

Aus der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock

Sektion: Neuroimmunologie

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Impfstatus, Impfwissen und Impfeinstellungen von Patienten mit Multipler Sklerose

Kumulative Dissertationsschrift

zur

Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

der Universitätsmedizin Rostock

vorgelegt von Silvan Elias Langhorst

geb. am 23.07.1995 in Göttingen

wohnhaft in Hamburg

Rostock, 2023

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Datum der Einreichung: 14.12.2023

Datum der Verteidigung: 05.11.2024

Inhaltsverzeichnis

| | | |
|-----------|---|-----------|
| 1 | Einleitung | 1 |
| 1.1 | Multiple Sklerose..... | 1 |
| 1.2 | Impfungen..... | 4 |
| 1.3 | Impfungen bei MS..... | 5 |
| 2 | Fragestellungen | 7 |
| 3 | Methoden | 9 |
| 3.1 | Patientenkohorte..... | 9 |
| 3.2 | Allgemeine Datenerhebung | 10 |
| 3.3 | Erfassung psychologischer und psychopathologischer Merkmale | 11 |
| 3.4 | Statistik | 12 |
| 4 | Ergebnisse | 14 |
| 4.1 | Publikation 1: <i>Vaccination Coverage against Tetanus, Diphtheria, Pertussis and Poliomyelitis and Validity of Self-Reported Vaccination Status in Patients with Multiple Sclerosis</i> | 14 |
| 4.2 | Publikation 2: <i>Vaccination Setting of Patients with Autoimmune Diseases in Times of Severe Acute Respiratory Syndrome Coronavirus Type 2 Pandemic Using the Example of Multiple Sclerosis Patients: A Longitudinal Multicenter Study</i> | 16 |
| 4.3 | Publikation 3: <i>Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic</i> | 18 |
| 5 | Diskussion | 21 |
| 6 | Zusammenfassung | 27 |
| 7 | Literaturverzeichnis | 29 |
| 8 | Publikationen | 40 |
| 8.1 | Publikation 1 | 40 |
| 8.2 | Publikation 2 | 61 |
| 8.3 | Publikation 3 | 70 |
| 9 | Abkürzungsverzeichnis | 81 |
| 10 | Thesen zur Dissertation | 82 |
| 11 | Selbstständigkeitserklärung | 85 |
| 12 | Danksagung | 86 |
| 13 | Curriculum vitae | 87 |

1 Einleitung

Multiple Sklerose (MS) ist eine chronisch-immunvermittelte Krankheit des zentralen Nervensystems (ZNS), welche mit im Vordergrund stehenden demyelinisierenden und neurodegenerativen Prozessen einhergeht. Das Infektionsrisiko ist für MS-Patienten im Vergleich zur Normalbevölkerung erhöht, was eine besondere Gefahr für sie darstellt (1,2). Aufgrund der erhöhten Anfälligkeit für Infektionen ist ein vollständiger Impfstatus als Schutz vor Infektionskrankheiten von größter Bedeutung. Im Rahmen der vorliegenden Arbeit wurde der Impfstatus, das Impfwissen und das Impfverhalten von MS-Patienten analysiert. Zudem wurden Impfeinstellungen sowie die Impfbereitschaft vor und während der SARS-CoV-2-Pandemie ermittelt und miteinander verglichen. Außerdem erfolgte eine Analyse der mit den Impfdaten assoziierten soziodemografischen, klinischen und psychologischen Parameter.

1.1 Multiple Sklerose

Weltweit leben mehr als 2,8 Millionen Menschen mit MS, wobei Frauen in Abhängigkeit von der klinischen Verlaufsform zwei- bis dreimal häufiger betroffen sind als Männer (3–5). MS ist eine der Hauptursachen für nicht-traumatisch bedingte neurologische Behinderungen bei jungen Erwachsenen (6). Die Erkrankung wird typischerweise im Alter zwischen 20 bis 49 Jahren diagnostiziert (7).

Bisher konnten mehrere genetische, epigenetische und umweltbedingte Faktoren identifiziert werden, von denen angenommen wird, dass sie in ihrer Kombination zur Krankheitsentwicklung der MS beitragen (8). Umwelt- oder Lebensstilbedingte Risikofaktoren sind: eine vorausgegangene Infektion mit Epstein-Barr-Virus (EBV), Nikotinabusus, niedrige Vitamin-D-Spiegel und Adipositas (9,10). Neueste Studienergebnisse deuten darauf hin, dass die EBV-Infektion ein wichtiger Faktor in der Pathogenese der MS sein könnte (11–13). Neben den umweltbedingten Risikofaktoren konnten bisher über 200 verschiedene genetische Varianten detektiert werden, die mit dem Krankheitsrisiko assoziiert sind (14).

Pathophysiologisch kommt es bei MS zur Invasion Myelin-reaktiver, peripherer Immunzellen über die Blut-Hirn-Schranke ins ZNS, was zu herdförmigen inflammatorischen Schädigungen mit Demyelinisierung, astroglialer Proliferation, Synapsenverlust und Neurodegeneration in der weißen und grauen Substanz führt (15,16).

Zur Diagnosestellung werden neben Anamnese, neurologischer Untersuchung und radiologischer Diagnostik (Magnetresonanztomographie, MRT) auch laborchemische Untersuchungen inklusive Analytik des cerebrospinalen Liquors sowie elektrophysiologische Verfahren genutzt. Entsprechend der McDonald-Kriterien ist eine MS-Diagnose nur zu stellen, wenn die Kriterien der zeitlichen (Entwicklung von MS-Herden im zeitlichen Verlauf) und räumlichen (Entwicklung von MS-Herden an zwei oder mehr ZNS-Regionen) Dissemination erfüllt sind. Diese sind durch klinische Symptome, Liquorveränderungen und MS-Läsionen im MRT nachweisbar. Zusätzlich zur Erfüllung der Kriterien sind Differenzialdiagnosen auszuschließen (17).

Um den Schweregrad der Behinderung systematisch zu erfassen, werden klinische Scoring-Instrumente, wie die *Expanded Disability Status Scale* (EDSS), genutzt (18).

Man unterscheidet drei MS-Verlaufsformen. Zu Beginn der Erkrankung unterteilt man die MS in die schubförmig remittierende MS (RRMS), die mit 85% betroffenen Patienten häufigste Verlaufsform, bei der neurologische Defizite in Schüben auftreten und sich vollständig oder unvollständig zurückbilden, und in die primär progrediente MS (PPMS), die seltener vorkommt (10-15% der Patienten). Die PPMS ist durch eine schleichende, langsam fortschreitende Akkumulation der neurologischen Behinderung im Verlauf gekennzeichnet, in der Regel ohne Schübe (19). Etwa 50% der RRMS-Patienten entwickeln innerhalb von 20 Jahren einen progressiven Verlauf (sekundär progrediente MS) mit einer allmählichen Zunahme der Behinderung bei gleichzeitiger Abnahme der Schubaktivität (20). Eine erste Episode neurologischer Symptome mit Hinweisen auf demyelinisierende Prozesse ohne Erfüllung der Diagnosekriterien wird als klinisch isoliertes Syndrom (CIS) bezeichnet. Die Konversionsrate in eine klinisch gesicherte MS liegt, je nach Dauer der Nachbeobachtungen, zwischen 42-82% (17,21).

Als Erkrankung des ZNS kann sich die Symptomatik von MS in unterschiedlichsten Organsystemen präsentieren. Anfänglich klagen die Patienten meist über Sensibilitätsstörungen, Paresen oder Sehstörungen. Im fortgeschrittenen Verlauf der Krankheit gehören Fatigue, Spastik, Blasenfunktionsstörungen, Ataxie, Schmerzen, Depressionen und kognitive Störungen zu den am häufigsten berichteten Symptomen (22,23).

Es existiert zurzeit keine kurative Therapie der MS. Die derzeitigen Behandlungsstrategien umfassen die Reduktion der Krankheitsaktivität und Behinderungsprogression.

Prinzipiell wird zwischen verlaufsmodifizierender Dauertherapie und akuter Schubtherapie unterschieden.

Die Therapie eines akuten MS-Schubes erfolgt standardmäßig durch intravenöse Applikation von hochdosierten Glukokortikosteroiden (GCS) über 3-5 Tage (24). Bei unzureichender Wirksamkeit hat sich, neben der Erhöhung der GCS-Dosis, die Plasmapherese bzw. Immunadsorption als weitere Eskalationsstufe etabliert (25).

Die krankheitsmodifizierenden Therapien (*disease-modifying drugs*, DMD) beeinflussen den Verlauf der MS durch Modulation oder Suppression des Immunsystems (26). Sie wirken entzündungshemmend, verringern die Schubrate, reduzieren die Häufung von MRT-Läsionen und bewirken in einigen Fällen eine Verbesserung des Behinderungsgrads (27). Aktuell (12/2023) stehen in Deutschland 18 DMD für die MS-Therapie zur Verfügung (25). Die Wahl des Therapeutikums sollte immer unter Abwägung des resultierenden Nutzens im Verhältnis zu möglichen Risiken, wie Verträglichkeit oder Nebenwirkungen, erfolgen (28).

Die DMD sind in ihrer Wirkstärke unterschiedlich. Die Leitlinie der deutschen Gesellschaft für Neurologie unterteilt die Substanzen hinsichtlich der Therapie der RRMS nach aufsteigender Wirkstärke in drei Kategorien. Dabei wird die Reduktion der Schubrate als primärer Parameter genutzt, um die Substanzen den Wirksamkeitskategorien zuzuordnen. Die Rate schwerer Nebenwirkungen ist i. d. R. in Kategorie 1 niedriger als in Kategorie 3. Zu Beginn der Therapie der RRMS werden normalerweise Substanzen der Wirksamkeitskategorie 1, wie Interferon-beta, Glatirameracetat, Teriflunomid oder Dimethylfumarat, eingesetzt. Bei wahrscheinlich hochaktivem Verlauf hingegen initiiert man die Therapie mit klinisch effektiveren Substanzen aus Kategorie 2 oder 3, wie Fingolimod, Cladribin, Alemtuzumab, Natalizumab oder Ocrelizumab. Die erhöhten Raten von Nebenwirkungen hochwirksamer DMD, wie die therapieassoziierte progressive multifokale Leukenzephalopathie (PML) oder das Risiko anderer infektiöser Komplikationen, sollten dabei beachtet werden (25). Die medikamentösen Möglichkeiten für die Behandlung chronisch progredienter Verlaufsformen sind limitiert. Für die PPMS ist der monoklonale Anti-CD20-Antikörper Ocrelizumab das einzige offiziell zugelassene

Medikament (27). Bei der SPMS stehen mit Limitierungen Beta-Interferone, Siponimod, Cladribin und CD20-Antikörper zur Verfügung. Mitoxantron wird aufgrund seines hohen Nebenwirkungsprofils nur noch in Ausnahmefällen empfohlen (25).

Aus der hohen Symptomvielfalt ergibt sich zudem ein umfangreiches Medikationsspektrum zur symptomatischen Therapie. Hinzukommen Komorbiditäten, die ebenfalls medikamentös behandelt werden (29) und Präparate der Alternativ- und Komplementärmedizin, die von einem Teil der MS-Patienten eingenommen werden und in ihrer Gesamtwirkung die Komplexität des Therapiemanagements erhöhen (30–32).

1.2 Impfungen

Impfungen können potenziell gefährliche und tödliche Infektionskrankheiten verhindern, wodurch sie wesentliche Auswirkungen auf die Gesundheit und Lebenserwartung von Menschen haben und daher als einer der größten Erfolge der Medizingeschichte gelten (33). Vor mehr als 300 Jahren wurde der erste Impfstoff entwickelt. Seitdem sind immer wieder neue Methoden zur Impfstoffentwicklung erforscht, angepasst und vorangetrieben worden (34). Insgesamt sind die infektionsbedingten Sterbefälle weltweit in den letzten Jahren rückläufig, stellen aber nach wie vor eine häufige Todesursache dar (35). Der Ausbruch der Pandemie des *severe acute respiratory syndrome coronavirus type 2* (SARS-CoV-2) 2020 verdeutlicht die Gefahr, die von Infektionskrankheiten ausgehen kann (36–38). Weltweit sind bisher geschätzt über 6,9 Millionen Menschen an *coronavirus disease 2019* (COVID-19) verstorben (39).

Die Fortschritte der Wissenschaft haben es ermöglicht, die Zeit der Entwicklung eines Impfstoffs deutlich zu verkürzen, was in der Pandemiebekämpfung von großer Bedeutung ist (40). Im Management gegen die SARS-CoV-2-Pandemie konnten COVID-19-Impfungen erfolgreich die Infektionsraten, schwere Krankheitsverläufe, Hospitalisierungen und Todesfälle reduzieren (41). In mathematischen Modellen wurde errechnet, dass durch die Impfkampagne der Tod von mehr als 14 Millionen Menschen im Jahr 2021 verhindert werden konnte (42).

Hohe Impfraten in einer Gesellschaft sind nicht nur ein Schutz für die Geimpften selbst, sondern schützen über die Herdenimmunität auch gefährdete Personen (z. B. Immungeschwächte), die keine Lebendimpfstoffe erhalten dürfen oder keinen

ausreichenden Impfschutz aufbauen können (43). Die Übertragung von Masern kann beispielsweise bei einer Durchimpfungsrate von 93-95% innerhalb einer Population unterbrochen werden (44).

Trotz des aktuellen Impferfolges und denen in der Vergangenheit, wie die weltweite Eradikation der Pocken Ende der 1970er Jahre (45), spielt die Skepsis und Ablehnung von Impfungen in der Gesellschaft eine zunehmende Rolle (46,47). Im Jahr 2019 bezeichnete die WHO Impfverweigerung als eine der aktuell zehn größten Bedrohungen für die globale Gesundheit (48). Die Gründe für Impfskepsis sind vielfältig. So spielen neben dem inzwischen widerlegten, aber hartnäckigen Glauben, die Impfung gegen Masern, Mumps und Röteln könne Autismus oder MS verursachen (49,50), auch Desinformationen über Impfungen eine Rolle (51–53). Die Frage nach der Sicherheit der neuen Vektor- und mRNA-Impfstoffe gegen SARS-CoV-2 beeinflusste die Impfbereitschaft in der Bevölkerung ebenfalls (54–56). Insgesamt lässt sich zusammenfassen, dass der Entscheidungsprozess, der zur Impfablenkung führt, vom Zusammenwirken kultureller, sozialer, politischer, emotionaler und kognitiver Faktoren geprägt ist (57).

1.3 Impfungen bei MS

Bei MS existieren seit Jahrzehnten Debatten um eine Korrelation zwischen der Erkrankung und Impfungen, was dazu geführt hat, dass Impfskepsis auch unter MS-Patienten weit verbreitet ist (58). Fallberichte von Patienten, die in den 1990er Jahren nach einer Hepatitis-B-Impfung an MS erkrankten, verunsicherten die Menschen (59). Bis heute konnten Studien allerdings keinen Zusammenhang nachweisen, dass Impfungen MS auslösen oder den Krankheitsverlauf negativ beeinflussen können. Auch die Verschlechterung der MS durch eine Gelbfieberimpfung, welche in der Vergangenheit diskutiert wurde (60), konnte in neueren Arbeiten nicht bestätigt werden (61,62). Insgesamt können Impfungen bei MS-Patienten als sicher betrachtet werden und sind, mit Ausnahme von Lebendimpfstoffen, welche unter Immunsuppression als kontraindiziert gelten (63), generell empfohlen (60,64–66). Neben den Impfempfehlungen der Ständigen Impfkommission (STIKO) (67) können die im Jahr 2023 erstmalig erschienenen multinationalen Konsensempfehlungen der *European Committee for Treatment and Research in Multiple Sclerosis* (ECTRIMS) als Leitfaden im Umgang mit Impfungen bei MS-Patienten genutzt werden (68,69).

Für MS-Patienten ist Impfbereitschaft und ein damit einhergehender vollständiger Impfstatus von höchster Bedeutung, da sie aufgrund ihrer immunmodulatorischen bzw. immunsuppressiven Therapie einem erhöhten Infektionsrisiko ausgesetzt sind (2). Infektionskrankheiten stellen die häufigste Todesursache bei MS-Patienten dar. Das Risiko an einer Infektion zu versterben ist für sie im Vergleich zur Allgemeinbevölkerung dreimal höher (70). Dass Infektionen zudem eine Rolle bei der Entstehung von MS spielen, wird seit langem diskutiert (71–73). Studien konnten zeigen, dass Infektionen das Risiko von Schüben bei MS-Patienten erhöhen können (2,74,75) und zusätzlich mit einem höheren Behinderungsgrad (gemessen anhand der EDSS (18)), im Vergleich zu infektionsunabhängigen Schüben, einhergehen (76). Außerdem sind die Hospitalisierungsraten und die Sterblichkeitsraten von MS-Patienten, die von Infektionen betroffen sind, im Vergleich zu Patienten ohne Infektionen erhöht (77,78).

Vor Beginn einer DMD-Therapie gilt daher die Empfehlung, Impfücken der Patienten zu schließen, um sie vor impfpräventablen Infektionskrankheiten zu schützen (64). Beispielsweise sollten MS-Patienten mit negativem Antikörperstatus gegen das Varizella-Zoster-Virus (VZV) vor Beginn einer Therapie mit Fingolimod eine VZV-Impfung erhalten, da eine primäre VZV-Infektion bei ihnen zum Tod führen kann (25) und die Immuntherapie die durch Impfungen ausgelösten humoralen und zellulären Immunantworten verringern kann (66). Impfungen, als ein Teil von Infektionsprävention, haben daher insgesamt für MS-Patienten einen besonders hohen Stellenwert (79,80). Trotz der Relevanz des Themas Impfen bei MS ist die Datenlage über den Impfstatus und die Impfbereitschaft bei MS-Patienten bisher gering (81). Um den Wissensstand in diesem Forschungsgebiet zu erweitern, wurden im Rahmen dieser Arbeit Studien zum Umgang von MS-Patienten mit Impfungen durchgeführt. Dabei wurden klinisch-demografische und psychologische Prädiktoren analysiert, die mit dem Impfverhalten assoziiert waren. Die Studienergebnisse sind in Kapitel 4 beschrieben.

2 Fragestellungen

MS-Patienten stellen eine vulnerable Patientengruppe dar, für die der Schutz vor Infektionskrankheiten durch Impfungen besonders bedeutsam ist (2). Diskussionen um die Sicherheit von Impfstoffen bei MS führten zur Verunsicherung der Patienten (64).

