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ARTICLE

A large case-control study on vaccination as risk factor for multiple sclerosis

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Abstract

Objective

To investigate the hypothesis that vaccination is a risk factor for multiple sclerosis (MS) by use of German ambulatory claims data in a case-control study.

Methods

Using the ambulatory claims data of the Bavarian Association of Statutory Health Insurance Physicians covering 2005–2017, logistic regression models were used to assess the relation between MS (n = 12,262) and vaccinations in the 5 years before first diagnosis. Participants newly diagnosed with Crohn disease (n = 19,296) or psoriasis (n = 112,292) and participants with no history of these autoimmune diseases (n = 79,185) served as controls.

Results

The odds of MS were lower in participants with a recorded vaccination (odds ratio [OR] 0.870, $p < 0.001$ vs participants without autoimmune disease; OR 0.919, $p < 0.001$ vs participants with Crohn disease; OR 0.973, $p = 0.177$ vs participants with psoriasis). Lower odds were most pronounced for vaccinations against influenza and tick-borne encephalitis. These effects were consistently observed for different time frames, control cohorts, and definitions of the MS cohort. Effect sizes increased toward the time of first diagnosis.

Conclusions

Results of the present study do not reveal vaccination to be a risk factor for MS. On the contrary, they consistently suggest that vaccination is associated with a lower likelihood of being diagnosed with MS within the next 5 years. Whether this is a protective effect needs to be addressed by future studies.

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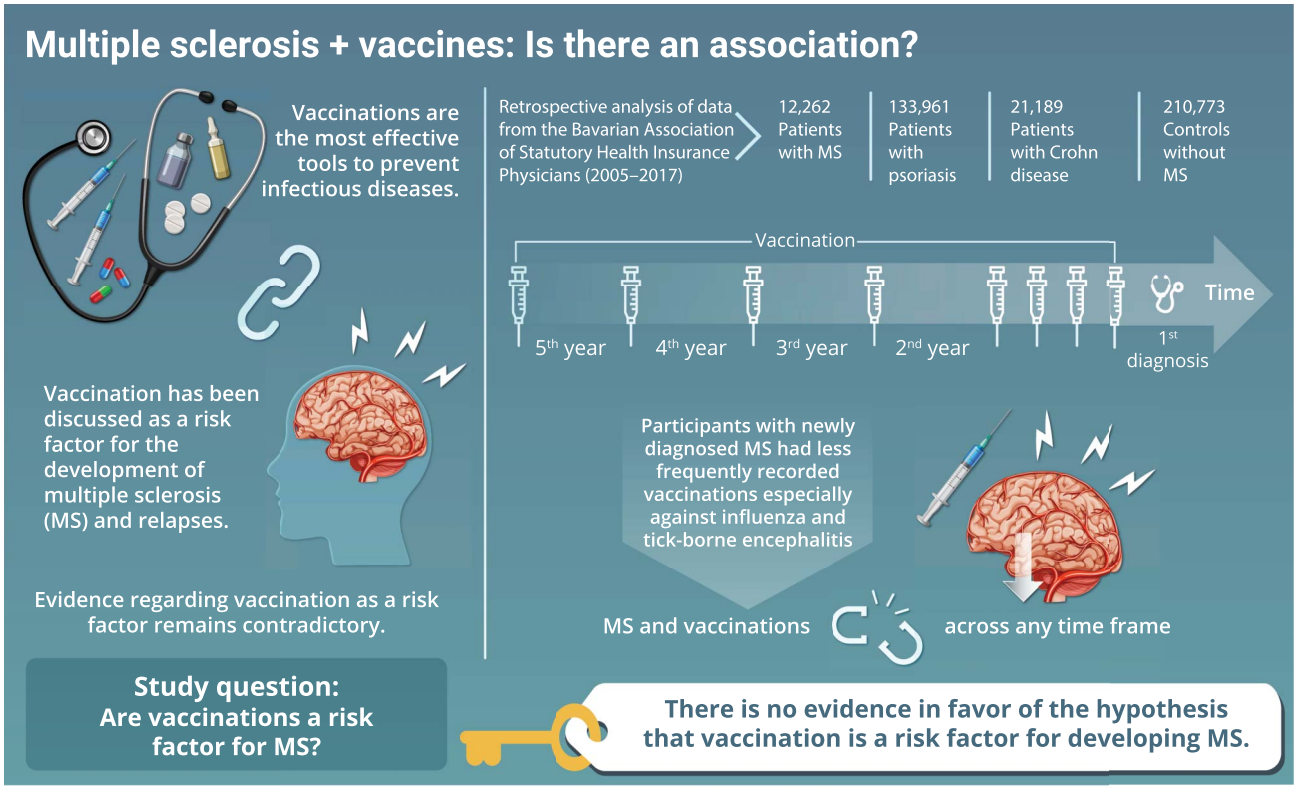
Glossary

