 12:15147
2022	Streckenbach B, Baldt J, Heidler F, Frahm N, Langhorst SE, Mashhadiakbar P, **Burian K**, Zettl UK, Richter J (2022) General vaccination willingness and current vaccination status in relation to clinical and psychological variables in patients with multiple sclerosis. Vaccine 40:3236–3243
2023	Baldt J, Frahm N, Hecker M, Streckenbach B, Langhorst SE, Mashhadiakbar P, **Burian K**, Meißner J, Heidler F, Richter J, Zettl UK (2023) Depression and Anxiety in Association with Polypharmacy in Patients with Multiple Sclerosis. J Clin Med 12
2024	**Burian K**, Heidler F, Frahm N, Hecker M, Langhorst SE, Mashhadiakbar P, Streckenbach B, Baldt J, Meißner J, Richter J, Zettl UK (2024) Vaccination status and self-reported side effects after SARS-CoV-2 vaccination in relation to psychological and clinical variables in patients with multiple sclerosis. Sci Rep 14:12248
2024	Meißner J, Frahm N, Hecker M, Langhorst SE, Mashhadiakbar P, Streckenbach B, **Burian K**, Baldt J, Heidler F, Richter J, Zettl UK (2024) Personality traits in patients with multiple sclerosis:

	their association with nicotine dependence and polypharmacy. Ther Adv Neurol Disord 17:17562864241279118
2025	Heidler F, Hecker M, Frahm N, Baldt J, Streckenbach B, Meißner J, **Burian K**, Langhorst SE, Mashhadiakbar P, Richter J, Zettl UK (2025) Trauma Burden Affected People with Multiple Sclerosis During SARS-CoV-2 Pandemic. J Clin Med 13:2665