In der vorliegenden kumulativen Promotionsarbeit werden rezente Untersuchungsergebnisse zum Impfstatus, der Bereitschaft von MS-Patienten sich impfen zu lassen und dem Interesse an Impfungen präsentiert. Dabei wurden diese impfbezogenen Variablen auf Assoziation mit klinisch-demografischen und psychologischen Variablen untersucht. Die Impfbereitschaft wurde im zeitlichen Verlauf vor und während der SARS-CoV-2-Pandemie analysiert und verglichen. Diese Arbeit hat somit das Ziel, einen Überblick über das Impfverhalten und die Impfeinstellungen in Bezug auf Standard- und SARS-CoV-2-Impfungen von MS-Patienten zu verschaffen.

Hierfür wurden folgende Fragestellungen untersucht:

Publikation 1 (Kapitel 8.1): *Vaccination Coverage against Tetanus, Diphtheria, Pertussis and Poliomyelitis and Validity of Self-Reported Vaccination Status in Patients with Multiple Sclerosis*

1. Wie hoch ist der Anteil an MS-Patienten, die einen vollständigen Impfstatus bezüglich Tetanus, Diphtherie, Pertussis und Poliomyelitis aufweisen und mit welchen soziodemografischen bzw. klinisch-neurologischen Variablen ist die Vollständigkeit des Impfstatus assoziiert?
2. Wie häufig tritt bei MS-Patienten eine Diskrepanz zwischen gedachtem (von Patienten berichtet) und realem (durch Impfausweis verifiziert) Impfstatus auf?
3. In welchen soziodemografischen bzw. klinisch-neurologischen Merkmalen unterscheiden sich MS-Patienten mit und ohne regelmäßige Kontrollen des Impfausweises?

Publikation 2 (Kapitel 8.2): *Vaccination Setting of Patients with Autoimmune Diseases in Times of Severe Acute Respiratory Syndrome Coronavirus Type 2 Pandemic Using the Example of Multiple Sclerosis Patients: A Longitudinal Multicenter Study*

1. Wie hoch ist der Anteil an MS-Patienten, die durch Auswirkungen der Pandemie ihre Einstellung gegenüber staatlich empfohlenen Standardimpfungen änderten?
2. Wie hoch ist der Anteil an MS-Patienten, die staatliche Schutzmaßnahmen gegen die SARS-CoV-2-Pandemie, Impfungen im Allgemeinen und eine bevorstehende Anti-SARS-CoV-2-Impfung ablehnen?
3. Welche soziodemografischen und klinischen Faktoren sind mit Ablehnung von Standard- oder SARS-CoV-2-Impfungen bei MS-Patienten assoziiert?

Publikation 3 (Kapitel 8.3): *Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic*

1. Wie häufig äußerten MS-Patienten die Bereitschaft, sich gegen SARS-CoV-2 impfen zu lassen, und zeigten eine befürwortende Haltung gegenüber empfohlenen Standardimpfungen vor als auch während der SARS-CoV-2-Pandemie?
2. Welche soziodemografischen, klinischen, psychologischen und Persönlichkeitsfaktoren sind mit der allgemeinen Impfbereitschaft und der Akzeptanz einer SARS-CoV-2-Impfung assoziiert?

3 Methoden

3.1 Patientenkohorte

Eine Kohorte von insgesamt 404 Patienten mit einem Mindestalter von 18 Jahren, bei denen ein klinisch isoliertes Syndrom (CIS) oder MS nach den überarbeiteten McDonald-Kriterien (17) diagnostiziert wurde, ist nach Aufklärung über das Projekt und Einverständnis zur Datenverarbeitung in eine bizenrische prospektive Beobachtungsstudie über Polypharmazie und Impfungen eingeschlossen worden. Das Design der Studie ist in Abbildung 1 dargestellt. Patienten der Untersuchungen 2 und 3 wurden im Rahmen von Follow-up Studien untersucht. Die untersuchten Kohorten der drei Publikationen stellen Subgruppen der Ausgangskohorte ($n=404$) dar.

- eine Kohorte von 327 MS-Patienten mit vorhandenem Impfausweis (Basisbefragung: Juni 2019 bis Juni 2020), bei der Daten zum Impfstatus, Impfverhalten und Impfwissen analysiert wurden (Publikation 1)
- eine Kohorte von 200 MS-Patienten (Basisbefragung: Juni 2019 bis Juni 2020; Follow-up 1: Juni 2020 bis Juli 2020), bei der Daten zur Impfbereitschaft und zu Impfeinstellungen vor und während der SARS-CoV-2-Pandemie analysiert wurden, bevor SARS-CoV-2-Impfstoffe verfügbar waren (Publikation 2)
- eine Kohorte von 157 MS-Patienten (Basisbefragung: Juni 2019 bis Juni 2020; Follow-up 1: Juni 2020 bis Juli 2020; Follow-up 2: März 2021 bis Mai 2021), bei der Daten zu Impfeinstellungen und zur Akzeptanz von Impfungen vor und während der SARS-CoV-2-Pandemie untersucht wurden, nachdem SARS-CoV-2-Impfstoffe zugelassen wurden (Publikation 3)

Rekrutiert wurden die Patienten im Rahmen regelmäßiger Besuche in den institutionellen MS-Ambulanzen oder während eines stationären Aufenthalts in der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock sowie in der Neurologischen Klinik des Ökumenischen Hainich-Krankenhauses in Mühlhausen.

Die Ethikkommission der Universität Rostock erteilte ein positives Votum (Registriernummer A 2019-0048) zu den präsentierten Studien, welche gemäß der Deklaration von Helsinki durchgeführt wurden.

Die Untersuchung der MS-Patienten erfolgte hinsichtlich soziodemografischer und klinischer Daten sowie zu Daten zum Impfstatus, zum Impfverhalten, zur Impfbereitschaft, zum Impfwissen und zu Impfeinstellungen.

Die Erhebung soziodemografischer Daten schloss Geschlecht, Alter, Bildungsstand (Anzahl der Schuljahre und Schulabschluss), Wohnort, Familienstatus, Anzahl der Kinder und Geschwister sowie den beruflichen Beschäftigungsstatus mit ein. Zu den klinischen Daten gehörten die Art der klinischen Versorgungssituation (stationär oder ambulant), MS-Verlaufsform, Krankheitsdauer (gemessen in Jahren seit Erstdiagnosezeitpunkt), Grad der Behinderung (EDSS), Anzahl der Komorbiditäten und Art der verwendeten DMD.

Die Impfdaten beinhalteten Informationen zum Impfverhalten, wie dem Wunsch der MS-Patienten nach und die Inanspruchnahme von Impfberatungsgesprächen. Außerdem wurden die Patienten zur Kenntnis über ihre eigene Impfvollständigkeit befragt (Impfwissen). Zusätzlich erfolgte eine Impfausweiskontrolle hinsichtlich Grundimmunisierungen und Auffrischungsimpfungen anhand der Impfungen gegen Tetanus, Diphtherie, Pertussis, Poliomyelitis und Influenza, um daran die Impfvollständigkeit zu beurteilen. Als Grundlage galten die aktuellen Empfehlungen der STIKO des Robert-Koch-Instituts (82). Vollständig gegen Influenza geimpft galten Patienten, die innerhalb des letzten Jahres eine Gripeschutzimpfung erhielten. Der Impfstatus gegen Tetanus, Diphtherie und Pertussis galt als vollständig, wenn zusätzlich zur Grundimmunisierung eine Auffrischungsimpfung innerhalb der letzten zehn Jahre verabreicht wurde. Wer eine vollständige Grundimmunisierung gegen Poliomyelitis erhalten hatte, wurde für diese Erkrankung als vollständig geimpft angesehen. In den beiden Follow-up-Studien (Publikationen 2 und 3) wurden Daten zu Impfeinstellungen gegenüber Standardimpfungen, zur Bereitschaft sich gegen SARS-CoV-2 impfen zu lassen und deren Veränderung im Zuge der SARS-CoV-2-Pandemie, sowie zur wahrgenommenen (Un-)Angemessenheit der staatlichen SARS-CoV-2-Sicherheitsmaßnahmen während der Pandemie erhoben.

3.3 Erfassung psychologischer und psychopathologischer Merkmale

Um die traumatische Belastung der Patienten durch die SARS-CoV-2-Pandemie hinweg zu erfassen, wurde in den Longitudinalstudien (Publikationen 2 und 3) ein

Trauma-Screening-Fragebogen, welcher sonst zur Erfassung der Symptome einer posttraumatischen Belastungsstörung dient (83), modifiziert und einzelne Items konkret auf die SARS-CoV-2-Pandemie als Trauma ausgerichtet. In der in Publikation 3 beschriebenen Studie wurde zudem die deutschsprachige Version des Fragebogens zur *Hospital Anxiety and Depression Scale* (HADS) verwendet, welcher den Schweregrad des psychopathologischen Syndroms in Form von Depressions- und Angstsymptomen misst (84). Zusätzlich wurden die Persönlichkeitsmerkmale der Patienten mit dem NEO-FFI, welcher auf der Grundlage des Big-5 Persönlichkeitsmodells beruht (85,86), ermittelt und durch die deutsche Version des *Temperament and Character Inventory-revised* (TCI-R), welcher auf dem psychobiologischen Persönlichkeitsmodell von Cloninger basiert (87), ergänzt.

3.4 Statistik

Nach der Pseudonymisierung der Patientendaten erfolgte die statistische Analyse mit SPSS Statistics 27 (IBM). Durch Testung mit dem Kolmogorov-Smirnov-Test wurde auf Normalverteilung der Daten geprüft.

In allen drei hier vorliegenden Publikationen wurden Mittelwerte und Standardabweichungen oder Mediane und Wertebereiche (Minima und Maxima) als Darstellungsform für metrische Daten (z. B. Alter, EDSS) genutzt, während Anzahl und Prozentwerte für kategoriale Daten (z. B. MS-Verlaufsform) angegeben wurden.

Unterschiede zwischen verschiedenen Patientengruppen (z. B. zwischen vollständig und unvollständig geimpften Patienten) wurden mittels einfaktorieller Varianzanalyse (ANOVA), Chi-Quadrat-Tests, exakten Fisher-Tests, Kruskal-Wallis-Tests, Mann-Whitney-U-Tests und ungepaarten, zweiseitigen Student-t-Tests ermittelt. p-Werte $<0,05$ zeigten statistisch signifikante Unterschiede an. Die Validität des selbstberichteten Impfstatus von vollständig und unvollständig geimpften Patienten wurde anhand der Maße der Sensitivität und Spezifität berechnet.

Mithilfe der Falscherkennungsrate (*false discovery rate*, FDR) wurde in Publikation 1 die Alphafehlerakkumulation aufgrund von Mehrfachtestungen berücksichtigt (88). Dies erfolgte in Publikation 2 und 3 nicht, da es sich um explorative Studien handelte. In Publikation 2 und 3 wurden außerdem Assoziationen zwischen Intervalldaten und ordinalen Daten (z. B. Intensität der traumatischen Belastung) oder nominalen Daten durch einfaktorielle Varianzanalysen (ANOVA) mit entsprechenden Post-hoc-Tests in

Abhängigkeit von der Gleichheit der Varianzen (gleiche Varianzen: Tukey b; ungleiche Varianzen: Games-Howell) untersucht. Zudem wurden Beziehungen zwischen intervallskalierten Daten mittels Spearman-Rho-Korrelationskoeffizienten berechnet und Beziehungen zwischen nominalen oder ordinalen Daten mittels Chi-Quadrat-Tests bzw. Kontingenzkoeffizienten bestimmt.

4 Ergebnisse

Im Rahmen dieser Dissertation entstanden drei Originalarbeiten (81,89,90). Diese sind in Kap. 8 der vorliegenden Arbeit integriert. Nachfolgend werden die drei Arbeiten jeweils zusammengefasst vorgestellt. Dabei liegt der Schwerpunkt auf der Präsentation der Ergebnisse. Um die Ergebnisse der jeweiligen Publikation besser einordnen zu können, werden zudem für jede Arbeit kurze Informationen zu den Hintergründen und zu den Methoden der Studie vorgestellt sowie eine Schlussfolgerung aus den Ergebnissen gezogen.

4.1 Publikation 1: *Vaccination Coverage against Tetanus, Diphtheria, Pertussis and Poliomyelitis and Validity of Self-Reported Vaccination Status in Patients with Multiple Sclerosis*

Hintergrund: MS-Patienten sind durch die Therapie mit DMD, die das Immunsystem modulieren, einem erhöhten Infektionsrisiko ausgesetzt (2). Infektionen können mit schwerwiegenden Folgen, die bis zum Tod führen können, einhergehen (78). Die Gefahr einer Therapie-assoziierten Infektion sollte bei MS-Patienten unter Risiko-Nutzen-Abwägung präventiv, z. B. mittels Impfungen, minimiert werden (79). Das Ziel dieser Arbeit war es, einen Überblick über den Impfstatus, das Impfwissen und den Umgang mit der Impftematik von MS-Patienten zu verschaffen.

Methoden: Es wurden 327 MS-Patienten bezüglich der Impfvollständigkeit (Tetanus, Diphtherie, Pertussis und Poliomyelitis), der Kenntnis über den eigenen Impfstatus sowie des Impfverhaltens untersucht. Zudem wurden diese Impfdaten auf Assoziationen mit soziodemografischen und klinischen Patientencharakteristika geprüft.

Ergebnis: Das Durchschnittsalter der Kohorte lag bei 47,3 Jahren und der Anteil an Frauen bei 68,8%. Die klinisch-neurologischen Daten ergaben einen mittleren EDSS-Score von 3,3 und das Datum der MS-Erstdiagnose lag im Median 10 Jahre zurück. Die häufigste MS-Verlaufsform war mit 67,6% die RRMS und 258 Patienten (78,9%) gaben an, zum Zeitpunkt der Befragung mit einer DMD behandelt zu werden.

Rund zwei Drittel der Patienten (67,9%) berichteten, im letzten Jahr keine Impfberatung erhalten zu haben und 35,5% wünschten sich zum Zeitpunkt der Befragung eine Impfberatung. Bei 72,8% der Patienten wurde der Impfausweis

bisher entweder durch den Hausarzt oder durch den Neurologen überprüft; 56 Patienten (17,1%) gaben hingegen an, nie eine Impfausweiskontrolle erhalten zu haben. Die Patienten ohne Impfausweiskontrolle unterschieden sich von Patienten mit ärztlicher Überprüfung des Impfausweises dadurch, dass sie signifikant häufiger männlich waren (44,6 vs. 29,4%; $p=0,037$) und signifikant weniger Geschwister hatten (1,1 vs. 1,6; $p=0,016$). Zudem beschäftigten sie sich im letzten Jahr weniger mit dem Thema Impfen (32,1 vs. 69,3%; $p<0,001$), erhielten signifikant seltener eine Impfberatung (38,7 vs. 12,5%; $p<0,001$) und wünschten sich dafür signifikant häufiger ein Impfberatungsgespräch (48,2 vs. 34,4%, $p=0,030$) als Patienten mit ärztlicher Impfausweiskontrolle.

Die Kontrolle der Impfausweise ergab mehrheitlich einen vollständigen Impfstatus gegen Tetanus (79,5%), Diphtherie (79,2%), Pertussis (74,8%) und Poliomyelitis (84,8%). Die durch die Patienten selbst eingeschätzte Vollständigkeit des Impfstatus war bei Tetanus signifikant höher (86,5%; $p=0,008$) und bei Diphtherie (69,4%; $p=0,002$), Pertussis (61,2%; $p<0,001$) und Poliomyelitis (75,9%; $p=0,005$) signifikant niedriger als der reale Impfstatus nach Impfausweiskontrolle. Im Impfverhalten konnten Unterschiede für die alle zehn Jahre aufzufrischenden Impfungen (Tetanus, Diphtherie und Pertussis) detektiert werden. Ein signifikant höherer Anteil unvollständig geimpfter Patienten hatte sich innerhalb des letzten Jahres nicht mit der Impftematik beschäftigt ($p\leq 0,002$) und auch keine Impfberatung erhalten ($p\leq 0,001$). Zudem erhielten unvollständig geimpfte Patienten signifikant häufiger keine Impfausweiskontrolle als vollständig geimpfte Patienten ($p<0,001$). Hohe Sensitivität (>80%) und niedrige Spezifität (<40%) wurde für alle vier Impfungen bezüglich der Einschätzung der eigenen Impfvollständigkeit und der im Impfausweis dokumentierten Impfvollständigkeit festgestellt.

In einer weiteren Subgruppenanalyse zwischen Patienten, die ihren Impfstatus korrekt einschätzten, und Patienten, die ihn falsch einschätzten, zeigten sich signifikante Unterschiede in Bildung, Krankheitsdauer, dem Zeitpunkt, wann sich die Patienten letztmalig mit Impfungen beschäftigt haben und der Impfausweiskontrolle. Bei allen vier Impfungen hatten deutlich mehr Patienten, die ihren Impfstatus falsch einschätzten, keine Impfausweiskontrolle durch Dritte erhalten ($p\leq 0,008$).

Schlussfolgerung: Die Impfquoten der für MS-Patienten als sicher angesehenen Totimpfstoffe (60) lagen in der untersuchten Kohorte wesentlich höher als in der

deutschen Gesamtbevölkerung (91). Diese Unterschiede in den Impfquoten könnten auf regelmäßige Arztkonsultationen und damit verbundene häufigere Impfausweiskontrollen bei MS-Patienten zurückzuführen sein. Daneben haben die jahrelangen Diskussionen über Risiken und Nutzen von Impfungen bei MS die Aufmerksamkeit der behandelnden Ärzte auf den Impfstatus ihrer Patienten mutmaßlich erhöht (49,64,92–94).

Die Ergebnisse der Untersuchung zeigen zudem, dass sowohl die Impfvollständigkeit als auch das Impfwissen von MS-Patienten deutlich mit dem Impfverhalten der Patienten einhergeht: Impfberatungen sowie Impfausweiskontrollen waren mit einem vollständigem Impfstatus assoziiert. Die Patienten mit fehlender Impfausweiskontrolle waren mehrheitlich Männer, was möglicherweise die generell höhere Inanspruchnahme medizinischer Angebote durch Frauen widerspiegelt (95).

Behandelnde Ärzte sollten ihren Patienten regelmäßig Beratungsgespräche über Impfungen und Impfausweisüberprüfungen anbieten, um das allgemeine Infektionsrisiko zu mindern. Aufgrund der hohen Diskrepanz zwischen gedachtem und realem Impfstatus sollte insbesondere darauf geachtet werden, die Patienten über alle enthaltenen Vakzine einer Kombinationsimpfung und die Wichtigkeit von Auffrischungsimpfungen aufzuklären, um die Validität des selbst berichteten Impfstatus zu erhöhen.