BASHIP = Bavarian Association of Statutory Health Insurance Physicians; **CI** = confidence interval; **GOP** = Gebührenordnungspositionen; **HPV** = human papilloma virus; **ICD-10** = International Classification of Diseases–10; **MMR** = measles, mumps, and rubella; **MS** = multiple sclerosis; **OR** = odds ratio; **TBE** = tick-borne encephalitis; **VZV** = varicella-zoster virus.



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In recent years, various environmental risk factors for the development of multiple sclerosis (MS) have been suggested, some of which could be confirmed in large studies.[1,2] Vaccination has been discussed as a risk factor for the development of MS and for the occurrence of relapses. Different case reports and smaller studies on the relation to vaccination showed conflicting results, however.[3] The authors of a recent systematic literature review[4] concluded that there was no overall change in the risk of developing MS following most of the investigated vaccinations, including hepatitis B; human papilloma virus (HPV); seasonal influenza; measles, mumps, and rubella (MMR); and others. Interestingly, they reported a possible preventive potential of tetanus and diphtheria vaccine, which was mostly based on studies with few cases and insufficient statistical power, however.

Vaccinations are the most effective tools to prevent many infectious diseases. Thus it is important to carefully investigate and clarify any risks believed to be associated with vaccination to prevent unwarranted reservations.

The objective of the present case-control study was therefore to investigate the hypothesis that vaccination is a risk factor for MS in a systematic retrospective analysis of ambulatory claims data of 223,035 participants (12,262 patients with MS and 210,773 controls), held by the Bavarian Association of Statutory Health Insurance Physicians (BASHIP).

Methods

Ambulatory claims data held by BASHIP cover all members of the statutory health insurance, approximately 85% of the population of Bavaria.[5] It was available for each quarterly billing period between 2005 and 2017. We defined a cohort of patients with new-onset MS with at least 2 secured ICD-10 diagnoses G35 in separate quarterly periods and 2 control cohorts of participants diagnosed with other autoimmune diseases, Crohn disease and psoriasis, using the ICD-10 diagnoses K50 and L40 in the same manner, respectively. Inclusion of these control cohorts into the analysis enables the identification of effects

that are specific to MS and are not shared by other autoimmune diseases. In order to facilitate the observation of all participants in the 5 years prior to diagnosis, we restricted all cohorts to participants with a first diagnosis in 2010 or later. Participants without record of these ICD-10 diagnoses were randomly selected without replacement from the BASHIP data and matched to the MS cohort in a 5:1 ratio according to year of birth, sex, and district of residence. For the control group, we considered the quarter of first diagnosis to be that of their matching partner. All participants of all cohorts had to be younger than 70 years and resident in Bavaria during the entire 5-year period prior to the first diagnosis. Participants in the MS cohort were further required to have a recorded visit with a neurologist at any time and no ICD-10 diagnosis G04—that is, no diagnosis of a clinically isolated syndrome (CIS)—before or after MS diagnosis. To enable sensitivity analyses, we defined 3 additional stricter and therefore more conservative definitions of the MS cohort. These required that there was no diagnosis of optic neuritis (ICD-10 H46), at most one MRI of the head, or at most one visit with a neurologist during the investigated 5-year period.

Reimbursement claims are coded using a 5-digit code called the Gebührenordnungspositionen (GOP). Each recorded GOP is uniquely linked to a participant, a quarterly period, and a specific physician consultation. All GOP records coding vaccinations were used to explore the incidence and frequency of vaccinations in the investigated cohorts. As vaccinations are also administered as combination vaccines, we grouped them accordingly into 10 sets of vaccinations: (1) tick-borne encephalitis (TBE) virus, (2) HPV, (3) pneumococci, (4) meningococci, (5) influenza virus, (6) hepatitis A, (7) hepatitis B, (8) MMR and varicella-zoster viruses (VZV), (9) *Clostridium tetani*, *Corynebacterium diphtheriae*, poliovirus, *Bordetella* pertussis, and *Haemophilus influenzae* type B, and (10) any vaccination. The infrequent combination of *H influenzae* type B plus hepatitis B was allocated to each of the sets (7) and (9). The same holds for the rare combination of 6 vaccines in a single administration, which was given by the 5 vaccines listed in set (9) plus hepatitis B. Combinations of vaccinations against hepatitis A and B were allocated to each of the groups (6) and (7). The listed vaccinations belong to the set of vaccinations recommended by the German Standing Committee on Vaccination (STIKO) and are therefore free of charge for members of the statutory health insurance.

Data availability statement

For reasons of data protection, the authors are unable to distribute the underlying data. Interested researchers may contact the corresponding author or the BASHIP to request access.

Standard protocol approvals, registrations, and patient consents

In this retrospective case-control study, we analyzed anonymous claims data held by the BASHIP. Approval by an ethical standards committee on human experimentation (institutional or regional) for any experiments using human participants was not needed according to the Guidelines and Recommendations for Good Practice of Secondary Data Analysis.[6] Approval was obtained from the responsible data protection officer of the BASHIP. Likewise, there was no need for written informed consent from participants. No photographs, videos, or other information of recognizable persons are used in this article. Authorization for disclosure was therefore not necessary.

Statistical analysis

To manage the high computational burden of processing the very large data set, we used unconditional logistic regression models to assess the association between vaccination and MS by means of odds ratios (ORs). Recent findings show that unconditional logistic regression is a proper method to perform for loose-matching data; that is, when only a few matching variables are used and matching between cases and controls is therefore not unique.[7] Separate models were built to contrast the MS cohort against each of the control cohorts. The modelled binary outcome was MS (yes/no) and the factorial covariates were vaccination (yes = at least once vs no = never) and the main effects as well as the interaction effect of sex and age categories (0–20 years, 21–30 years, 31–40 years, …, 61–70 years). The effect measures of the analyses, given by the ORs and corresponding confidence intervals (CIs), are therefore adjusted for any combination of sex and age categories. The crude numbers of participants with any vaccination are given along the size of the cohorts.

We repeated each analysis for the 3 additional definitions of the MS cohort and for different time frames before first diagnosis to be able to explore the robustness of the results and the variation in time. The time frames comprise the whole 5-year period excluding the quarter immediately prior to the first diagnosis (= overall), the quarter before first diagnosis (-1st quarter), the quarters 2 to 4 before first diagnosis (-234th quarter), and each of the whole years before first diagnosis, starting with the second year and ending with the 5th year (-2nd year, -3rd year, -4th year, and -5th year).

The multiple analyses conducted in this study create a multiple testing problem. This is a rather strict interpretation of the present testing situation, which does not formally necessitate a correction for multiple testing because of its exploratory nature. We addressed this problem by defining a single primary analysis that covers all kinds of vaccinations (any/none). Hypothesis testing was performed on an exploratory 2-sided 5% significance level and corresponding 2-sided 95% CIs were computed for this primary analysis. Additional secondary analyses that addressed specific vaccinations were adjusted by Sidak correction for multiple testing. The correction was applied to p values as well as to CIs to provide a familywise error

Table 1 Descriptive statistics of the cohorts

Cohort	Size	Observable time,[a] y, median (IQR)	Women, n (%)	Age at first diagnosis, y, mean ± SD	Vaccinations,[a] categories 0, 1–2, >2 (respective %s)
MS	12,262	8.75 (7.00–10.50)	8,528 (69.5)	39.3 ± 12.5	6,800, 3,662, 1,800 (55.5, 29.9, 14.7)
Crohn disease	19,296	8.75 (7.25–10.75)	10,734 (55.6)	37.5 ± 15.4	9,814, 5,986, 3,496 (50.9, 31.0, 18.1)
Psoriasis	112,292	8.75 (7.25–10.50)	58,169 (51.8)	44.8 ± 15.9	57,644, 31,793, 22,855 (51.3, 28.3, 20.4)
Controls	79,185	9.00 (7.25–10.75)	54,915 (69.4)	39.5 ± 12.7	41,062, 25,451, 12,672 (51.9, 32.1, 16.0)

Abbreviations: IQR = interquartile range; MS = multiple sclerosis.
[a] Prior to first diagnosis.

control on a 5% significance level. There were 9 secondary analyses in total, resulting in an adjusted significance level of 0.568% and 2-sided 99.4% CIs. We did not adjust hypothesis testing for repeated analyses across the investigation of different control groups and time frames. All analyses were performed using R 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A data query in the BASHIP database identified 15,046 participants with a first diagnosis of MS, 21,189 participants with a first diagnosis of Crohn disease, and 133,961 participants with a first diagnosis of psoriasis in 2010 or later. Another 83,610 controls without any of the 3 autoimmune diseases were matched to the MS cohort. These numbers decreased to 12,262 in the MS cohort, 19,296 in the Crohn disease cohort, 112,292 in the psoriasis cohort, and 79,185 in the cohort of participants without these autoimmune diseases after removal of participants who were older than 70 years at the quarter of first diagnosis and by exclusion of participants who did not fulfill the definition of a patient with MS as outlined in the Methods. Concerning comorbidities, there were 456 participants with Crohn disease and psoriasis, 216 participants with MS and psoriasis, 48 participants with Crohn disease and MS, and 2 participants with Crohn disease, psoriasis, and MS. These participants were allocated to each of the respective cohorts and were not treated differently due to the comparatively small sample sizes.