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

Hintergrund: Die Thematik der Impfeinstellung und Impfbereitschaft von MS-Patienten wurde durch den Ausbruch der SARS-CoV-2-Pandemie im Jahr 2020 noch bedeutsamer. Für MS-Patienten ist das Risiko einer Krankenhauseinweisung aufgrund einer Infektion viermal höher als in der Allgemeinbevölkerung (77). Daher wurde zu Beginn der Pandemie angenommen, dass SARS-CoV-2 ein hohes Gesundheitsrisiko für MS-Patienten darstelle (96). Das Ziel dieser Arbeit war es, vor Verfügbarkeit eines SARS-CoV-2-Impfstoffes, die Impfbereitschaft und die Impfeinstellungen von MS-Patienten zu erheben sowie die Akzeptanz von staatlichen Pandemiemaßnahmen zu ermitteln.

Methoden: Es wurden Daten zu Impfeinstellungen von 200 MS-Patienten vor (Basisbefragung) und während der SARS-CoV-2-Pandemie (1. Follow-up) erhoben und miteinander verglichen. Zudem wurden, neben soziodemografischen und klinischen Parametern, Daten zum Impfstatus von Standardimpfungen und zum Impfverhalten erhoben. Ergänzend wurde mithilfe eines modifizierten Trauma-Screening-Fragebogens (83) die pandemische Belastung (physisch, psychisch und sozial) erfasst. Ferner wurde der Standpunkt zu pandemischen, staatlich festgelegten Sicherheitsmaßnahmen erfragt.

Ergebnis: Die Kohorte ($n=200$) beinhaltete 65,5% Frauen und das Durchschnittsalter lag bei 48,2 Jahren. Klinisch-neurologisch konnte ein mittlerer EDSS-Score von 3,5 und eine durchschnittliche Krankheitsdauer von 11,7 Jahren ermittelt werden. Die Mehrheit der Patienten (64,0%) war von der schubförmig remittierenden Verlaufsform betroffen. Ein vollständiger Impfstatus konnte für Influenza bei 13,5% der Patienten festgestellt werden. Von den Frauen waren 13,7% und von den Männern 13,0% vollständig gegen Grippe geimpft. Über Nebenwirkungen nach einer vergangenen Impfung berichteten häufiger Frauen (39,0%) als Männer (24,6%). 75,0% der Patienten erklärten die Bereitschaft, alle für sie empfohlenen Schutzimpfungen durchführen zu lassen.

Nach Beginn der COVID-19-Pandemie (März 2020) gaben 60,5% an, sich potenziell gegen SARS-CoV-2 impfen zu lassen, sobald ein Impfstoff verfügbar sei. Bezüglich der Auswirkungen der Pandemie auf die Einstellung gegenüber staatlich empfohlenen Standardimpfungen schilderten 6,5% der Patienten eine ablehnende und 6,0% eine befürwortende Veränderung der Impfbereitschaft, während 48,0% erklärten, sie hätten schon immer die staatlichen Impfempfehlungen akzeptiert. Keine Veränderung der Impfbereitschaft gegenüber Standardimpfungen wurde von 39,5% der Patienten angegeben. Es konnte eine positive Assoziation zwischen Alter und der Offenheit für eine SARS-CoV-2-Impfung festgestellt werden ($p<0,001$). Der Anteil an Patienten, die bereit waren, eine SARS-CoV-2-Impfung durchführen zu lassen, war bei denen, die den staatlichen Impfempfehlungen vor der Pandemie folgten, signifikant höher, als bei denen, die die Empfehlungen ablehnten (66,7 vs. 42,0%; $p=0,006$). Es zeigte sich eine leichte, aber nicht signifikante Tendenz, dass Patienten, die vor der Pandemie eine Impfbereitschaft bezüglich staatlich empfohlener Standardimpfungen zeigten, die staatlichen Maßnahmen zur

Pandemiebekämpfung eher akzeptierten als Patienten ohne Impfbereitschaft (75,3 vs. 62,0%; $p=0,101$).

Im Zuge der Pandemie berichteten 28,5% über psychische, physische oder soziale Belastungszustände. Die MS-Verlaufsform war signifikant mit der erlebten Belastung durch die Pandemie (erhoben durch den Trauma-Screening-Fragebogen) assoziiert ($p<0,001$). Patienten mit progressivem Verlauf gaben die stärkste Belastung durch die Pandemie an, während CIS- oder RRMS-Patienten über die geringsten Auswirkungen berichteten. Zudem wiesen Patienten, die die staatlichen Sicherheitsmaßnahmen als eher unangemessen empfanden, eine längere MS-Erkrankungsdauer auf als Patienten, die die Maßnahmen angemessen fanden ($p=0,034$).

Schlussfolgerung: Die überwiegende Bereitschaft von MS-Patienten, sich impfen zu lassen, wird durch das Ergebnis dieser Analyse verdeutlicht, dass 75,0% der Patienten vor der Pandemie die Bereitschaft zeigten, alle empfohlenen Schutzimpfungen durchführen zu lassen. Dass zum damaligen Zeitpunkt nur 60,5% eine SARS-CoV-2 Impfung hätten durchführen lassen wollen, steht im Widerspruch zur überwiegenden Akzeptanz der staatlichen Impfempfehlungen, was an der Angst bzw. der Ungewissheit vor einem neu entwickelten Impfstoff liegen könnte. Die positive Assoziation von Alter und Impfbereitschaft gegenüber SARS-CoV-2-Impfstoffen könnte darauf zurückzuführen sein, dass das Risiko für einen schweren COVID-19-Verlauf bei älteren Menschen erhöht ist (97). Zusammenfassend ist behandelnden Ärzten von MS-Patienten zu empfehlen, besonders bei jüngeren Patienten darauf zu achten, sie umfassend über empfohlene Impfungen zu informieren und zudem transparent über neu entwickelte Impfstoffe aufzuklären.

4.3 Publikation 3: *Vaccination willingness in association with personality traits in patients with multiple sclerosis in the course of SARS-CoV-2 pandemic*

Hintergrund: Seit Sommer 2020 sind weltweit mehrere Impfstoffe gegen COVID-19 zugelassen (98). Unter dem Eindruck der SARS-CoV-2-Pandemie, inklusive der Impfempfehlungen durch die STIKO (67), war das Ziel dieser Studie, die Bereitschaft zur SARS-CoV-2-Impfung, die Akzeptanz staatlicher Schutzmaßnahmen zur Pandemiebekämpfung und die Einstellung zu empfohlenen Standardimpfungen vor

und während der SARS-CoV-2-Pandemie (nach Verfügbarkeit eines COVID-19-Impfstoffes) bei MS-Patienten zu untersuchen. Zudem sollten soziodemografische, klinische, psychosoziale und Persönlichkeitsmerkmale von MS-Patienten identifiziert werden, die mit der allgemeinen und der SARS-CoV-2-Impfbereitschaft assoziiert sind.

Methoden: Die Datenerhebung erfolgte als longitudinale und bizenrische Studie. Insgesamt wurden 404 Patienten zu soziodemografischen, klinisch-neurologischen und psychologischen Attributen ab Juni 2019 untersucht (Basisbefragung). Die Daten zur SARS-CoV-2-Impfbereitschaft wurden in zwei Folgeuntersuchungen erhoben (Follow-up 1 (vor Verfügbarkeit der SARS-CoV-2-Impfstoffe, $n=200$) und Follow-up 2 (nach Verfügbarkeit des ersten SARS-CoV-2-Impfstoffs, $n=157$)).

Ergebnis: In der Basisbefragung gaben 73,5% der 404 untersuchten Patienten an, den staatlichen Impfempfehlungen zu folgen. Die Akzeptanz einer SARS-CoV-2-Impfung lag in den beiden Folgeuntersuchungen bei 60% (Follow-up 1) bzw. 61% (Follow-up 2), während 23% (Follow-up 1) bzw. 21% (Follow-up 2) der Patienten angaben, keine SARS-CoV-2-Impfung erhalten zu wollen. Die Bereitschaft vor der Pandemie, alle empfohlenen Schutzimpfungen durchführen zu lassen, war signifikant mit der Bereitschaft, eine SARS-CoV-2-Impfung durchführen zu lassen, in der ersten ($p=0,006$), aber nicht in der zweiten Nachuntersuchung, assoziiert ($p=0,253$). Standardimpfungen ablehnende Patienten wollten sich häufiger nicht gegen SARS-CoV-2 impfen lassen als Patienten, die den staatlichen Impfempfehlungen positiv gegenüber standen (38% vs. 17%). Es wurde zudem festgestellt, dass ältere Patienten in beiden Nachuntersuchungen signifikant häufiger ihre Einstellung gegenüber empfohlenen Standardimpfungen änderten ($p=0,003/p=0,017$) und die SARS-CoV-2-Impfung eher durchführen lassen würden ($p<0,001/p=0,017$) als jüngere Patienten.

In der Analyse psychopathologischer Variablen zeigten Patienten mit einem während der Pandemie hohen Trauma-Score in der ersten Nachuntersuchung eine positive Assoziation mit der SARS-CoV-2-Impfakzeptanz ($p=0,039$) und in der zweiten Nachuntersuchung eine negative Assoziation mit der allgemeinen Impfbereitschaft ($p=0,003$). Zwei Persönlichkeitsmerkmale, die signifikant mit der Bereitschaft für Schutzimpfungen korrelierten, waren Extraversion ($p=0,007$) und Neugierde ($p=0,017$). Je eigenverantwortlicher (2. Folgeuntersuchung: $p=0,018$) und je

kooperativer (2. Folgeuntersuchung: $p=0,018$) die Patienten waren, desto eher änderten sie ihre Meinung (zwischen dem Zeitraum vor Pandemiebeginn und den Folgeuntersuchungen während der Pandemie) gegenüber den staatlichen Impfeempfehlungen in Richtung Akzeptanz. Hohe Werte für Neurotizismus (2. Folgeuntersuchung: $p<0,001$) und Gewissenhaftigkeit (2. Folgeuntersuchung: $p=0,009$) im TCI-R hingegen waren mit einer ablehnenden Haltung gegenüber allgemeinen Impfeempfehlungen assoziiert.

Schlussfolgerung: Der Anteil an Patienten, die bereit waren, eine SARS-CoV-2-Impfung durchführen zu lassen, lag mit 60% (Follow-up 1) bzw. 61% (Follow-up 2) etwas niedriger als bei MS-Patienten in den USA (66-70,1%) (99,100). Die Gründe für die niedrigere Impfbereitschaft der Untersuchungskohorte können vielfältig sein. Zum einen befürchten viele MS-Patienten eine Verschlechterung des Krankheitsverlaufs durch eine Impfung allgemein (64) und zum anderen könnte die anfängliche Sorge um die Sicherheit der neuen Nukleinsäure-basierten Impfstoffe gegen SARS-CoV-2 eine Rolle gespielt haben (54,55).

Die niedrigere Impfbereitschaft von Patienten mit höherem Trauma-Score zur zweiten Nachuntersuchung könnte auf das zunehmende Misstrauen gegenüber den SARS-CoV-2-Impfstoffen, bedingt durch mediale Berichterstattung über Nebenwirkungen, abnehmenden Impfschutz im zeitlichen Verlauf und die Beschleunigung des Zulassungsverfahrens, zurückzuführen sein (101–103). In dieser Studie wurden erstmalig Erkenntnisse über Persönlichkeitsmerkmale von MS-Patienten, die mit der Ablehnung oder Befürwortung von Impfungen assoziiert sind, gewonnen. Die Erkenntnis, dass manche Patienten sensibler für die Impftematik sind als andere, sollte künftig bei Beratungen zu Schutzimpfungen von ärztlicher Seite aus berücksichtigt werden.

5 Diskussion

Im Folgenden werden die Ergebnisse der drei Subgruppenanalysen von MS-Patienten im Umgang mit Impfungen diskutiert. Generell sollte das Ziel behandelnder Ärzte von MS-Patienten sein, sie möglichst effektiv vor Infektionen zu schützen. Um einen adäquaten Schutz vor Infektionen aufzubauen, sind ein vollständiger Impfstatus gegen vermeidbare Infektionskrankheiten und die damit verbundene Bereitschaft für Schutzimpfungen von MS-Patienten wesentliche Bausteine (66,69,80,104,105). Ziel dieser Arbeit war es, einen Überblick über den Impfstatus (anhand ausgewählter Impfungen), das Impfverhalten und die Impfbereitschaft von MS-Patienten zu erhalten. Die Impfraten der Standardimpfungen gegen Tetanus, Diphtherie, Pertussis und Poliomyelitis (Publikation 1) sowie von der Grippeimpfung (Publikation 2) wurden analysiert. Zudem wurden Impfeinstellungen vor und nach dem Ausbruch der SARS-CoV-2-Pandemie untersucht (Publikation 2 und 3).

Die erhobenen Impfquoten der zehnjährlich aufzufrischenden Standardimpfungen waren in der untersuchten MS-Kohorte im Vergleich zur deutschen Allgemeinbevölkerung deutlich höher (Tetanus: 79,5 vs. 54,4%; Diphtherie 79,2 vs. 53,4%; Pertussis: 84,8 vs. 49,8%) (91). In Studien zu Patienten mit anderen Autoimmunerkrankungen wurde im Vergleich zur untersuchten MS-Kohorte über niedrigere Impfquoten berichtet (106–111). Die erhöhten Impfquoten der MS-Kohorte könnten auf höher frequentierte ärztliche Konsultationen und damit verbundene Impfausweisüberprüfungen sowie Impfangebote zurückzuführen sein. Ein scheinbar widersprüchliches Ergebnis zu dieser Hypothese ist die niedrige Grippeimpfrate (13,5%) der zu Beginn der COVID-19-Pandemie untersuchten Kohorte. Im Vergleich wurden in anderen Ländern höhere Influenzaimpfquoten (20,4% bis 79,9%) bei MS-Patienten berichtet (112,113). In der deutschen Bevölkerung wurde ebenfalls eine höhere Impfrate gegen Influenza (35,4%) bei Erwachsenen mit relevanten Grunderkrankungen erfasst (91). Die angestrebten nationalen Impfquoten von über 75% für die Influenzaimpfung bei Risikogruppen oder über 90 bis über 95% für Tetanus, Diphtherie und Pertussis (114) wurden in der untersuchten MS-Kohorte jeweils verfehlt. Die allgemeine Impfbereitschaft der untersuchten MS-Kohorte lag bei 75,0% bzw. 73,5% (Publikationen 2 bzw. 3) und damit niedriger als die ermittelten Impfraten für Tetanus, Diphtherie, Pertussis, Poliomyelitis und höher als die ermittelte Influenzaimpfquote. Um als vollständig immunisiert zu gelten, muss laut

Empfehlungen des RKI (82) die Grippeimpfung jährlich aufgefrischt werden. Auffrischungsimpfungen gegen die anderen untersuchten Erkrankungen sind, mit Ausnahme von Poliomyelitis, nur alle zehn Jahre notwendig (67). Dies könnte eine Erklärung für die niedrigere Grippeimpfquote, im Vergleich zur angegebenen allgemeinen Impfbereitschaft der untersuchten MS-Patienten, sein. Ein weiterer Grund für die niedrige Grippeimpfquote könnte das durchschnittlich relativ niedrige Alter der Patienten sein (7). Junge Patienten sind in der Regel von weniger Komorbiditäten betroffen und könnten die Influenzaimpfung daher auch nicht als essenziell ansehen (115). Die Impfung gegen Influenza wird allerdings, neben Über-60-Jährigen, Schwangeren und Personen mit erhöhter Gefährdung, allen Patienten mit relevanten Grunderkrankungen (MS mit eingeschlossen) empfohlen (67).

Die niedrige Grippeimpfrate der in Studie 2 untersuchten Kohorte stellt für die Patienten ein Risiko dar. Eine Infektion mit dem Influenzavirus ist mit einer 6-fach erhöhten Wahrscheinlichkeit einer Exazerbation der MS im Vergleich zur Influenzaimpfung assoziiert (116) und geht zudem mit einem erhöhten Risiko für akute Hospitalisierung einher (117). Prädiktoren, die zur Ablehnung einer Gripeschutzimpfungen von MS-Patienten führen, wurden in verschiedenen Studien bereits untersucht. Zu wenig Informationen über den Impfstoff, Angst vor der Impfung oder vor Verschlechterung der MS, Neben- und Wechselwirkungen, negative Impferfahrungen oder generelle Ablehnung von Impfungen waren die Gründe, die von den Patienten am häufigsten angegeben wurden (113). Dies sollten behandelnde Ärzte beachten und dabei individuell auf die Patienten und deren Sorgen und Ängste bezüglich einer Impfung eingehen. Kliniker sollten allerdings ebenfalls die klinische Impferfolgsquote der Gripeschutzimpfung berücksichtigen, welche bei Erwachsenen nur zwischen 37 und 51% geschätzt wird (118). Eine Möglichkeit, den Impfstatus der Patienten besser zu überwachen und künftig auf notwendige Impfungen hinzuweisen, stellt die elektronische Gesundheitskarte dar (119). Patel et al. konnten zeigen, dass ein elektronisches Patientenaktensystem, welches den behandelnden Arzt informiert, ob dem Patienten eine Grippeimpfung anzuraten sei, die Influenzaimpfquoten signifikant um 6,6% erhöht (120). Solche Systeme könnten in Zukunft auch bei anderen aufzufrischenden Impfungen eingesetzt werden.

Für behandelnde Ärzte von MS-Patienten ist es von besonderem Interesse, welche Faktoren mit der Vollständigkeit bzw. Unvollständigkeit des Impfstatus assoziiert sind. Als Faktoren, die vollständig und unvollständig geimpfte Patienten unterscheiden, wurden in der in Publikation 1 beschriebenen Untersuchung der MS-Kohorte in erster Linie Impfverhaltensweisen detektiert. Regelmäßige Impfausweiskontrollen ($p < 0,001$), jährliche Impfberatungen ($p \leq 0,001$) und sich innerhalb des letzten Jahres mit Impfungen beschäftigt zu haben ($p \leq 0,002$) gingen signifikant mit einem vollständigen Impfstatus für Tetanus, Diphtherie und Pertussis einher. Das Wissen über den eigenen Impfstatus wurde, wie die Impfquoten, vor allem durch das Impfverhalten beeinflusst. Insgesamt gaben 17% der Patienten an, keine regelmäßige Impfausweiskontrolle zu erhalten, was sich mit Studienergebnissen bei Lupus-erythematoses-Erkrankten deckt, in denen der Anteil bei 24% lag (106). In der Subgruppe der Patienten ohne Überprüfung des Impfausweises waren signifikant mehr Männer ($p = 0,037$), Patienten mit wenigen Geschwistern ($p = 0,016$) und Patienten, die den Wunsch nach einer Impfberatung hegten ($p = 0,030$) im Vergleich zu MS-Patienten mit ärztlicher Impfausweiskontrolle. In künftigen Arztkonsultationen sollten vor allem Patienten, die diese Attribute vorweisen, zur Impfausweiskontrolle angestoßen und ggf. vor dem Termin benachrichtigt werden, den Impfausweis mitzubringen. Zudem sollten regelmäßige Impfberatungen und Impfausweiskontrollen stattfinden, bei denen die Patienten für das Thema Impfungen sensibilisiert und über deren Nutzen aufgeklärt werden. Böhmer et al. konnten ebenfalls nachweisen, dass Impfberatungen mit einem vollständigem Impfstatus assoziiert sind (121). Die niedrige Spezifität (<40%) für den selbst-berichteten im Vergleich zum dokumentierten Impfstatus zeigt, dass Patienten mit einem unvollständigen Impfstatus eher glauben, sie seien vollständig geimpft. Auch in der Literatur wurde über vergleichbare Ergebnisse für den selbst-angegebenen Tetanusimpfstatus berichtet (122,123). Dies unterstreicht die Relevanz von Aufklärung und Informationstransparenz über die enthaltenen Impfstoffe in Kombinationsimpfungen, die Dauer des Impfschutzes einzelner Impfungen sowie die damit verbundene Notwendigkeit von Auffrischungsimpfungen, um letztlich das Vertrauen sowie das Wissen der Patienten über den eigenen Impfstatus zu stärken.