The 3 additional definitions of MS cohorts that required that there was no diagnosis of optic neuritis (ICD-10 H46), at most 1 MRI of the head, or at most 1 visit with a neurologist during the investigated 5-year period led to sample sizes of 11,675, 11,663, and 9,272, respectively.

Descriptive statistics of the distribution of age at first diagnosis, sex, and the number of vaccinations in the 5 years prior to first diagnosis are presented in table 1. These statistics are purely illustrative and should not be used to infer on the relation between vaccinations and MS or the other 2 investigated autoimmune diseases. This research question has been addressed more thoroughly by the computation of age- and sex-adjusted ORs as presented along the following lines.

The ability to accurately define the quarter of first diagnosis for each participant is crucial to this study. It determines the

Figure 1 Illustration of studied time frames before first diagnosis

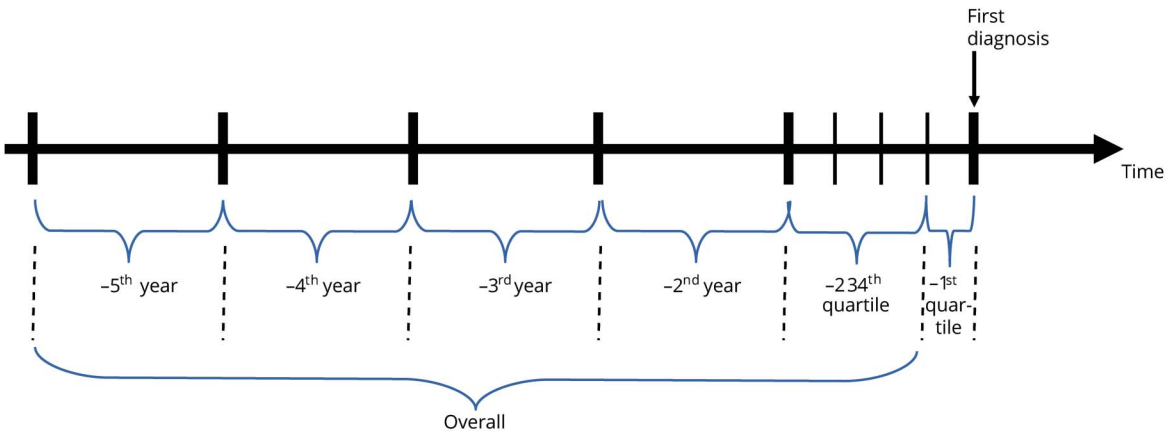


Table 2 Number (%) of participants with vaccination and cohort sizes

	Multiple sclerosis (n = 12,262)	Control (n = 79,185)	Crohn disease (n = 19,296)	Psoriasis (n = 112,292)
Overall[a]	5,462 (44.5)	38,123 (48.1)	9,482 (49.1)	54,648 (48.7)
1st quarter	457 (3.7)	3,589 (4.5)	893 (4.6)	6,382 (5.7)
234th quarter	1,428 (11.6)	9,907 (12.5)	2,527 (13.1)	16,530 (14.7)
2nd year	1,784 (14.5)	12,873 (16.3)	3,384 (17.5)	21,646 (19.3)
3rd year	1,940 (15.8)	13,978 (17.7)	3,608 (18.7)	22,861 (20.4)
4th year	2,177 (17.8)	14,831 (18.7)	3,885 (20.1)	23,766 (21.2)
5th year	2,185 (17.8)	15,343 (19.4)	3,974 (20.6)	24,245 (21.6)

Absolute and relative frequencies of patients with at least one vaccination in the displayed time frames.
[a] Overall number of participants with at least one vaccination in the investigated 5-year period excluding the quarter before first diagnosis.

individual 5-year periods that are to be analyzed and that are also required for the inclusion of a participant into the study cohorts. Due to the study design, any preceding diagnoses of the same kind as the respective first diagnosis (i.e., ICD-10 G35, K50, or L40) could be ruled out for a period of at least 5 years for each participant. For 70% of the participants it was even possible to observe a period of more than 7.5 years before first diagnosis. Further percentiles of the distribution of individual observation periods before first diagnosis are given in table 1.