Durch den Ausbruch der SARS-CoV-2-Pandemie konnte die Impfbereitschaft von MS-Patienten im Verlauf anhand der SARS-CoV-2-Impfungen analysiert werden. Zu

Beginn der Pandemie gaben 60% und in der 2. Folgeuntersuchung (Frühjahr 2021) 61% der Patienten an, eine SARS-CoV-2 Impfung durchführen lassen zu wollen. Diese Zahlen sind niedriger und stehen damit im Widerspruch zur signalisierten generellen Bereitschaft von 73,5% der MS-Patienten aus der Basisbefragung, sich impfen zu lassen. In einer Metaanalyse aus dem Jahr 2022 wurde bei insgesamt 5983 MS-Patienten eine Impfbereitschaft von 76% für eine Impfung gegen SARS-CoV-2 ermittelt (124). Ehde et al. untersuchten in einer Verlaufsstudie die SARS-CoV-2-Impfbereitschaft von MS-Patienten in den USA. Dort konnte ein Anstieg der Impfbereitschaft von 66% auf 74% detektiert werden. In Deutschland wurde in der Allgemeinbevölkerung im Jahr 2020 eine Impfbereitschaft für eine SARS-CoV-2-Impfung von 70% festgestellt (125). Jäckle et al. konnten niedrigere SARS-CoV-2-Impfraten in ostdeutschen Bundesländern im Vergleich zur gesamten Bundesrepublik Deutschland aufzeigen (126). Da die im Zuge dieser Doktorarbeit ausgewerteten Daten zu Patienten aus ostdeutschen Bundesländern erhoben wurden, könnte dies eine Erklärung für die niedrigere Impfbereitschaft zur SARS-CoV-2-Impfung sein. Impfbablehnung ist allerdings kein regionales, sondern ein globales Problem, welches in den letzten Jahren zugenommen und vor allem während der COVID-19-Pandemie erhöhte Aufmerksamkeit generiert hat (46,127–129). Schon vor Pandemiebeginn, zwischen 2015 und 2019, ist in vielen Ländern das Vertrauen in die Bedeutung, Sicherheit und Wirksamkeit von Impfstoffen gesunken (130). Verschiedene Studien haben Impfskepsis in der Allgemeinbevölkerung untersucht. Dabei waren unter anderem Faktoren wie Arbeitslosigkeit, niedriges Einkommen, junges Alter, niedriges Bildungsniveau, weibliches Geschlecht und Religiosität mit der Ablehnung von Impfstoffen assoziiert (128,129).

In dieser Arbeit waren bei MS-Patienten die Faktoren Neurotizismus und Gewissenhaftigkeit als Persönlichkeitsmerkmale negativ mit der generellen oder der SARS-CoV-2-Impfakzeptanz assoziiert. Eine positive Assoziation mit der allgemeinen oder der SARS-CoV-2-Impfakzeptanz zeigte sich für verschiedene soziodemografische und Persönlichkeitsfaktoren, wie Alter, Extraversion und Neugierde. Alter konnte von Uhr und Mateen ebenfalls als ein positiv mit der COVID-19-Impfbereitschaft assoziierter Faktor detektiert werden (131). Für MS-Patienten werden die SARS-CoV-2-Impfstoffe im Allgemeinen als weitestgehend sicher

angesehen und von der STIKO empfohlen (65,98,134). In der Arbeit von Frahm et al. konnten keine erhöhten Schubraten nach einer SARS-CoV-2-Impfung im Vergleich zu einem definierten Zeitraum vor der Impfung festgestellt werden (135). Allerdings klagten rund zwei Drittel der Patienten über Impfreaktionen und einer von zehn Geimpften über eine subjektiv empfundene Verschlechterung der bestehenden MS-Symptome nach der SARS-CoV-2-Impfung (136,137). In der Literatur sind Sicherheitsbedenken bezüglich des Impfstoffs, neben Sorgen über die Auswirkung auf die MS, der Hauptgrund für die Ablehnung einer SARS-CoV-2-Impfung von MS-Patienten (58,100,131). Ein niedriges Bildungsniveau, ein niedriges wahrgenommenes persönliches Risiko einer SARS-CoV-2-Infektion sowie ein mangelndes Vertrauen in Gesundheitsinstitutionen waren in anderen Studien ebenfalls mit Impfzögerlichkeit assoziiert (100,132). Fehlende Informationen und Ungewissheit über die neu entwickelten Vektor- und mRNA-Impfstoffe gegen SARS-CoV-2 könnten zudem zur Ablehnung einer COVID-19-Impfung geführt haben (54,55). Ob die Verfügbarkeit anderer Impfstoffe, wie Totimpfstoffe gegen SARS-CoV-2 (133), zu einer höheren Impfbereitschaft führt, muss in weiteren Studien eruiert werden.

Im Folgenden werden die Limitationen dieser Arbeit thematisiert. Aufgrund des bizenrischen Studiendesigns kann es durch individuell unterschiedliche Befragungsstile der Untersucher (z. B. Verwendung von Suggestivfragen) zur Verzerrung der Ergebnisse gekommen sein. Zudem erfolgte die Patientenrekrutierung der Basisbefragung bis Juni 2020, was durch die erhöhte mediale Aufmerksamkeit zur SARS-CoV-2-Ausbreitung dazu geführt haben könnte, dass sich die Patienten, die nach Pandemiebeginn befragt wurden, vermehrt mit dem Thema Impfungen und ihrem Impfstatus auseinandergesetzt haben als Patienten, die vor Pandemiebeginn befragt wurden. Zur Zeit des 2. Follow-up war die SARS-CoV-2-Impfkampagne erst wenige Monate angelaufen, weswegen dieser früh gewählte Zeitpunkt ein Grund dafür gewesen sein könnte, dass einige Patienten noch kein Vertrauen in die neu entwickelten Impfstoffe hatten oder auf einen Protein-basierten SARS-CoV-2-Impfstoff warten wollten (133). Der Impfstatus wurde in der vorliegenden Arbeit nur für fünf Impfungen untersucht, weswegen hier kein Gesamtüberblick über den Impfstatus von MS-Patienten gegeben werden kann. Ein

weiterer limitierender Faktor könnte sein, dass die psychologischen und psychopathologischen Daten auf Basis von Selbst-Berichten der Patienten beruhen.

Nichtsdestotrotz kann diese Arbeit anhand von jährlich bzw. zehnjährlich aufzufrischenden Impfungen einen guten Einblick in die Impfvollständigkeitsraten und damit assoziierten Faktoren von MS-Patienten geben. In Zukunft können durch die zunehmende Globalisierung und Vernetzung der Welt zudem weitere Pandemien nicht ausgeschlossen werden, weswegen der Schutz vor Infektionen speziell von Risikogruppen eine gesamtgesellschaftliche Aufgabe ist. MS-Patienten gelten als Risikogruppe, da Infektionskrankheiten für sie eine signifikante Gefahr und die häufigste Todesursache darstellen (70,77). Deshalb ist der Schutz vor impfpräventablen Infektionskrankheiten für sie von höchster Bedeutung (64,68). Das Ziel behandelnder Ärzte muss sein, neben Gewährleistung von Sicherheit und klinischem Nutzen neuer Impfstoffe, das Vertrauen in Impfungen bei MS-Patienten zu stärken, da dies der am stärksten mit der Impfbereitschaft assoziierte Faktor ist (130). Dabei spielen Impfberatungsgespräche eine wesentliche Rolle (81). Die in dieser Arbeit neu gewonnenen Erkenntnisse zum Impfwissen, zum Impfverhalten und zur Impfbereitschaft von MS-Patienten können künftig von behandelnden Ärzten während dieser Beratungsgespräche berücksichtigt werden. Allerdings sollte die jeweilige Lebenssituation der Patienten, inklusive soziodemografischer Faktoren wie Alter, Beruf oder Lebensstil sowie klinisch-neurologischer Aspekte wie Medikation und Krankheitsverlauf bei der Impfindikation beachtet werden (68,80). Dabei spielt für das individuelle Infektionsrisiko auch die Unterscheidung von Basis-, Indikations- und Reiseimpfung eine Rolle (67). Es sollten zudem strukturelle Faktoren, wie sozioökonomische Barrieren oder Differenzen in der Gesundheitsversorgung, die eine unzureichende Inanspruchnahme von Impfungen bewirken können, bedacht werden (129). Die Möglichkeit des elektronischen Gesundheitsmonitorings könnte behandelnden Ärzten künftig die Möglichkeit bieten, den Impfstatus ihrer Patienten besser zu überwachen und zudem die interdisziplinäre Zusammenarbeit zwischen Hausärzten und Spezialisten verbessern.

6 Zusammenfassung

Impfstatus, Impfbereitschaft und Impfverweigerung sind durch die SARS-CoV-2-Pandemie in den Fokus der Öffentlichkeit gerückt. Für MS-Patienten hatten diese Themen jedoch schon vor der Pandemie eine hohe Relevanz, da sie durch ihre immunmodulatorische Therapie einem erhöhten Infektionsrisiko ausgesetzt sind und Infektionen für sie schwerwiegende Folgen haben können, weswegen der Schutz durch Impfungen von besonderer Bedeutung für diese Patienten ist (104). Durch die zunehmenden Hinweise, dass eine EBV-Infektion an der Entwicklung von MS beteiligt ist (11–13), könnte in Zukunft ggf. die Modulierung von Faktoren, welche für die Krankheitsentstehung bedeutsam sind, durch eine Impfung eine entscheidende Rolle in der Krankheitsprävention spielen (138).

Das Ziel dieser Arbeit war es, einen Einblick zu erhalten, inwiefern sich MS-Patienten mit dem Thema Impfungen auseinandersetzen, ob sie sich der Notwendigkeit eines vollständigen Impfstatus bewusst sind sowie zu eruieren, welche Faktoren mit dem Impfverhalten und den Impfeinstellungen assoziiert sind.

Eine Kohorte von 404 MS-Patienten wurde in Subgruppenanalysen bezüglich des Impfstatus und des Impfwissens (Publikation 1) sowie zur Impfbereitschaft (Publikation 2 und 3) untersucht. Die Impfvollständigkeit wurde anhand von im Erwachsenenalter aufzufrischenden Basis- bzw. Indikationsimpfungen überprüft. Die Analyse der Impfeinstellungen und der Impfbereitschaft wurde in Studien zu Beginn und im Verlauf der COVID-19-Pandemie durchgeführt. Dazu erfolgte die Untersuchung psychischer Auswirkungen der Pandemie auf die Patienten (Publikation 2) und die Identifikation von Persönlichkeitsmerkmalen, welche mit der allgemeinen und der SARS-CoV-2-Impfbereitschaft assoziiert sind (Publikation 3).

Die ermittelten Impfquoten der MS-Patienten lagen für Tetanus bei 79,5%, für Diphtherie bei 79,2%, für Pertussis bei 74,8%, für Poliomyelitis bei 84,8% (Publikation 1) und für Influenza bei 13,5% (Publikation 2). Eine signifikante Diskrepanz fand sich zwischen dem selbst-berichteten und dem realen Impfstatus. Regelmäßige Impfberatungen und Impfausweiskontrollen waren die wesentlichen Faktoren, die mit einem vollständigen Impfstatus sowie einem besseren Wissensstand über den eigenen Impfstatus assoziiert waren. Zudem enthielt die Subgruppe der Patienten ohne regelmäßige Impfausweiskontrollen (17%) mehr

Männer und Patienten mit wenig Geschwistern (Publikation 1). In der Basisbefragung gaben 73,5% der Patienten eine allgemeine Impfbereitschaft an. Zu Beginn der Pandemie waren aber nur 60% (Publikation 2) bereit, sich speziell gegen SARS-CoV-2 impfen zu lassen. Auch nach Zulassung erster Impfstoffe lag die Impfbereitschaft gegen SARS-CoV-2 nur bei 61%, sodass kein wesentlicher Anstieg der Akzeptanz eines SARS-CoV-2-Impfstoffs erfasst werden konnte (Publikation 3). Mit der allgemeinen und der SARS-CoV-2 Impfbereitschaft negativ assoziiert waren neben soziodemografischen Variablen, wie einem jungen Alter, auch Persönlichkeitsfaktoren. Neurotizismus und Gewissenhaftigkeit als Persönlichkeitsmerkmale sowie eine empfundene traumatische Belastung durch die Pandemie waren mit einer ablehnenden Haltung gegenüber Impfungen assoziiert (Publikation 2 und 3).

Die neu gewonnenen Erkenntnisse der präsentierten Studien zu den Impfraten, zur Impfbereitschaft und den assoziierten Faktoren erlauben behandelnden Ärzten, ungeimpfte Patienten sowie Patienten mit ablehnenden Haltungen zum Impfen leichter zu detektieren und sind daher im klinischen Alltag relevant. Auf Basis dieser Ergebnisse könnten zukünftig nationale Datenerhebungen durchgeführt werden, um regionale Unterschiede in der Impfbereitschaft und bei den Impfzeiten von MS-Patienten innerhalb von Deutschland zu eruieren, so wie es bereits Daten zur Masernimpfquote in den verschiedenen deutschen Bundesländer gibt (139). Zudem sollten die gewonnenen Erkenntnisse zu den Impfquoten als Ausgangspunkt für weitere Studien zu anderen Impfungen bei MS-Patienten genutzt werden, um einen besseren Gesamtüberblick über den Impfstatus von MS-Patienten zu gewinnen. Es könnte künftig versucht werden, elektronische Gesundheitssysteme in Praxen zu integrieren, um den Impfstatus besser zu überwachen, die Patienten auf fehlende Impfungen hinzuweisen und ihnen gezielt ein Impfangebot zu unterbreiten. Das Ziel sollte sein, die Impfquoten zu erhöhen und so das Risiko infektionsbedingter Komplikationen zu minimieren.

7 Literaturverzeichnis

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8 Publikationen

8.1 Publikation 1

Vaccination Coverage against Tetanus, Diphtheria, Pertussis and Poliomyelitis and Validity of Self-Reported Vaccination Status in Patients with Multiple Sclerosis

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J Pers Med. 2022 Apr 23;12(5):677.

doi: 10.3390/jpm12050677

Article

Vaccination Coverage against Tetanus, Diphtheria, Pertussis and Poliomyelitis and Validity of Self-Reported Vaccination Status in Patients with Multiple Sclerosis

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Citation: Langhorst, S.E.; Frahm, N.; Hecker, M.; Mashhadiakbar, P.; Streckenbach, B.; Baldt, J.; Heidler, F.; Zettl, U.K. Vaccination Coverage against Tetanus, Diphtheria, Pertussis and Poliomyelitis and Validity of Self-Reported Vaccination Status in Patients with Multiple Sclerosis. *J. Pers. Med.* **2022**, *12*, 677. <https://doi.org/10.3390/jpm12050677>

Academic Editors: Roger E. Thomas and Reginald M. Gorczynski

Received: 15 February 2022

Accepted: 15 April 2022

Published: 23 April 2022

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Abstract: Multiple sclerosis (MS) is a chronic immune-mediated disease with a neurodegenerative component of the central nervous system. Immunomodulatory therapy can increase the risk of infection, which is a particular risk for MS patients. Therefore, a complete vaccination status is of utmost importance as protection against vaccine-preventable infectious diseases. Our aim was to investigate the vaccination status, vaccination card knowledge and the vaccination behavior of MS patients with regard to vaccinations against tetanus, diphtheria, pertussis and poliomyelitis. Three hundred twenty-seven patients with MS were evaluated by anamnesis, clinical examination, structured interview and vaccination card control in this two-center study. Based on the recommendations of the Robert Koch Institute, we assessed the completeness of the vaccination status of the examined vaccinations. Furthermore, a comparative analysis of patients with complete/incomplete or correctly/wrongly self-reported vaccination status was performed. In the cohort analyzed, the vaccination coverage was 79.5% for tetanus, 79.2% for diphtheria, 74.8% for pertussis and 84.8% for poliomyelitis. The assumed vaccination status was higher for tetanus (86.5%) and lower for diphtheria (69.4%), pertussis (61.2%) and poliomyelitis (75.9%). Patients who were unvaccinated or only partially vaccinated against tetanus had received vaccination advice from a physician less often in the past year (13.4 vs. 36.9%, $p < 0.001$) and had no one to check the vaccination card more often (35.8 vs. 12.3%, $p < 0.001$). High sensitivity (93.7%) and low specificity (30.3%) were determined regarding the validity of self-reported tetanus vaccination status. Patients with a correctly reported tetanus vaccination status were more likely to have their vaccination card checked by a physician than those who overestimated or underestimated their vaccination status (76.7 vs. 63.0/43.8%, $p = 0.002$). Similar findings were seen with regard to diphtheria, pertussis and poliomyelitis vaccination. Patients without a regular vaccination card control (17.1%) were more likely to be male (44.6 vs. 29.4%, $p = 0.037$), had fewer siblings on average (1.1 vs. 1.6, $p = 0.016$), dealt less frequently with the issue of vaccination in the past year (32.1 vs. 69.3%, $p < 0.001$) and more frequently had the wish to receive vaccination advice (48.2 vs. 34.4%, $p = 0.030$) than patients in whom the vaccination card was checked regularly by a physician. To minimize the risk of infection in MS patients, treating physicians should provide regular vaccination counseling and perform vaccination card controls, as these factors are associated with a higher vaccination coverage and a higher validity of self-reported vaccination statuses.

Keywords: multiple sclerosis; vaccination coverage; vaccination behavior; vaccination status self-assessment; tetanus; diphtheria; pertussis; poliomyelitis

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system [1,2] that affects more than 2.8 million people worldwide [3], with a higher incidence in women than in men [4]. Generally, the disease is diagnosed between the ages of 20 and 49 years [5,6]. In the development of MS, genetic and environmental factors play a crucial role [7–10]. The symptoms can be remarkably diverse: Initially, patients often complain about dysesthesias, paresis, or visual problems. As the disease progresses, fatigue, spasticity, bladder dysfunction, ataxia, pain, depression and cognitive dysfunction are among the most commonly reported symptoms [11]. Several courses of the disease have been distinguished [12]. The most common disease course at onset is relapsing-remitting MS (RRMS), in which neurological deficits occur during relapses and resolve completely or incompletely. Secondary progressive MS (SPMS), which can develop from RRMS in the course of the disease and the rarer primary progressive MS (PPMS) are characterized by a steadily progressive accumulation of disability over time. In PPMS, there are no relapses from the onset of the disease. Clinically isolated syndrome (CIS), refers to patients who are affected by an initial clinical event that is strongly suggestive of MS but does not yet meet the diagnostic criteria for MS [13]. Current treatment strategies for MS focus on treating acute relapses, relieving symptoms and reducing disease activity. These disease-modifying therapies influence the course of MS by suppressing or modulating immune functions [14]. More than a dozen disease-modifying drugs (DMDs) are currently available for the treatment of MS [15,16]. A disadvantage of these immunomodulatory and immunosuppressive therapies is the increased risk of infection observed in MS patients [17]. It has long been discussed that infections play a role in the development of MS [18–20]. In addition, other studies have shown that infections may increase the risk of relapses in MS patients [17,21,22], with more sustained disability (as measured by the Expanded Disability Status Scale (EDSS) [23]) compared to infection-independent relapses [24]. Furthermore, the hospitalization rate and the mortality of MS patients affected by infections is increased compared to those without infections [25,26].

Due to the adverse effects of infections, special attention should be paid to the prevention of infections in MS patients, for instance through vaccinations [27]. While vaccinations are considered one of the most important successes in the history of medicine, with vaccines having saved countless lives by preventing potentially dangerous and life-limiting infectious diseases, the relation of MS and vaccination has been debated for decades. However, studies have not confirmed the concern that vaccinations may exacerbate MS or even be a trigger of the disease (with the exception of yellow fever vaccination, which may increase the relapse risk) [28,29]. Overall, the advantages of vaccinations outweigh the potential risks and before starting DMD therapy, completion of vaccination status is recommended in MS patients [30]. In addition to this special priority of vaccinations for MS patients, we live in a time in which vaccination hesitancy plays an increasingly important role in society [31,32].

We aimed to examine the vaccination status (completeness), the validity of self-reported vaccination status, vaccination knowledge and vaccination behavior of MS patients. Furthermore, our objective was to determine whether the vaccination status and the vaccination behavior of MS patients are associated with sociodemographic or clinical patient characteristics. To our knowledge, this study is the first to present data on the willingness of MS patients to get vaccinated and their interest in vaccinations. We investigated vaccination statuses based on the common vaccinations for tetanus, diphtheria, pertussis and poliomyelitis because these have been administered as a combination vaccination in Germany for many years [33]. They have been administered in this manner as it is recommended that tetanus, diphtheria and pertussis vaccinations are boosted every ten years [34]. The investigation of the completeness of these important vaccinations allows us to gain an insight into the vaccination awareness of MS patients.

2. Materials and Methods

2.1. Study Cohort

This cross-sectional multi-center study was conducted at the Department of Neurology (Section of Neuroimmunology) of the Rostock University Medical Center and at the Neurological Department of the Ecumenical Hainich Hospital in Mühlhausen (Germany). Data from a total of 327 patients (157 from Rostock and 170 from Mühlhausen) with a confirmed diagnosis of MS according to the revised McDonald criteria from 2017 [13] were collected in the years 2019 and 2020. The medical centers have special outpatient and inpatient wards for MS patients. The inpatients were either hospitalized to relieve disease activity or drug side effects or were admitted for emergency care and further examinations. In the outpatient wards, patients usually had medical appointments for routine checkups. The participation of inpatients and outpatients in this study was on a voluntary basis after we gave them spoken and written information and an appropriate time to consider the opportunity to participate in this study. After obtaining informed consent, patient data were collected on the basis of four sources of information: an anamnesis as well as patient records (including the vaccination card), a clinical examination and a structured patient interview. This study was approved by the ethics committee of the University of Rostock, the ethics committee of Thuringia and conducted according to the Declaration of Helsinki.

2.2. Data Acquisition

We collected sociodemographic, clinical-neurological and vaccination data of the patients. Sociodemographic data included sex, age, years in school (not including training or higher education), educational level, employment status, partnership status and place of residence (rural community— ≤ 5000 residents, provincial town— 5000 – $19,999$ residents, medium-sized town— $20,000$ – $99,999$ residents, city— $\geq 100,000$ residents) as well as numbers of children and siblings.

The clinical-neurological data included type of care (inpatient or outpatient), course of MS, disease duration (years), degree of disability (EDSS), number of comorbidities (defined according to the recommendations from the “International Workshop on Comorbidities in MS”) [35,36] and type of DMD used.

Vaccination data covered information on the patients’ attitudes regarding vaccinations, e.g., whether they received a vaccination consultation in the past year, whether they dealt with the issue of vaccinations in the past year, the wish for vaccination advice, and information on who regularly checks the patient’s vaccination card. Additionally, we checked the patients’ vaccination cards for childhood basic immunizations and adult booster immunizations to evaluate the completeness of immunizations against tetanus, pertussis, diphtheria and poliomyelitis. To consider the vaccination status as complete, we followed the German national recommendations by the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute (RKI) [37] (Table 1). Tetanus, diphtheria and pertussis vaccination statuses were considered complete if, in addition to basic immunization, a booster vaccination had been administered within the last ten years. Poliomyelitis vaccination status was defined as complete if the patients received the full basic immunization. We also obtained patients’ opinions on the completeness of tetanus, diphtheria, pertussis and poliomyelitis vaccinations in order to compare them with the actual vaccination statuses according to their vaccination cards.

2.3. Statistics

We analyzed the data of all patients whose vaccination cards indicated that they had either a complete or an incomplete vaccination status against tetanus, diphtheria, pertussis or poliomyelitis. Patients with an incomplete vaccination status were either unvaccinated or did not receive all necessary vaccinations. Missing data resulted when information was available for a patient for one of these vaccinations but not for another. Therefore, for pertussis and poliomyelitis vaccination, only 317 and 303 of the 327 patients were evaluated, respectively.

Table 1. German national recommendations by the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute (RKI) for tetanus, diphtheria, pertussis and poliomyelitis vaccination [37].

| Vaccination | RKI Recommendations 2020/21 | | |
|---------------|---|------------------------------------|---|
| | Childhood Basic Immunization | Childhood Booster Immunization | Adult Immunization |
| Tetanus | Three vaccinations at 2, 4 and 11 months of age | At 5–6 years and 9–16 years of age | All persons in case of missing or incomplete basic immunization or if the last basic immunization or the last booster vaccination is longer than 10 years ago |
| Diphtheria | Three vaccinations at 2, 4 and 11 months of age | At 5–6 years and 9–16 years of age | All persons in case of missing or incomplete basic immunization or if the last basic immunization or the last booster vaccination is longer than 10 years ago |
| Pertussis | Three vaccinations at 2, 4 and 11 months of age | At 5–6 years and 9–16 years of age | It is recommended that the next Td vaccinations given as a single Tdap combination vaccination |
| Poliomyelitis | Three vaccinations at 2, 4 and 11 months of age | Between the ages of 9–16 years | All persons with missing or incomplete basic immunization and all persons without a booster vaccination |

RKI—Robert Koch Institute; Td—tetanus-diphtheria vaccine; Tdap—tetanus-diphtheria-pertussis vaccine.

The statistical analysis was performed using PASW Statistics 27 (IBM). The data were tested for normal distribution using Kolmogorov–Smirnov tests. Means and standard deviations or medians and ranges are presented for metric data, whereas counts and percentages are reported for categorical data. Differences between patient groups were examined using one-way analysis of variance (ANOVA), chi-squared tests, Fisher’s exact tests, Kruskal–Wallis tests, Mann–Whitney U tests, McNemar’s test and two-tailed Student’s *t*-tests as appropriate. *p*-values < 0.05 indicated statistically significant differences. The false discovery rate (FDR) was applied to consider alpha error accumulation due to multiple testing [38]. Differences that were significant even after FDR correction were marked with an asterisk in the tables. The validity of self-reported vaccination status of fully and incompletely vaccinated patients was assessed using the measures sensitivity and specificity. Only those patients who reported their vaccination status as complete or incomplete were included in this calculation. Bar charts and boxplots were created using Microsoft Excel 2016 (Version 2203, Microsoft Corporation, Redmond, WA, USA).

3. Results

3.1. Sociodemographic and Clinical Data

The study included 327 MS patients with an average age of 47.3 ± 13.1 years and the proportion of women was 68.8%. The majority of patients lived in a partnership (75.2%), had ≥1 child (72.2%) and ≥1 sibling (90.2%). The duration of schooling was 10.6 ± 1.3 years and the majority of MS patients (60.6%) had completed training as a skilled worker. A subset of 41.0% of the patients were already retired due to illness or age. Clinical neurological examination revealed a median EDSS score of 3.0 (range: 0–8.0) with median disease duration of 10 years (range: 0–41 years). A total of 221 patients (67.6%) had a diagnosis of RRMS and almost 75% of the patients suffered from comorbidities in addition to MS. A subset of 78.9% of the patients were treated with a DMD at the time of the data acquisition (Table 2). The most commonly used DMDs were interferon-beta preparations (15.3% of the patients), glatiramer acetate (10.1%), fingolimod (8.0%), natalizumab (7.0%) and ocrelizumab (6.7%).

Table 2. Sociodemographic and clinical data of the examined patients with multiple sclerosis ($n = 327$).

| | <i>n</i> (%) | Range | Mean (SD) | Median |
|---------------------------------|--------------|-------|-------------|--------|
| Sex | | | | |
| Female | 225 (68.8) | | | |
| Male | 102 (31.2) | | | |
| Age (years) | | 19–80 | 47.3 (13.1) | 49.0 |
| Place of residence | | | | |
| Rural area | 133 (40.7) | | | |
| Small town | 49 (15.0) | | | |
| Medium-sized town | 61 (18.7) | | | |
| City | 84 (25.7) | | | |
| Partnership | | | | |
| Single | 61 (18.7) | | | |
| In a relationship | 65 (19.9) | | | |
| Married | 181 (55.4) | | | |
| Divorced | 12 (3.7) | | | |
| Widowed | 8 (2.4) | | | |
| Number of children | | 0–4 | 1.2 (0.9) | 1.0 |
| 0 | 91 (27.8) | | | |
| 1 | 88 (26.9) | | | |
| 2 | 130 (39.8) | | | |
| 3 | 15 (4.6) | | | |
| 4 | 3 (0.9) | | | |
| Number of siblings | | 0–9 | 1.5 (1.1) | 1.0 |
| 0 | 32 (9.8) | | | |
| 1 | 169 (51.7) | | | |
| ≥2 | 126 (38.5) | | | |
| School years | | 8–18 | 10.6 (1.3) | 10.0 |
| Educational level | | | | |
| No training | 11 (3.4) | | | |
| Skilled worker | 198 (60.6) | | | |
| Technical college | 59 (18.0) | | | |
| University | 59 (18.0) | | | |
| Employment status | | | | |
| Training/student | 5 (1.5) | | | |
| Fulltime employed | 94 (28.7) | | | |
| Part-time employed | 74 (22.6) | | | |
| Unemployed | 13 (4.0) | | | |
| Disability pension | 105 (32.1) | | | |
| Retirement pension | 29 (8.9) | | | |
| Other | 7 (2.1) | | | |
| Patient care | | | | |
| Outpatients | 258 (78.9) | | | |
| Inpatients | 69 (21.1) | | | |
| Course of disease | | | | |
| CIS | 16 (4.9) | | | |
| RRMS | 221 (67.6) | | | |
| SPMS | 63 (19.3) | | | |
| PPMS | 27 (8.3) | | | |
| Disease duration (years) | | 0–41 | 11.6 (8.6) | 10.0 |
| EDSS score | | 0–8.0 | 3.3 (2.1) | 3.0 |

Table 2. Cont.

| | <i>n</i> (%) | Range | Mean (SD) | Median |
|----------------------|--------------|-------|-----------|--------|
| DMD treatment | | | | |
| Yes | 258 (78.9) | | | |
| No | 69 (21.1) | | | |
| Comorbidities | | | | |
| Yes | 244 (74.6) | | | |
| No | 83 (25.4) | | | |

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; SD—standard deviation; SPMS—secondary progressive MS.

3.2. Vaccination Survey Data

Over 35% of the patients ($n = 116$) wished to receive vaccination advice from a physician and 67.9% ($n = 222$) of the patients did not receive a consultation on vaccination within the past year. Considering the awareness of vaccinations, 37.0% ($n = 121$) of the patients stated that they had last dealt with the topic more than a year ago. A subset of 17.1% ($n = 56$) reported not having their vaccination status checked by anyone, while 72.8% ($n = 238$) of the patients reported that their vaccination cards were routinely checked by their family doctor or by a neurologist and 10.1% ($n = 33$) indicated that other people checked their immunization records. By checking the patients' vaccination cards, we found a complete vaccination status for tetanus in 79.5%, for diphtheria in 79.2%, for pertussis in 74.8% and for poliomyelitis in 84.8% of the patients. We compared these documented immunization statuses with the patients' self-reported vaccination statuses. The assumed vaccination completeness was significantly higher for tetanus ($p = 0.008$) and significantly lower for the other three vaccinations ($p \leq 0.005$) than the real vaccination status (Figure 1a). The proportion of patients who correctly assessed their own vaccination status was highest for tetanus (78.6%) and lowest for pertussis (56.5%). The proportion of patients who reported not knowing their vaccination status was 2.4% for tetanus and approximately 20% for the other vaccinations (Figure 1b).

3.3. Comparison between Patients with Complete and Incomplete Vaccination Status

We divided the patient cohort into patients with a complete vaccination status (PwCV) and patients with an incomplete vaccination status (PwIV) for each type of vaccination and compared the patient groups with regard to differences in sociodemographic, clinical, and vaccination data. The comparisons revealed no significant differences in terms of age and sex for all vaccinations (Table 3), although there was a consistent tendency that males were overrepresented among PwIV. PwIV for tetanus and diphtheria had significantly fewer siblings than those who were fully vaccinated (1.2 vs. 1.6; $p \leq 0.008$). PwCV for poliomyelitis were found to be more likely to live in rural areas and cities compared to PwIV ($p = 0.010$). The groups did not differ with respect to other sociodemographic factors. Analysis of the clinical data also revealed no significant differences between the patient groups except for poliomyelitis vaccination: PwIV for poliomyelitis ($n = 46$) were significantly more likely to have SPMS than PwCV (28.3 vs. 16.3%; $p = 0.013$). For the vaccinations that need to be boosted every 10 years (tetanus, diphtheria and pertussis), differences between PwCV and PwIV were seen in vaccination awareness: significantly more PwIV did not receive vaccination counseling by a physician in the past year ($p \leq 0.001$) (Figure 2a) and did not deal with the issue of vaccinations during the past year (Figure 2b). However, no significant differences could be elicited in the desire for vaccination advice between the groups ($p \geq 0.349$). The proportion of patients without any independent vaccination card check was significantly higher in those patients that were incompletely immunized against tetanus, diphtheria and pertussis ($p < 0.001$) (Figure 2c). A similar but non-significant difference between PwCV and PwIV was found for poliomyelitis vaccination ($p = 0.058$). There were also significant differences between PwCV and PwIV in

the correctness of self-reported vaccination statuses. For all vaccinations, we found high sensitivity and low specificity in self-reported vaccination status when compared to the documented vaccination status ($p \leq 0.014$). Less than half of the PwIV correctly reported their vaccination status as incomplete for each of the four vaccinations (Figure 2d).

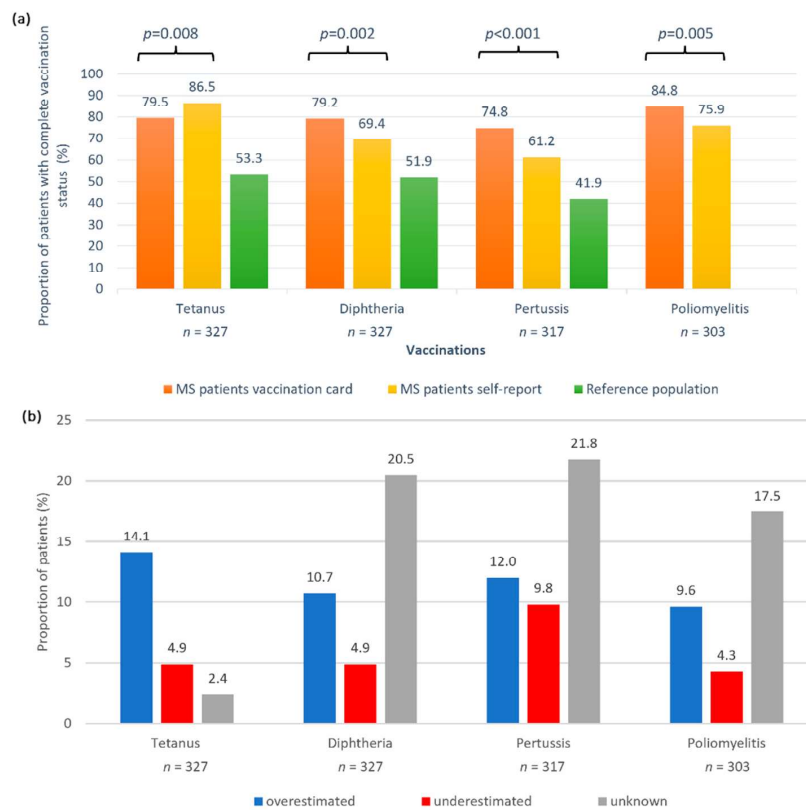


Figure 1. Concordance of self-reported vaccination status and vaccination card information in patients with MS. (a) There was a significant difference in immunization status as documented in the vaccination cards (orange bars) and as assumed by the patients (yellow bars). More patients with MS thought they were fully vaccinated against tetanus than was actually the case ($p < 0.008$ McNemar). In contrast, for the other vaccinations, the assumed vaccination status was lower than the documented vaccination rates: more patients were actually fully vaccinated than the self-reports indicated ($p \leq 0.005$ McNemar). Vaccination rates were markedly higher than for the general population in Germany (no data on polio vaccines were available) [34]. (b) More patients overestimated vaccination completeness than underestimated it. The proportion of patients who reported not knowing their vaccination status was 2.4% for tetanus and roughly 20% for the other vaccinations under consideration. McNemar—McNemar’s test; MS—multiple sclerosis; n —number of patients; p — p -value.