We analyzed the occurrence of vaccinations in patients with MS and the 3 control groups during the 5 years before first diagnosis (figure 1). The overall effects, which are computed for the 5-year period excluding the quarter before first diagnosis, were OR 0.870 (95% CI 0.837–0.904), OR 0.919 (95% CI 0.876–0.963), and OR 0.973 (95% CI 0.936–1.012) for the control cohorts of participants without autoimmune disease, of participants with Crohn disease, and of participants with psoriasis, respectively. Considering a possible trend in time, the ORs of the respective control cohorts steadily decrease from the −5th year to the −2nd year and the −1st quarter before first diagnosis. Overall the odds of MS were lower in participants with any vaccination (figure 2). This result is consistent across all studied time frames and control cohorts. Statistical significance is almost always reached with only a few exceptions for the Crohn disease and psoriasis control cohorts. Corresponding vaccination frequencies and cohort sizes are given in table 2.

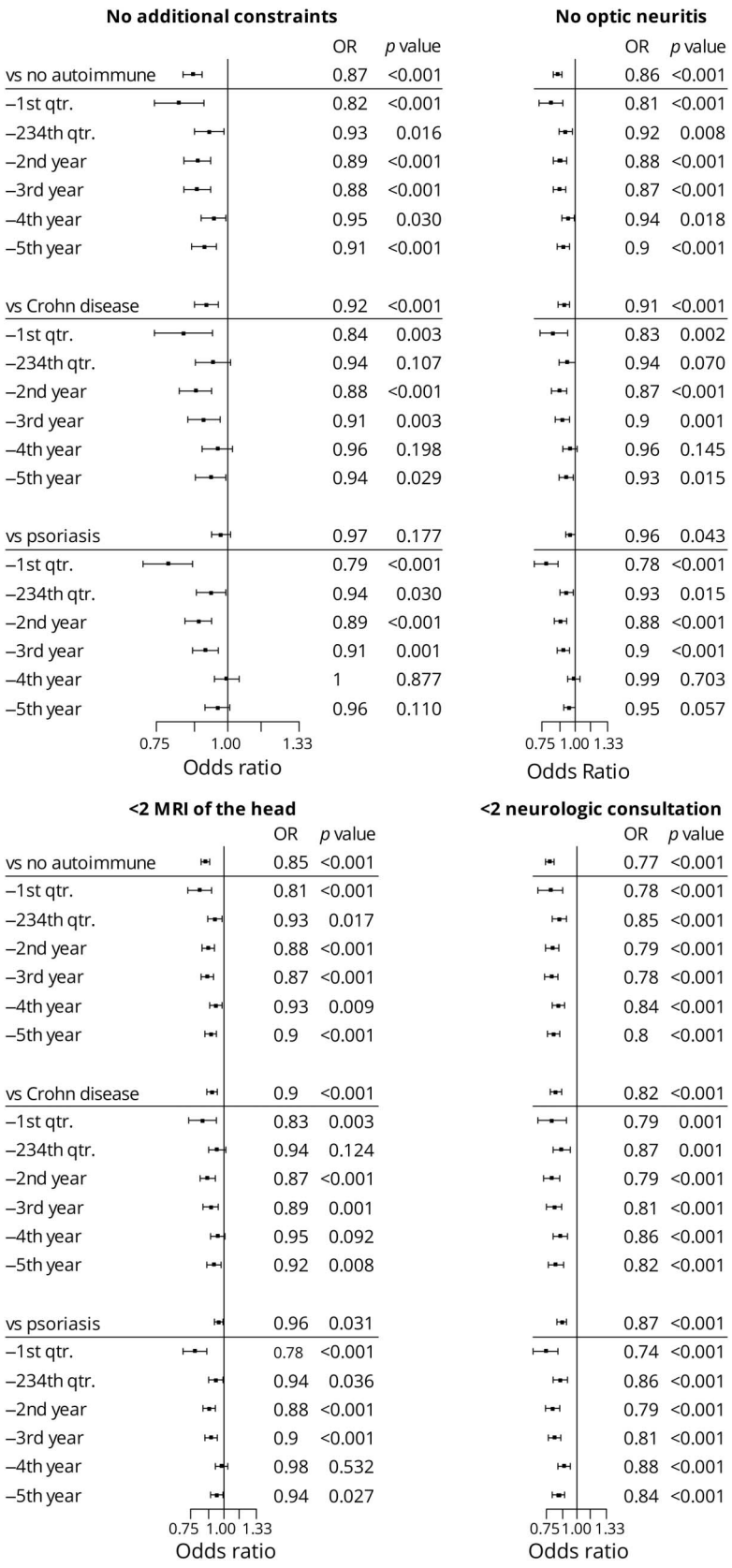
Further sensitivity analyses involving more strict definitions of the MS cohort are provided in figure 2. Interestingly, these results mirrored those obtained in the primary analysis, with decreased odds of MS in participants with any vaccination and a trend toward stronger effects in periods that are closer to first diagnosis. The strongest effects were observed for the stricter definition of the MS cohort, which requires that participants had at most one neurologic consultation during the investigated 5-year period (figure 2). In this analysis, significant differences were observed between MS and all control groups even 5 years before first diagnosis.