Table 3. Comparison of MS patients with complete vs. incomplete vaccination status with regard to sociodemographic and clinical data.

| | Tetanus (n = 327) | | Diphtheria (n = 327) | | Pertussis (n = 317) | | Polio (n = 303) | |
|---------------------------------------|-----------------------------|----------------------|-----------------------------|----------------------|-----------------------------|----------------------|-----------------------------|----------------------|
| | Complete vs. Incomplete | p-Value | Complete vs. Incomplete | p-Value | Complete vs. Incomplete | p-Value | Complete vs. Incomplete | p-Value |
| n | 260 vs. 67 | | 259 vs. 68 | | 237 vs. 80 | | 257 vs. 46 | |
| Sex^c | | 0.077 F [†] | | 0.056 F [†] | | 0.069 F [†] | | 0.302 F [†] |
| Female | 185 (71.2) vs. 40 (59.7) | | 185 (71.4) vs. 40 (58.8) | | 170 (71.7) vs. 48 (60.0) | | 179 (69.7) vs. 28 (60.9) | |
| Male | 75 (28.8) vs. 27 (40.3) | | 74 (28.6) vs. 28 (41.2) | | 67 (28.3) vs. 32 (40.0) | | 78 (30.3) vs. 18 (39.1) | |
| Age (years)^a | 47.7 (12.9) vs. 45.9 (13.8) | 0.325 t | 47.7 (12.9) vs. 45.9 (13.7) | 0.306 t | 47.8 (12.9) vs. 45.2 (13.5) | 0.127 t | 46.7 (12.7) vs. 49.2 (14.3) | 0.213 t |
| Place of residence^c | | 0.284 Chi | | 0.322 Chi | | 0.135 Chi | | 0.010 Chi |
| Rural area | 109 (41.9) vs. 24 (35.8) | | 108 (41.7) vs. 25 (36.8) | | 102 (43.0) vs. 27 (33.8) | | 112 (43.6) vs. 15 (32.6) | |
| Small town | 34 (13.1) vs. 15 (22.4) | | 34 (13.1) vs. 15 (22.0) | | 29 (12.2) vs. 18 (22.5) | | 33 (12.8) vs. 13 (28.3) | |
| Medium-sized town | 50 (19.2) vs. 11 (16.4) | | 50 (19.3) vs. 11 (16.2) | | 44 (18.6) vs. 14 (17.5) | | 40 (15.6) vs. 11 (23.9) | |
| City | 67 (25.8) vs. 17 (25.4) | | 67 (25.9) vs. 17 (25.0) | | 62 (26.2) vs. 21 (26.2) | | 72 (28.0) vs. 7 (15.2) | |
| Partnership^c | | 0.872 Chi | | 0.773 Chi | | 0.898 Chi | | 0.143 Chi |
| Single | 48 (18.5) vs. 13 (19.4) | | 48 (18.5) vs. 13 (19.1) | | 43 (18.1) vs. 17 (21.3) | | 48 (18.7) vs. 11 (23.9) | |
| In a relationship | 49 (18.8) vs. 16 (23.9) | | 48 (18.5) vs. 17 (25.0) | | 46 (19.4) vs. 18 (22.5) | | 56 (21.8) vs. 6 (13.0) | |
| Married | 147 (56.5) vs. 34 (50.7) | | 147 (56.8) vs. 34 (50.0) | | 134 (56.5) vs. 40 (50.0) | | 140 (54.5) vs. 24 (52.2) | |
| Divorced | 10 (3.8) vs. 2 (3.0) | | 10 (3.9) vs. 2 (2.9) | | 8 (3.4) vs. 3 (3.7) | | 6 (2.3) vs. 4 (8.7) | |
| Widowed | 6 (2.3) vs. 2 (3.0) | | 6 (2.3) vs. 2 (2.9) | | 6 (2.5) vs. 2 (2.5) | | 7 (2.7) vs. 1 (2.2) | |
| Number of children^a | 1.3 (0.9) vs. 1.2 (0.9) | 0.479 t | 1.3 (0.9) vs. 1.2 (0.9) | 0.542 t | 1.3 (0.9) vs. 1.1 (0.9) | 0.248 t | 1.2 (0.9) vs. 1.2 (1.0) | 0.644 t |
| Number of siblings^a | 1.6 (1.2) vs. 1.2 (0.8) | 0.008 *t | 1.6 (1.2) vs. 1.2 (0.8) | 0.007 *t | 1.6 (1.1) vs. 1.3 (1.1) | 0.083 t | 1.4 (1.0) vs. 1.7 (1.1) | 0.159 t |
| School years^a | 10.6 (1.3) vs. 10.6 (1.2) | 0.959 t | 10.6 (1.3) vs. 10.6 (1.2) | 0.992 t | 10.6 (1.3) vs. 10.7 (1.3) | 0.270 t | 10.7 (1.3) vs. 10.3 (1.1) | 0.090 t |
| Educational level^c | | 0.826 Chi | | 0.813 Chi | | 0.131 Chi | | 0.160 Chi |
| No training | 8 (3.1) vs. 3 (4.5) | | 8 (3.1) vs. 3 (4.4) | | 7 (2.9) vs. 4 (5.0) | | 5 (2.0) vs. 3 (6.5) | |
| Skilled worker | 160 (61.5) vs. 38 (56.7) | | 160 (61.8) vs. 38 (55.9) | | 148 (62.5) vs. 40 (50.0) | | 153 (59.5) vs. 28 (60.9) | |
| Technical college | 47 (18.1) vs. 12 (17.9) | | 46 (17.8) vs. 13 (19.1) | | 44 (18.6) vs. 15 (18.7) | | 47 (18.3) vs. 10 (21.7) | |
| University | 45 (17.3) vs. 14 (20.9) | | 45 (17.4) vs. 14 (25.6) | | 38 (16.0) vs. 21 (26.3) | | 52 (20.2) vs. 5 (10.9) | |
| Employment status^c | | 0.796 Chi | | 0.782 Chi | | 0.911 Chi | | 0.646 Chi |
| Training / student | 4 (1.5) vs. 1 (1.5) | | 4 (1.5) vs. 1 (1.5) | | 3 (1.3) vs. 2 (2.5) | | 4 (1.6) vs. 1 (2.2) | |
| Full time employed | 74 (28.5) vs. 20 (29.8) | | 73 (28.2) vs. 21 (30.9) | | 70 (29.5) vs. 23 (28.7) | | 82 (31.9) vs. 9 (19.5) | |
| Part timer employed | 59 (22.7) vs. 15 (22.4) | | 59 (22.8) vs. 15 (22.1) | | 55 (23.2) vs. 18 (22.5) | | 59 (22.9) vs. 11 (23.9) | |
| Unemployed | 8 (3.1) vs. 5 (7.5) | | 8 (3.1) vs. 5 (7.3) | | 8 (3.4) vs. 5 (6.3) | | 11 (4.3) vs. 1 (2.2) | |
| Disability pension | 85 (32.7) vs. 20 (29.8) | | 85 (32.8) vs. 20 (29.4) | | 74 (31.2) vs. 24 (30.0) | | 74 (28.8) vs. 18 (39.1) | |
| Retirement pension | 24 (9.2) vs. 5 (7.5) | | 24 (9.3) vs. 5 (7.3) | | 22 (9.3) vs. 6 (7.5) | | 21 (8.2) vs. 5 (10.9) | |
| Other | 6 (2.3) vs. 1 (1.5) | | 6 (2.3) vs. 1 (1.5) | | 5 (2.1) vs. 2 (2.5) | | 6 (2.3) vs. 1 (2.2) | |

Table 3. Contd.

| | Tetanus (n = 327) | | Diphtheria (n = 327) | | Pertussis (n = 317) | | Polio (n = 303) | |
|---|--------------------------|---------------------|--------------------------|---------------------|--------------------------|---------------------|--------------------------|---------------------|
| | Complete vs. Incomplete | p-Value | Complete vs. Incomplete | p-Value | Complete vs. Incomplete | p-Value | Complete vs. Incomplete | p-Value |
| Patient care^c | | | | | | | | |
| Outpatients | 207 (79.6) vs. 51 (76.1) | 0.507 ^{Fi} | 206 (79.5) vs. 52 (76.5) | 0.617 ^{Fi} | 190 (80.2) vs. 58 (72.5) | 0.160 ^{Fi} | 205 (79.8) vs. 33 (71.7) | 0.243 ^{Fi} |
| Inpatients | 53 (20.4) vs. 16 (23.9) | | 53 (20.5) vs. 16 (23.5) | | 47 (19.8) vs. 22 (37.5) | | 52 (20.2) vs. 13 (28.3) | |
| Course of disease^c | | 0.588 Chis | | 0.311 Chis | | 0.422 Chis | | 0.013 Chis |
| CIS | 11 (4.2) vs. 5 (7.5) | | 10 (3.9) vs. 6 (8.8) | | 10 (4.2) vs. 6 (7.5) | | 12 (4.7) vs. 4 (8.7) | |
| RRMS | 179 (68.8) vs. 42 (62.7) | | 179 (69.1) vs. 42 (61.8) | | 167 (70.5) vs. 49 (61.3) | | 185 (72.0) vs. 22 (47.8) | |
| SPMS | 48 (18.5) vs. 15 (22.3) | | 48 (18.5) vs. 15 (22.1) | | 41 (17.3) vs. 17 (21.2) | | 42 (16.3) vs. 13 (28.3) | |
| PPMS | 22 (8.5) vs. 5 (7.5) | | 22 (8.5) vs. 5 (7.3) | | 19 (8.0) vs. 8 (10.0) | | 18 (7.0) vs. 7 (15.2) | |
| Disease duration (years)^b | 10.0 vs. 8.0 | 0.096 ^U | 12.0 vs. 9.8 | 0.059 ^U | 10.0 vs. 7.5 | 0.050 ^U | 10.0 vs. 9.0 | 0.468 ^U |
| EDSS score^b | 3.0 vs. 2.5 | 0.550 ^U | 3.0 vs. 2.5 | 0.416 ^U | 3.0 vs. 3.0 | 0.641 ^U | 3.0 vs. 3.5 | 0.331 ^U |
| DMD treatment^c | | 1.000 ^{Fi} | | 0.868 ^{Fi} | | 0.875 ^{Fi} | | 0.847 ^{Fi} |
| Yes | 205 (78.9) vs. 53 (79.1) | | 205 (79.1) vs. 53 (77.9) | | 185 (78.1) vs. 64 (80.0) | | 200 (77.8) vs. 36 (78.3) | |
| No | 55 (21.1) vs. 14 (20.9) | | 54 (20.9) vs. 15 (22.1) | | 52 (21.9) vs. 16 (20.0) | | 57 (22.2) vs. 10 (21.7) | |
| Comorbidities^c | | 0.532 ^{Fi} | | 0.639 ^{Fi} | | 0.140 ^{Fi} | | 0.720 ^{Fi} |
| Yes | 196 (75.4) vs. 48 (71.6) | | 195 (75.3) vs. 49 (72.1) | | 181 (76.4) vs. 54 (67.5) | | 187 (72.8) vs. 35 (76.1) | |
| No | 64 (24.6) vs. 19 (28.4) | | 64 (24.7) vs. 19 (27.9) | | 56 (23.6) vs. 26 (32.5) | | 70 (27.2) vs. 11 (23.9) | |

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; SD—standard deviation; SPMS—secondary progressive MS; ^a mean value (standard deviation); ^b median; ^c number of patients (%); chi-squared test; ^{Fi} Fisher's exact test; ^t two-sample two-tailed Student's *t*-test; ^U Mann-Whitney U test; * significant after FDR correction.

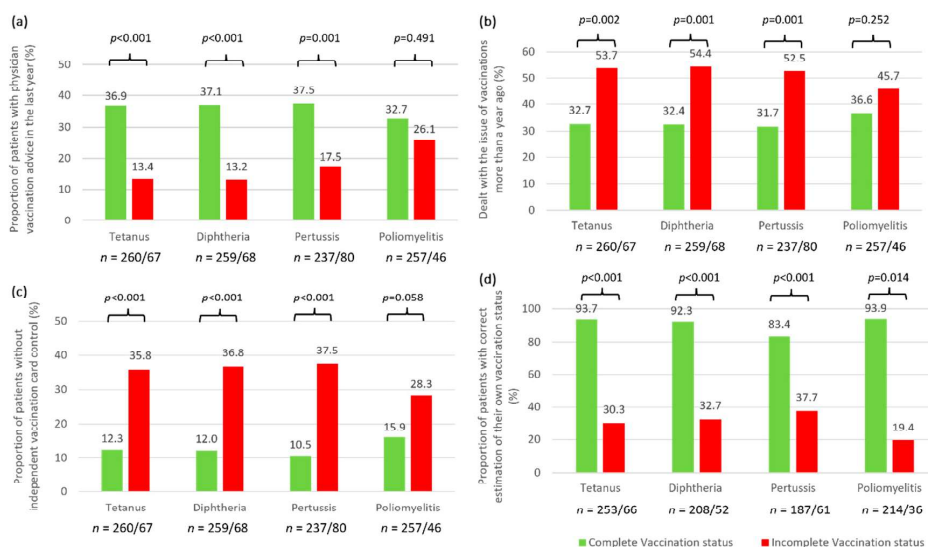


Figure 2. Comparison of MS patients with complete vs. incomplete vaccination status with regard to vaccination advice, interest, control and knowledge. (a) The proportion of patients with physician counseling on vaccination within the past year was generally lower among PwIV than among PwCV. (b) A higher proportion of PwIV did not deal with the issue of vaccinations during the past year. (c) Comparing the two groups in terms of general vaccination card control, the proportion of patients whose vaccination card was not regularly checked by anyone was markedly higher among PwIV. These differences were significant for all vaccinations ($p < 0.001$ F_i), except for polio vaccination. (d) Concerning patients’ knowledge of their own vaccination status, the proportion of patients who correctly estimated it was significantly lower for PwIV compared to PwCV ($p \leq 0.014$ F_i). F_i —Fisher’s exact test; n —number of patients; p — p -value; PwCV—patients with complete vaccination status; PwIV—patients with incomplete vaccination status.

3.4. Comparison between Patients with Correct and Incorrect Vaccination Self-Assessment

Next, we examined patients with correctly and incorrectly self-reported vaccination status for differences in sociodemographic, clinical and vaccination data (Figure 3 and Supplemental Table S1). Misreported vaccination status was subdivided into overestimated and underestimated vaccination status. For tetanus, there was a higher proportion of male patients among the incorrectly reporting group. However, this difference was not statistically significant ($p = 0.119$). Significant differences were repeatedly found for education, disease duration, the date when the patients last dealt with the issue of vaccinations and vaccination card contact person (Supplemental Table S1). Underestimating patients (with respect to diphtheria and pertussis immunization) were in school for fewer years ($p \leq 0.006$) than overestimating and correctly reporting patients. The disease duration was significantly longer in patients who correctly reported their vaccination status for tetanus and diphtheria than in those who reported it incorrectly ($p \leq 0.026$). This difference was also seen for the self-assessment regarding vaccination against pertussis and poliomyelitis but did not reach the significance level. Significantly more patients with correctly reported vaccination status for tetanus, diphtheria and poliomyelitis had dealt with the topic of vaccinations within the past year compared to patients who reported their vaccination status incorrectly or as unknown ($p \leq 0.024$). For all four vaccinations, a significantly higher proportion of correctly reporting patients had their vaccination card checked by their family doctor/neurologist, whereas the proportion of patients who did not have a contact person on the subject of vaccinations was significantly lower compared to incorrectly reporting patients ($p \leq 0.008$).

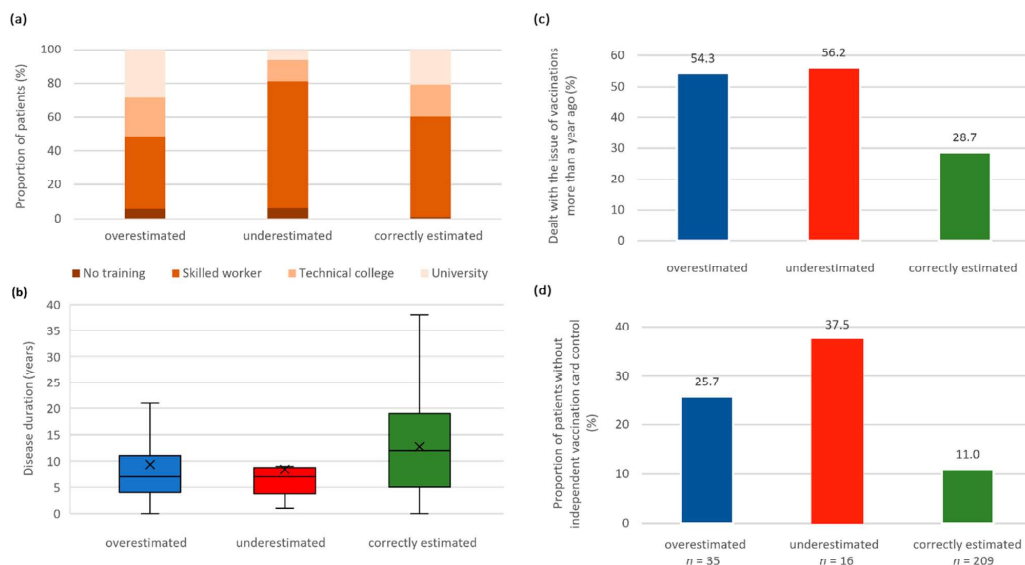


Figure 3. Assessment of diphtheria vaccination status by MS patients in relation to education, disease duration, vaccination interest, and vaccination control. Patients who underestimated their vaccination status were significantly more likely to be educated as skilled workers and less likely to have a university degree ($p = 0.004$ Chi) (a). Patients who correctly estimated their vaccination status had a significantly longer disease duration ($p = 0.004$ Chi) (b), were less likely to not address the issue of vaccinations for more than a year ($p = 0.001$ Chi) (c) and were less likely to not have a contact person for vaccination card control ($p = 0.005$ Chi) (d). Chi—chi-squared test; n —number of patients; p — p -value.

3.5. Comparison of Patients with Different Persons Who Regularly Check Their Vaccination Cards

In the last part, the patients were stratified according to the persons who regularly check their vaccination card: physicians (family doctor/neurologist), other persons or nobody (Table 4). The patients for whom nobody checked the vaccination card were significantly more often men (44.6 vs. 29.4%; $p = 0.037$) and had significantly fewer siblings than those with a physician contact person (1.1 vs. 1.6; $p = 0.016$). Furthermore, the patient group “nobody controls the vaccination card” was younger (44.8 vs. 47.9 years), had fewer children on average (1.0 vs. 1.3) and had a lower median disease duration (8.5 vs. 10.0 years) than the patient group “vaccination card checked by a physician”. However, these differences were not statistically significant ($p > 0.05$).

Table 4. Comparison of sociodemographic and clinical data between MS patients with different persons checking their vaccination card.

| | Nobody | Family Doctor/ Neurologist | Others | p -Value |
|--------------------------------|-------------|-------------------------------|-------------|----------------------------|
| n | 56 (17.1%) | 238 (72.8%) | 33 (10.1%) | |
| Sex^c | | | | 0.037^{Chi} |
| Female | 31 (55.4) | 168 (70.6) | 26 (78.8) | |
| Male | 25 (44.6) | 70 (29.4) | 7 (21.2) | |
| Age (years)^a | 44.8 (13.3) | 47.9 (13.2) | 48.0 (11.5) | 0.270 ^{ANOVA} |

Table 4. Cont.

| | Nobody | Family Doctor/ Neurologist | Others | p-Value |
|--|------------|-------------------------------|------------|------------------------|
| Place of residence ^c | | | | 0.136 ^{Chi} |
| Rural area | 25 (44.6) | 91 (38.2) | 17 (51.5) | |
| Small town | 6 (10.7) | 41 (17.2) | 2 (6.1) | |
| Medium-sized town | 13 (23.2) | 39 (16.4) | 9 (27.3) | |
| City | 12 (21.4) | 67 (28.1) | 5 (15.1) | |
| Partnership ^c | | | | 0.625 ^{Chi} |
| Single | 14 (25.0) | 41 (17.2) | 6 (18.2) | |
| In a relationship | 12 (21.4) | 44 (18.5) | 9 (27.3) | |
| Married | 26 (46.4) | 137 (57.6) | 18 (54.5) | |
| Divorced | 2 (3.6) | 10 (4.2) | 0 (0.0) | |
| Widowed | 2 (3.6) | 6 (2.5) | 0 (0.0) | |
| Number of children ^a | 1.0 (0.9) | 1.3 (0.9) | 1.4 (1.1) | 0.121 ^{ANOVA} |
| Number of siblings ^a | 1.1 (0.8) | 1.6 (1.2) | 1.6 (0.9) | 0.016 ^{ANOVA} |
| School years ^a | 10.3 (1.1) | 10.6 (1.3) | 10.8 (1.3) | 0.151 ^{ANOVA} |
| Educational level ^c | | | | 0.126 ^{Chi} |
| No training | 2 (3.6) | 8 (3.4) | 1 (3.0) | |
| Skilled worker | 37 (66.1) | 142 (59.7) | 19 (57.6) | |
| Technical college | 7 (12.5) | 50 (21.0) | 2 (6.1) | |
| University | 10 (17.9) | 38 (16.0) | 11 (33.3) | |
| Employment status ^c | | | | 0.797 ^{Chi} |
| Training/student | 2 (3.6) | 3 (1.3) | 0 (0.0) | |
| Fulltime employed | 18 (32.1) | 68 (28.6) | 8 (24.2) | |
| Part-timer employed | 9 (16.1) | 54 (22.7) | 11 (33.3) | |
| Unemployed | 3 (5.4) | 9 (3.8) | 1 (3.0) | |
| Disability pensioned | 20 (35.7) | 75 (31.5) | 10 (30.3) | |
| Retirement pensioned | 3 (5.4) | 23 (9.7) | 3 (9.1) | |
| Other | 1 (1.8) | 6 (2.5) | 0 (0.0) | |
| Patient care ^c | | | | 0.616 ^{Chi} |
| Outpatients | 45 (80.4) | 185 (77.7) | 28 (84.8) | |
| Inpatients | 11 (19.6) | 53 (22.3) | 5 (15.2) | |
| Course of disease | | | | 0.833 ^{Chi} |
| CIS | 4 (7.1) | 11 (4.6) | 1 (3.0) | |
| RRMS | 36 (64.3) | 161 (67.6) | 24 (72.7) | |
| SPMS | 12 (21.4) | 44 (18.5) | 7 (21.2) | |
| PPMS | 4 (7.1) | 22 (9.2) | 1 (3.0) | |
| Disease duration (years) ^b | 8.5 | 10.0 | 12.0 | 0.216 ^H |
| EDSS score ^b | 3.0 | 3.0 | 2.5 | 0.886 ^H |
| DMD treatment ^c | | | | 0.769 ^{Chi} |
| Yes | 42 (75.0) | 189 (79.4) | 26 (78.8) | |
| No | 14 (25.0) | 49 (20.6) | 7 (21.2) | |
| Comorbidities ^c | | | | 0.643 ^{Chi} |
| Yes | 39 (69.6) | 180 (75.6) | 25 (75.8) | |
| No | 17 (30.4) | 58 (24.4) | 8 (24.2) | |

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; SD—standard deviation; SPMS, secondary progressive MS. ^a mean value (standard deviation). ^{ANOVA} Analysis of variance. ^b median. ^c number of patients (%). ^{Chi} chi-squared test. ^H Kruskal-Wallis H test.

Analyzing the vaccination survey data, the rate of patients who received a vaccination advice in the last year was more than twice as high for patients who had their vaccination card checked by their physician than for patients without an independent vaccination card

check (38.7 vs. 12.5%; $p < 0.001$). In the group “nobody checked the vaccination card”, significantly fewer patients had dealt with the topic of vaccination within the last year compared to patients where a physician checked their vaccination card (32.1 vs. 69.3%; $p < 0.001$). On closer inspection, males without a vaccination card check showed as a proportion of 72.0%, the highest proportion of patients who had last dealt with the issue of vaccinations more than a year ago (Figure 4). Of note, significantly more patients without independent vaccination card control had a desire for a vaccination advice than patients with regular vaccination card check by a physician (48.2 vs. 34.4%, $p = 0.030$).

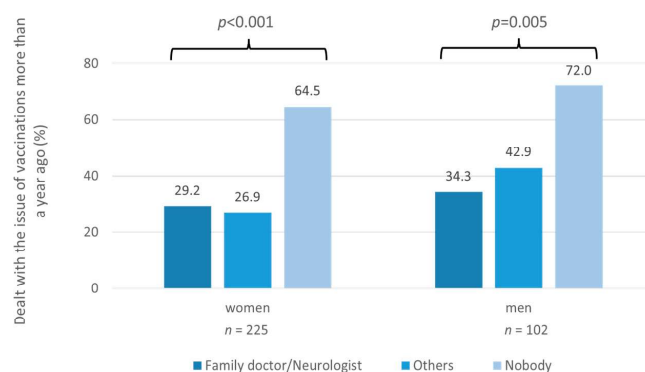


Figure 4. Vaccination interest of MS patients stratified by sex and by persons who regularly checked their vaccination card. Women and men were separately examined for an association between their interest in vaccinations and the person checking their vaccination card. Of the men who did not have their vaccination card checked by anyone, about 70% had not dealt with the issue of vaccinations within the past year (chi-squared test: $p = 0.005$). n —number of patients; p — p -value.

4. Discussion

Due to the high relevance of an appropriate vaccination status for MS patients, the aim of our study was to investigate the vaccination status, vaccination attitude and vaccination card knowledge of patients with MS. In those patients, indication-appropriate vaccinations can be considered largely safe as the benefits outweigh the disadvantages, and, therefore, they are usually recommended [29,30,39]. An exception is the use of certain live vaccines, which are contraindicated under immunosuppressive medication. Inactivated vaccines, on the other hand, can generally be used without an increased risk of adverse effects [40]. Infectious diseases pose a severe risk to patients with MS [17,26]. Disease-modifying therapies for MS, aside from interferon-beta and glatiramer acetate, make patients more susceptible to infections by suppressing or modulating normal immune response [41,42]. To minimize this risk, generally recommended vaccinations against vaccine-preventable diseases are of utmost importance. To be adequately protected, vaccination gaps should be closed, ideally before starting a DMD therapy [30]. In our analysis, we focused on tetanus, diphtheria, pertussis and poliomyelitis vaccines, which are all inactivated vaccines and are considered safe or probably safe for patients with MS according to recent studies [29]. In addition, it is recommended by the STIKO to have booster vaccinations for tetanus, diphtheria and pertussis every ten years, which is why these vaccinations are relevant in the clinical routine of physicians treating MS patients [37]. Our study population was a representative MS patient cohort in terms of age, sex and disease course when compared with data from the German MS registry [6,43].

Considering the vaccination coverage of our patients, a complete vaccination status was found for tetanus in 79.5%, for diphtheria in 79.2%, for pertussis in 74.8% and for poliomyelitis in 84.8% of the patients. The finding that the proportion of fully vaccinated patients was lowest for pertussis compared with the other vaccinations is presumably explained by the fact that the recommendation to combine the next due tetanus-diphtheria

vaccination with a pertussis vaccine was issued only in 2009 [44]. Prior to 2009, there was no recommendation for booster pertussis vaccination in adulthood. This underscores the observation that the use of combination vaccines is associated with improved coverage rates [45]. To our knowledge, there are no previous data on vaccination coverage rates for tetanus, diphtheria, pertussis and poliomyelitis in MS patients.

However, when compared to the general population in Germany, we observed markedly higher vaccination coverage rates than reported in the latest national evaluation by the federal government's research institute for disease control and prevention (Robert Koch Institute). Among more than 56 million people for whom vaccination data were assessed, coverage rates were only 51.9% for tetanus, 53.3% for diphtheria and 41.9% for pertussis [34]. No current data are available for poliomyelitis. The most recent findings indicate a lifetime prevalence of at least one polio vaccination of 85.6% [46]. In the studies on nationwide vaccination coverage rates, the proportions of people with complete vaccination status were between 5 and 25% higher in eastern German states than in western German federal states [34,46–48]. Studies that have examined vaccinations in patients with other autoimmune diseases report relatively low vaccination completion rates for tetanus, diphtheria, pertussis and poliomyelitis [49–54]. For instance, in the study by Chehab et al., of the 579 lupus patients examined, 65.8% had a complete vaccination status for tetanus [49]. The higher vaccination coverage rates in our MS patients as compared with nationwide data and the vaccination coverage rates of patients with other autoimmune diseases may be due to more regular clinical visits and thus more frequent vaccination card checks in MS patient care. In addition, our study was conducted at centers in two eastern German federal states, where a historically higher willingness to vaccinate and a higher acceptance of vaccination recommendations favor a more complete vaccination status [46,55]. Besides these facts, years of discussion about the potential risks and benefits of vaccinations in MS may have increased the attention on patients' vaccination status by treating physicians [28,30,56–58]. In addition to the vaccinations examined in this study, further research on other vaccinations is needed to provide a more complete view of the vaccination status and the willingness of MS patients to get vaccinated. The annual influenza vaccination would be of great interest in this regard, as it implies more regular vaccination status tracking by treating physicians. Furthermore, the vaccination status for live vaccines such as the varicella vaccine should be investigated, as these are more controversial in the context of immunomodulatory treatments than the safer inactivated vaccines [40]. However, for live vaccines, completeness is often achieved through childhood baseline immunization before the patients develop MS and therefore does not provide information on the vaccination awareness of MS patients [37].

The comparison of PwCV with PwIV revealed that patients who were fully vaccinated against tetanus and diphtheria had significantly more siblings on average than those who were unvaccinated or partially vaccinated (1.6 vs. 1.2; $p \leq 0.008$). Inconsistent findings have been reported on this in the literature. For instance, it has been found that children with a higher number of siblings more often do not have complete vaccination status against measles [59]. Differences in study design (e.g., children vs. adults, type of vaccination studied, etc.) may explain such discrepancies. Other associations that were described in the literature, such as increased tetanus vaccination rates in men [60] and in patients with higher levels of education [61], were not reflected in our results. In clinical practice, it must be considered that there may be a reduced immune response following vaccination in patients receiving a DMD for MS. Antibody titers may be determined after vaccination, since studies have shown reduced antibody responses under therapy with DMDs, with the exception of beta-interferons [62,63]. Our findings, however, demonstrate that vaccination coverage is mostly influenced by vaccination attitudes. We found that vaccination consultations and vaccination card checks by physicians were clearly related to vaccination completeness. This confirmed results from previous studies show that patients with vaccination counseling or vaccination card control by a physician were significantly more likely to be fully vaccinated and that the family doctor/specialist is

typically the most important advisor on vaccinations [47,53]. The relevance of vaccination advice for MS patients has been demonstrated in our study and should prompt physicians to perform regular vaccination counseling and vaccination card checks in order to reduce the risk of infection for MS patients. Continuous vaccination monitoring in the form of an electronic vaccination card could be helpful in the future to detect PwIV and make them an offer of vaccination [64]. Some PwIV may not be adequately informed about vaccination recommendations, such as the need for booster vaccinations for tetanus, diphtheria and pertussis [65]. On the other hand, some PwIV may reject vaccinations in general due to their attitudes or personal beliefs, and therefore do not want to be vaccinated and are not interested in their own vaccination status [66]. These considerations need to be taken into account in further studies looking at the vaccination attitudes, knowledge of vaccination recommendations and personalities of MS patients.

Concerning the validity of patients' self-reported vaccination status, a high sensitivity and a low specificity were found for all vaccinations, implying that PwIV are poorly aware of their own vaccination status and that they are more likely to think that they are fully vaccinated even though they are not. These results are consistent with those in the current literature on tetanus vaccination self-reports [67,68]. A high sensitivity of tetanus vaccination self-reports may reflect a high awareness of the tetanus vaccination [69]. Tetanus is caused by bacteria that enter the body through contaminated wounds. Since people are frequently confronted with this danger, for example when they are injured while gardening, they presumably deal with their tetanus vaccination status more frequently or are more aware of the tetanus vaccination [70]. In contrast to our results are the findings from the study by Loulergue et al., who observed low sensitivity (<50%) and high specificity (70–95%) for tetanus, diphtheria, pertussis and polio vaccination self-reports [71] but this study was conducted in French health care students with an average age of 23 years. In the patient interviews, we got the impression that in the context of combination vaccinations containing tetanus, some patients were not sufficiently informed about the additionally included vaccines besides tetanus.

In the analyses of patients with correctly vs. incorrectly self-reported vaccination status, the main differences were found in education, disease duration and vaccination behavior. A low educational level was a predictor for underestimating vaccination completeness. This fact was seen for diphtheria as well as for pertussis but not for tetanus, possibly because patients with lower levels of education were not adequately informed about the inclusion of diphtheria and pertussis vaccine in the decennial booster with tetanus. In general, low school qualifications have been shown to be associated with a low health status and a low health literacy [72]. Patients with correct reports had a longer disease duration than those who were incorrect. The longer disease duration could have led patients to pay more attention to their state of health and their vaccination status over time. Interest in vaccinations, on the one hand, and implementation of a vaccination card control, on the other hand, emerged as parameters that distinguished our patients with correctly and incorrectly self-reported vaccination status. Regular physician vaccination advice and stronger interest in vaccinations increased the validity of self-reported immunization status in our patients. A possible implication of these results is that physicians should conduct regular vaccination card controls and educate their MS patients about their vaccination status and the vaccines included in combination vaccinations. In this context, special attention should be paid to MS patients with low levels of education and short disease durations.

In our patient cohort, the most frequently mentioned control authority of the vaccination card was the family doctor/neurologist with 72.8%. In contrast, approximately 17% of our patients stated that they did not have their vaccination card checked by anyone. These results are consistent with the literature on patients with other autoimmune diseases, where the family doctor/specialist was stated as the person checking the immunization record by 69% of the patients [54] and 24% of the patients did not have regular vaccination card controls [49]. In the present study, as well as in the literature, vaccination card control was

associated with patients with a more complete vaccination status and a better knowledge of their own vaccination status [53]. This raises the question of what distinguishes patients with and without vaccination card control. In our data, men more often did not have a contact person for an independent vaccination card check, which may reflect the generally higher utilization of medical services by women [73]. Of those patients without vaccination card control, a lower proportion dealt with the subject of vaccinations within the past year than patients with control by a physician (32.1 vs. 69.3%, $p < 0.001$). However, among patients without a check, a larger proportion expressed a desire for vaccination counseling compared to patients with control (48.2 vs. 34.4%, $p = 0.030$), emphasizing that some patients are clearly interested in discussing their own vaccination status with a physician. In particular, for male patients with few siblings, more attention should be paid to offering them regular vaccination card control, as they are less likely to be completely vaccinated.

A potential limitation of our study is that the patient recruitment ran through June 2020, which may have caused the results to be skewed by media attention of the SARS-CoV-2 pandemic beginning in March 2020. Due to the potential risk of SARS-CoV-2 infection, more patients may have been concerned with vaccinations and their vaccination status. A further limitation is that our patients came almost exclusively from the former east Germany, and hence no national data were collected, which could have led to some bias. While we included only patients who are treated in a hospital, there could be differences with patients who are treated exclusively by neurologists in private practices. Furthermore, we only collected cross-sectional data and no longitudinal data of the patients. Last but not least, since only four selected vaccinations were examined by the authors, the present study cannot provide an overall view of the vaccination status of MS patients, according to the RKI recommendations on standard, indications, and travel vaccinations [37]. Nonetheless, to the best of our knowledge, this study was the first to collect data on vaccination rates, vaccination knowledge and vaccination behavior in MS patients, which may serve as the basis for further studies that are clearly needed to further improve the monitoring of vaccination rates in MS patients in the future.

5. Conclusions

In summary, vaccination rates against tetanus, diphtheria, pertussis, and poliomyelitis within our MS patient cohort were higher than for the average German population and patients with other autoimmune diseases. However, as vaccinations are of particular importance for MS patients, treating physicians, especially family doctors and neurologists, should offer regular vaccination consultations to their patients and check vaccination cards, as both vaccination coverage and patients' knowledge of their own vaccination status are significantly influenced by these factors. To increase the congruence of assumed and real vaccination status, patients should be informed of all the vaccines contained in a combination vaccination. Furthermore, special attention should be paid to men and patients with few siblings, since these patients more often did not have their vaccination cards checked by an independent person. To prove or reject causality, these factors should be investigated in long-term studies. Continuous vaccination monitoring, for example in the form of individual electronic vaccination cards, could help physicians keep better track of their patients' vaccination status. Further research is needed to explore reasons for incomplete vaccination status, poor vaccination knowledge and vaccination refusal in patients with MS.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jpm12050677/s1>, Table S1: Comparison of MS patients who overestimated, underestimated, correctly estimated, or reported their vaccination status as unknown according to sociodemographic, clinical, and vaccination data.