Next we analyzed the effect of specific vaccinations on the occurrence of MS. Sufficient numbers for meaningful analyses were available for vaccinations against TBE virus, HPV, pneumococci, meningococci, influenza, hepatitis A and B, meningococci, MMR, and varicella viruses. We found a consistently negative relation between the development of MS and the incidence of vaccinations with a single non-significant exception for the vaccination against HPV using the psoriasis control group, which shows the inverse effect (figure 3 and table 3). Most pronounced were the negative relations for vaccinations against TBE, hepatitis B, and influenza viruses, while the effect was less pronounced for the other vaccinations. Sensitivity analyses with strict definitions of the MS cohort showed even more pronounced effects especially in the subgroup that requires that participants had at most one visit with a neurologist during the investigated 5-year period (data not shown).

Discussion

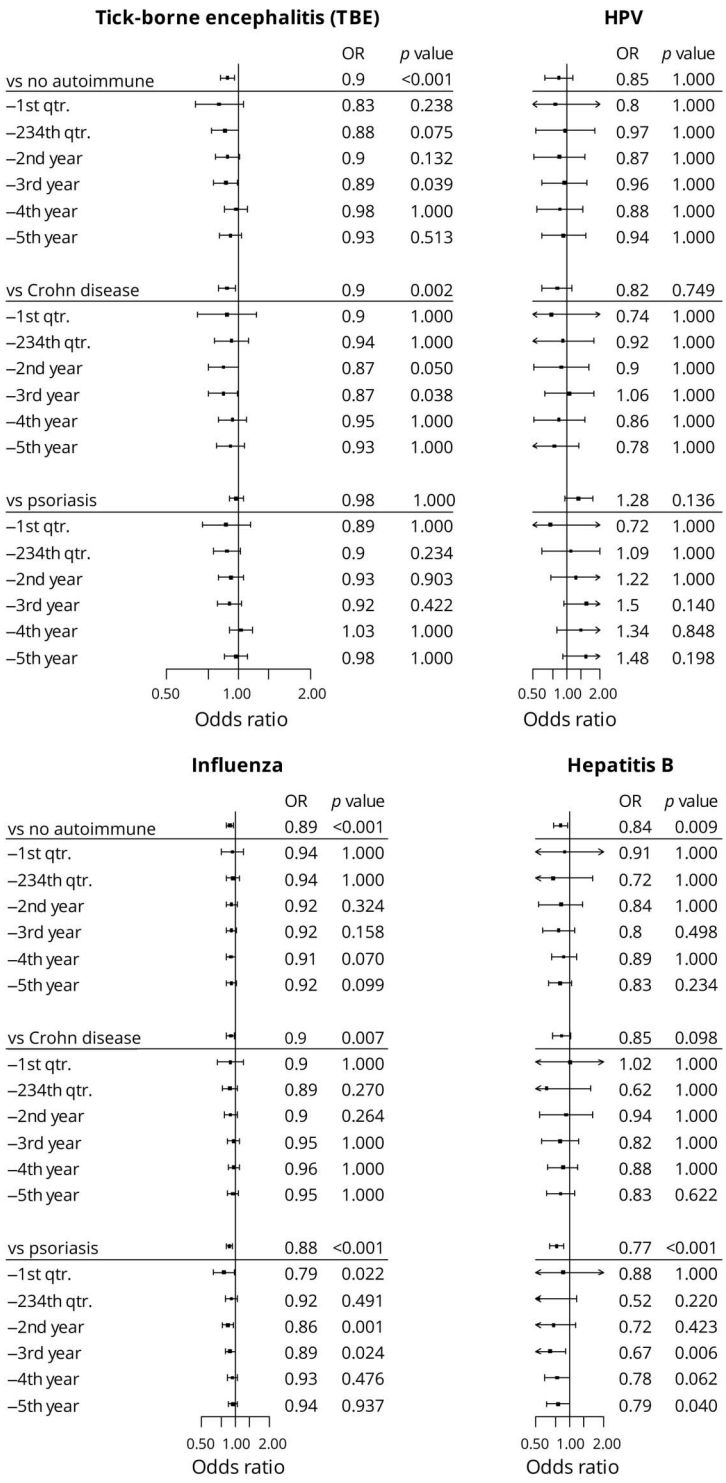
Despite the large number of studies conducted, the role of vaccination as a risk factor for the development of MS is uncertain. The present study did not reveal vaccination to be a risk factor for MS. It differs from recent research in 2 major aspects.[8–11] First, it provides substantial evidence from a large population-based sample of 223,035 participants (12,262 patients with MS and 210,773 controls). Second, it is focused on a single specific risk factor. It therefore does not share the risk of spurious findings that is present in studies that explore a large set of potential risk factors.

Figure 2 Odds ratios (ORs) of multiple sclerosis (MS) for any vaccination



ORs of MS for participants with at least one recorded vaccination compared to participants without any recorded vaccination. Results are presented for each of the investigated time frames, control cohorts, and the 3 stricter definitions of the MS cohort. The overall effect, excluding the quarter before first diagnosis, is given in the respective top rows.

Figure 3 Odds ratios (ORs) of multiple sclerosis (MS) for specific vaccinations



ORs of MS for participants with at least one recorded vaccination compared to participants without such a vaccination. Results are presented for each of the investigated time frames, control cohorts, and for specific vaccinations. The overall effect, excluding the quarter before first diagnosis, is given in the respective top rows. Confidence intervals (CIs) = 2-sided 99.4% CIs. Wide CIs exceeding the limits 0.5 or 2.0 are clipped to arrows. HPV = human papilloma virus.

Inconsistent findings have been reported with respect to the association of HPV, influenza, measles, mumps, typhoid, VZV, rubella, and hepatitis B vaccinations with MS risk.[12–28] Meta-analyses have lacked sufficient precision to prove or disprove an association of these different vaccinations with MS risk. However, the majority of these studies suggest that vaccinations are not associated with a higher risk of developing MS. For some of the vaccines (e.g., HPV, tetanus toxoid), some studies even reported a lower likelihood of a subsequent MS diagnosis.

Our findings, derived from a very large number of patients and 3 matched control cohorts, are in line with previous studies and support the assumption that vaccinations are not associated with a higher likelihood of an MS diagnosis during the

Table 3 Odds ratios (2-sided 99.4% confidence intervals using Sidak correction for multiple testing of 9 hypotheses) of multiple sclerosis (MS) vs control participants by type of vaccination

	Controls		
Vaccination	**No autoimmune disease[a]**	**Crohn disease**	**Psoriasis**
Tick-borne encephalitis	0.901 (0.844, 0.961)	0.899 (0.831, 0.972)	0.981 (0.919, 1.047)
Human papilloma virus	0.852 (0.641, 1.133)	0.824 (0.604, 1.124)	1.284 (0.965, 1.709)
Pneumococci	0.900 (0.673, 1.203)	0.640 (0.465, 0.882)	0.638 (0.482, 0.844)
Meningococci	0.977 (0.713, 1.339)	0.751 (0.537, 1.051)	0.620 (0.456, 0.843)
Influenza	0.892 (0.834, 0.955)	0.905 (0.833, 0.983)	0.877 (0.819, 0.938)
Hepatitis A	0.932 (0.726, 1.196)	0.961 (0.709.1.301)	0.952 (0.741, 1.223)
Hepatitis B	0.837 (0.721, 0.972)	0.849 (0.710, 1.015)	0.771 (0.664, 0.894)
Mumps, measles, rubella and varicella	0.878 (0.742, 1.039)	0.983 (0.801, 1.206)	0.844 (0.712, 1.000)
Tetanus, diphtheria, mumps, poliomyelitis, pertussis, and *Haemophilus influenzae* type B	0.924 (0.865, 0.987)	0.977 (0.901, 1.059)	0.999 (0.934, 1.068)

Values are odds ratio (2-sided 99.4% confidence interval using Sidak correction for multiple testing of 9 hypotheses) of MS for participants with at least one recorded vaccination compared to participants without any recorded vaccination. The overall effect, excluding the quarter before first diagnosis, is presented for each of the predefined subsets of vaccinations and control cohorts.
[a] Persons not diagnosed with MS, Crohn disease, or psoriasis.

following 5 years. Our findings rather suggest a lower likelihood of an MS diagnosis after vaccination. In addition, the low rate of vaccination during the months before MS diagnosis also argues against a major role of vaccination in the induction of MS relapses. Several reasons may account for the lower rate of vaccinations during the 5 years prior to MS diagnosis.