Author Contributions: Conceptualization, S.E.L., N.F., M.H. and U.K.Z.; methodology, N.F., S.E.L. and P.M.; formal analysis, S.E.L.; investigation, N.F., S.E.L., P.M., B.S., J.B. and F.H.; resources, S.E.L.; data curation, N.F., S.E.L., P.M., B.S., J.B. and F.H.; writing—original draft preparation, S.E.L.; writing—review and editing, M.H., N.F. and U.K.Z.; visualization, S.E.L.; supervision, U.K.Z.; project administration, S.E.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the University of Rostock and the ethics committee of Thuringia.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. The participation of inpatients and outpatients in this study was on a voluntary basis after they were given spoken and written information and an appropriate time to consider the opportunity to participate in this study. Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request.

Acknowledgments: The authors would like to express their special thanks to the nurses and physicians of the outpatient and inpatient MS wards of the Department of Neurology at the Rostock University Medical Center and the Department of Neurology at the Eucenemic Hainich Hospital Mühlhausen for providing help in the data acquisition and the study patients for participating in this research.

Conflicts of Interest: S.E.L., P.M., B.S., F.H. and J.B. declare no competing interests. N.F. received travel funds for research meetings from Novartis. M.H. received speaking fees and travel funds from Bayer HealthCare, Biogen, Merck Serono, Novartis and Teva. U.K.Z. received speaking fees, travel support and/or financial support for research activities from Alexion, Almirall, Bayer HealthCare, Biogen, Bristol-Myers-Sqibb, Janssen, Merck Serono, Novartis, Octapharm, Roche, Sanofi Genzyme, Teva as well as EU, BMBF, BMWi and DFG. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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8.2 Publikation 2

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

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Eur Neurol. 2022;85(2):104-111.

doi: 10.1159/000519582

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

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Keywords

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

Abstract

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

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

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Introduction

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

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

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

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

Methods

Study Population and Design

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

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

Data Acquisition

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

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

Statistics

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

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

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

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

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

Results

Demographic and Clinical Characteristics

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

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

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

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

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

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

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

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

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

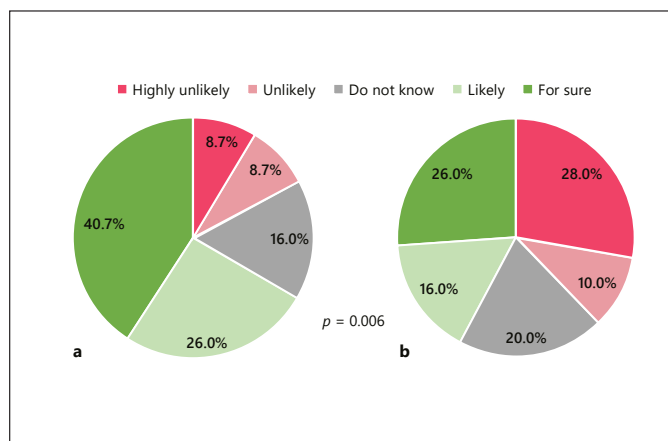
Experienced psychological, physical, or social burden caused by the SARS CoV-2 pandemic and the governmental safety measures implemented were each reported as high or very high by 28.5% of the MS patients, respectively. Attitudes toward SARS CoV-2 safety measures changed due to the pandemic course in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

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

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

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

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



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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

Conclusions

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

Acknowledgments

We appreciate the patients' willingness and engagement while participating in the 2 assessments.

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Statement of Ethics

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

Conflict of Interest Statement

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

Funding Sources

No funding source was required, as no costs were due for materials or similar. The authors were students or employees of the clinics.

Author Contributions

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

Data Availability Statement

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

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8.3 Publikation 3

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

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Sci Rep. 2022 Sep 7;12(1):15147.

doi: 10.1038/s41598-022-18912-3



OPEN

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

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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 deaths¹. 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 vaccine⁹ and 69% in U.S. American residents¹⁰. 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 vaccination¹¹. 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 vaccinated¹². 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 vaccines¹².

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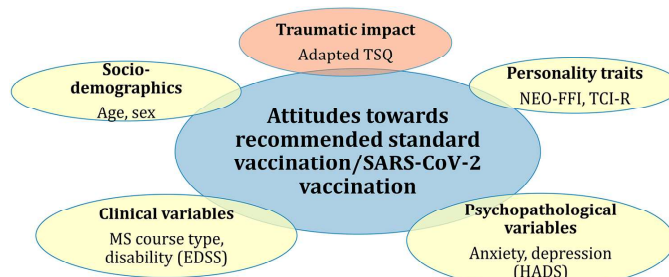


Figure 1. Variables to be analysed for associations with vaccination willingness in general and regarding SARS-CoV-2. *EDSS* Expanded Disability Status Scale, *HADS* Hospital Anxiety and Depression Scale, *MS* Multiple sclerosis, *NEO-FFI* NEO Five Factor Inventory; *TCI-R* Temperament and Character 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 hyposensitivity, 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 pandemic²³. 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 2021²⁵.

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 willingness²⁹. 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 people³¹. 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 phenomena³².

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 status³⁰. 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 criteria³³ 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 included 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 monitoring³⁵. Data on the MS course type, EDSS score³⁶, 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 tests³⁷ (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 validity³⁹. 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 disclosures⁴⁰. Cronbach's alpha coefficients between 0.66 for Openness and 0.84 for Neuroticism or 0.71 for Oennes, 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 Germany⁴¹.

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 version³⁷. 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 adapted³⁸. 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.

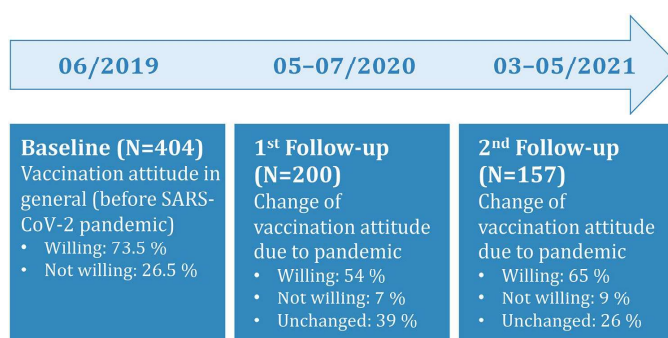


Figure 2. Development of general vaccination attitude before and during the course of the SARS-CoV-2 pandemic. *N* number of patients, SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2.

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.

| 1st follow-up (2020) | 2nd follow-up (2021) | | |
|----------------------|----------------------|-------|-------|
| | 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 ($r_{\text{pbis}} = -0.09$, $p = 0.190$).

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 ($c^2 [12] = 23.13$; $p = 0.027$): 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-CoV-2 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 (2nd 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 it³⁴. 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%^{34,42}. A higher rate of vaccination endorsement (80.9%) was found in a small Portuguese study²⁵. 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-2⁴³. 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

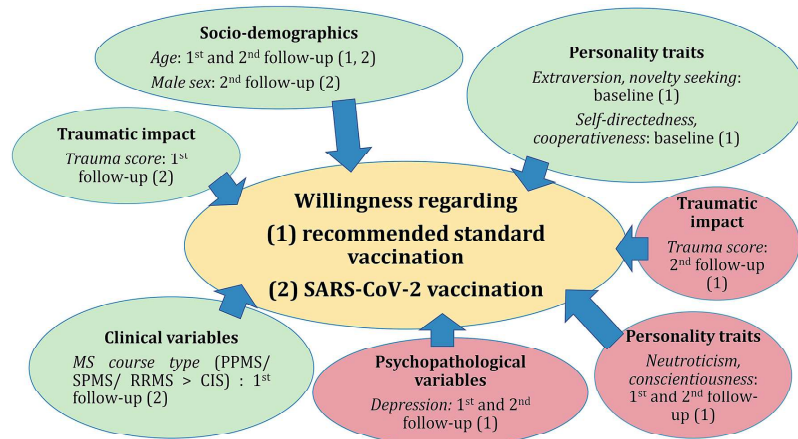


Figure 3. Patient characteristics associated with the willingness regarding recommended standard vaccinations and SARS-CoV-2 vaccinations. The coloured elements show the significant positive (green) or negative (red) associations of socio-demographic, clinical variables, personality traits, psychopathological 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 vaccinated³⁰. 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 causes⁴⁴. 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 all⁴⁴. 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.-population⁴⁷. 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 study⁴⁸), 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 depression⁵⁰. Another investigation revealed a negative correlation to vaccination readiness in depression⁵¹. 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 study³⁴ 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.

Received: 22 December 2021; Accepted: 22 August 2022

Published online: 07 September 2022

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Acknowledgements

We appreciate the patients' willingness and engagement while participating in the two assessments.

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E.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.


Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-022-18912-3>.

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9 Abkürzungsverzeichnis

| | |
|------------|--|
| ANOVA | <i>analysis of variance</i> |
| CIS | <i>clinically isolated syndrome</i> |
| COVID-19 | <i>coronavirus disease 2019</i> |
| DMD | <i>disease-modifying drug</i> |
| EBV | Epstein-Barr-Virus |
| ECTRIMS | <i>European Committee for Treatment and Research in Multiple Sclerosis</i> |
| EDSS | <i>Expanded Disability Status Scale</i> |
| FDR | <i>false discovery rate</i> |
| HADS | <i>Hospital Anxiety and Depression Scale</i> |
| mRNA | <i>messenger ribonucleic acid</i> |
| MRT | Magnetresonanztomographie |
| MS | Multiple Sklerose |
| n | Anzahl der Patienten |
| OR | <i>odds ratio</i> |
| p | p-Wert |
| PPMS | Primär progrediente Multiple Sklerose |
| RRMS | Schubförmig remittierende Multiple Sklerose |
| SARS-CoV-2 | <i>severe acute respiratory syndrome coronavirus 2</i> |
| SPMS | Sekundär progrediente Multiple Sklerose |
| STIKO | Ständige Impfkommission |
| TCI-R | <i>Temperament and Character Inventory-revised</i> |
| ZNS | Zentrales Nervensystem |

10 Thesen zur Dissertation

1. Die Multiple Sklerose (MS) ist eine immunvermittelte Erkrankung des zentralen Nervensystems (ZNS), welche typischerweise im jungen Erwachsenenalter diagnostiziert wird.
2. Neben umweltbedingten Risikofaktoren, wie einer Epstein-Barr-Virus-Infektion, spielen genetische und epigenetische Faktoren bei der Krankheitsentwicklung eine Rolle.
3. Die verlaufsmodifizierende (sekundärprophylaktische) Therapie der Erkrankung erfolgt mit immunmodulatorischen bzw. immunsuppressiven Medikamenten.
4. Aufgrund ihrer Erkrankung und ihrer Immuntherapie sind MS-Patienten einem erhöhten Infektionsrisiko ausgesetzt, welches von Verschlechterung der MS bis zum Tod führen kann.
5. Um das Infektionsrisiko seitens der MS-Patienten zu minimieren, sind ein vollständiger Impfstatus und die damit verbundene Akzeptanz der Schutzimpfungen von MS-Patienten von großer Bedeutung.
6. Nach jahrelangen Diskussionen um die Sicherheit von Impfstoffen bei MS gibt es bislang nur wenig Daten zu Impfquoten und der Impfbereitschaft von MS-Patienten.
7. Ziel dieser Arbeit war es einerseits, die Impfquoten der Standard- und Indikationsimpfungen von Tetanus, Diphtherie, Pertussis, Poliomyelitis und Influenza zu erheben. Andererseits sollte das Impfwissen der Patienten und deren Impfverhalten untersucht werden. Außerdem wurde die Impfbereitschaft vor und während der Pandemie der *coronavirus disease 2019* (COVID-19) verglichen. Additiv erfolgten Subgruppenanalysen hinsichtlich soziodemografischer, klinisch-neurologischer und psychologischer

Unterschiede der MS-Patienten in Impfvollständigkeitsraten, Impfwissen, Impfverhalten und Impfbereitschaft.

8. Insgesamt 404 Patienten wurden zwischen Juni 2019 und Mai 2021 in der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock sowie in der Neurologischen Klinik des Ökumenischen Hainich-Krankenhauses in Mühlhausen für die vorliegende Arbeit rekrutiert.
9. Die Datenerhebung zum Studieneinschluss erfolgte mittels Anamnese, klinischer Untersuchung, Patientenaktendurchsicht und Patienteninterviews. Die Daten für die Follow-up-Studien wurden per Telefoninterviews und Fragebögen zum Selbstausfüllen erhoben.
10. Einen vollständigen Impfstatus konnten für Tetanus 79,5%, für Diphtherie 79,2%, für Pertussis 74,8%, für Poliomyelitis 84,8% und für Influenza 13,5% der Patienten vorweisen.
11. In den selbst-berichteten Impfdaten überschätzten die Patienten signifikant ihren Tetanusimpfstatus und unterschätzten hingegen die Vollständigkeit für Diphtherie, Pertussis und Poliomyelitis.
12. Faktoren, die mit signifikant höheren Impfquoten und einem besseren Impfwissen der Patienten einhergingen, waren regelmäßige Impfberatungen und Impfausweiskontrollen.
13. Die Subgruppe der Patienten ohne regelmäßige Impfausweiskontrolle bestand aus signifikant mehr Männern und Patienten mit weniger Geschwistern.
14. Eine allgemeine Impfbereitschaft gaben 73,5% der insgesamt 404 befragten Patienten an. Nach Beginn der Pandemie und vor Verfügbarkeit eines Impfstoffs gegen das *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) berichteten in der befragten Subgruppe 60% der Patienten, sich gegen COVID-19 impfen lassen zu wollen. Nach der Zulassung von SARS-CoV-2-Impfstoffen stieg die SARS-CoV-2-Impfbereitschaft nur minimal auf 61% an.

15. Junges Alter, Neurotizismus und Gewissenhaftigkeit als Persönlichkeitsmerkmale sowie eine empfundene traumatische Belastung durch die Pandemie waren Faktoren, die negativ mit der allgemeinen bzw. der SARS-CoV-2-Impfbereitschaft assoziiert waren.
16. Die Ergebnisse dieser Arbeit liefern neue Erkenntnisse zur Impftematik bei MS-Patienten. Es wurden neue Daten zum Impfwissen, zum Impfverhalten und zum Status der Impfungen gegen Tetanus, Diphtherie, Pertussis, Poliomyelitis und Influenza von MS-Patienten erhoben und folglich der aktuelle Forschungsstand in diesem Themenbereich enorm erweitert.
17. Künftig sollten in Studien die Impfquoten weiterer Impfungen bei MS-Patienten erhoben werden, um den Überblick über deren Impfstatus zu vergrößern sowie in nationalen Studien die Impfbereitschaft und die Impfeinstellungen von MS-Patienten analysiert werden. Zudem könnten digitalisierte Impfmanagementsysteme in Arztpraxen integriert und getestet werden.

11 Selbstständigkeitserklärung

Ich erkläre hiermit, dass ich die vorliegende Dissertation selbstständig und ohne unerlaubte Hilfe verfasst habe. Ich versichere, dass ich ausschließlich die angegebenen Quellen und Hilfsmittel verwendet habe. Die Regeln zur Sicherung guter wissenschaftlicher Praxis wurden beachtet. Die Arbeit wurde nie zuvor einer anderen Prüfungsbehörde vorgelegt.

Ort, Datum

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12 Danksagung

Ich möchte mich herzlich bei allen Personen bedanken, die an dieser Arbeit mitgewirkt haben.

Allen voran gilt mein besonderer Dank Prof. Dr. Uwe Klaus Zettl, der mir die Möglichkeit gegeben hat zu promovieren und diese Thematik in meiner Dissertation zu behandeln. Ich fühlte mich von ihm durchgehend hervorragend wissenschaftlich betreut und profitierte im Rahmen der regelmäßigen Treffen von seinen konstruktiven Vorschlägen, neuen Ideen und Anreizen für die Ausarbeitung meines Themas. Durch seine ermutigende und dabei stets freundliche Art sowie langjährige Erfahrung in der Betreuung von Doktoranden half er mir dabei die richtigen Schwerpunkte in dieser Arbeit zu legen.

Des Weiteren möchte ich mich bei Dr. Michael Hecker und Dr. Niklas Frahm bedanken. Als direkte Ansprechpartner waren beide jederzeit für mich erreichbar, hatten immer ein offenes Ohr bei Problemen, nahmen sich dabei viel Zeit und machten pragmatische Lösungsvorschläge. Michael konnte mir in kürzester Zeit statistische Untersuchungsmethoden kompetent vermitteln und nahm sich in unseren „Brainstorm-Meetings“ viel Zeit, gemeinsam Ideen zu entwickeln und Schwierigkeiten in der Umsetzung zu behandeln. Niklas erleichterte mir nicht nur den Einstieg und die Einarbeitung in die Doktorarbeit, sondern war auch nach der Datenerhebung durchgängig mit mir in sehr regelmäßigem, engem Austausch, sei es zur Statistik, zur Erstellung der Publikationen oder zur Dissertationsstruktur. Die herzliche, kompetente und vertrauensvolle Betreuung der beiden half mir sehr dabei, die Arbeit voranzubringen.

Ich danke dem Personal der Klinik und Poliklinik für Neurologie der Universitätsmedizin Rostock, darunter besonders Antje Bombor, Deborah Sonnenberg, Iris Kell und allen beteiligten Mitarbeitern der Neurologischen Klinik des Ökumenischen Hainich-Krankenhauses in Mühlhausen für die stets freundliche Hilfe und großartige Zuarbeit bei der Datenakquise.

Ein besonderer Dank gilt meiner Familie, meiner Freundin und meinen Freunden. Ohne ihre durchgängige Unterstützung, Zusprüche und Ermutigungen wäre ich nicht so weit gekommen. Dafür werde ich ihnen immer dankbar sein.

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09/2017 **Erstes Staatsexamen der Ärztlichen Prüfung**
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Promotionsstudium

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Publikationen

2023

Baldt J, Frahm N, Hecker M, Streckenbach B, Langhorst SE, Mashhadiakbar P, Burian K, Meißner J, Heidler F, Richter J, Zettl UK. Depression and Anxiety in Association with Polypharmacy in Patients with Multiple Sclerosis. J Clin Med. 2023 Aug 18;12(16):5379.

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Frahm N, Hecker M, Langhorst SE, Mashhadiakbar P, Haker MC, Zettl UK. The risk of polypharmacy, comorbidities and drug-drug interactions in women of childbearing age with multiple sclerosis. *Ther Adv Neurol Disord*. 2020 Dec 19;13:1756286420969501.

Datum, Unterschrift