Previous studies have reported altered behavior and an increased prevalence of neuropsychiatric symptoms up to 5 years before MS diagnosis, which might be related to an awareness of the participants of their disease even before the diagnosis is made.[11] For instance, a lower rate of pregnancies has been found in women with MS as compared to controls. A causal relation of lower pregnancy rates with the development of MS seems unlikely. On that note, it has been assumed that the onset of disease might occur up to several years before the actual first diagnosis and that participants change their behavior along the course of the disease, even before the diagnosis is made.

Similarly, increased levels of sick leave and disability pension have been reported for patients with MS even 15 years before first diagnosis of the disease.[29] In this respect, disease burden may affect the lifestyle of a patient with MS long before it is diagnosed. In addition, higher rates of physician services utilization as compared to the general population have been observed at least 5 years before diagnosis.[30]

These findings are of relevance for the interpretation of the results of the present study. Possible explanations of the lower vaccination rates in patients with MS up to 5 years before diagnosis might be that the patients are aware of their disease or are affected by the burden of disease even before the first diagnosis, which may lead to altered behavior.

Similar results would be expected if the MS group was inaccurately defined and wrongfully included patients who have already been diagnosed with MS at an earlier time point. It could be expected that patients with MS get vaccinated less often as compared to healthy individuals. However, as the observed effects were even stronger in patients with not more than one neurologist consultation within the 5 years before diagnosis, we consider it unlikely that our findings are due to the contamination of the MS group with previously diagnosed patients.

Vaccinations might also directly affect the immunopathogenesis of MS. Infections are associated with MS relapses and the prevention of infections might thus decrease relapses and MS risk. In this study, the negative relation of vaccination with the development of MS is most pronounced for influenza. The conclusion that the prevention of influenza infection might decrease the risk of developing MS or relapses in patients with MS cannot be drawn from the present findings, however. Moreover, vaccination itself might influence the autoimmune response in MS. Stimulation of the immune system with vaccine antigens might have an ameliorating effect on the autoimmune response underlying onset and progression of disease.[31,32]

A limitation of the present study is the subjective definition of the MS cohort, potentially leading to flawed findings. This issue was addressed by multiple strict definitions of the MS cohort, enabling the implementation of sensitivity analyses. Another limitation is given by the data source itself. Entry errors and incorrect coding cannot be ruled out, even for databases with high-quality standards like the BASHIP database.

Our data show a negative association of vaccinations with MS. This could be seen when considering all reported vaccinations

and specifically for influenza, hepatitis B, and TBE vaccinations. These data alone do not allow for any conclusion regarding a possible protective effect of vaccinations regarding the development of MS. However, our results do not support the assumption that vaccinations are a risk factor for the development of MS.

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Disclosure

A. Hapfelmeier received a speaker honorarium from Biogen for the Biogen Symposium on Statistical Methods in Real World Evidence 2017. C. Gasperi and E. Donnachie report no disclosures relevant to the manuscript. B. Hemmer has served on scientific advisory boards for Novartis; has served as DMSC member for AllergyCare and TG Therapeutics; he or his institution have received speaker honoraria from Desitin; and he holds part of 2 patents, one for the detection of antibodies against KIR4.1 in a subpopulation of patients with MS and one for genetic determinants of neutralizing antibodies to interferon-β. No conflicts are relevant to the topic of the study. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Role	Contribution
Alexander Hapfelmeier, PhD	Technical University of Munich, Germany	Author	Analyzed the data, interpreted the data, drafted and revised the manuscript for intellectual content
Christiane Gasperi, MD	Technical University of Munich, Germany	Author	Interpreted the data, drafted and revised the manuscript for intellectual content
Ewan Donnachie	BASHIP, Germany	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Bernhard Hemmer, MD	Technical University of Munich, Germany	Author	Designed and conceptualized study, interpreted the data, drafted and revised the manuscript for intellectual content

References

1. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol 2016;13:25.
2. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol 2004;3:709–718.
3. Kalincik T. Multiple sclerosis relapses: epidemiology, outcomes and management: a systematic review. Neuroepidemiology 2015;44:199–214.
4. Mailand MT, Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. J Neurol 2017;264:1035–1050.
5. Daltrozzo T, Hapfelmeier A, Donnachie E, Schneider A, Hemmer B. A systematic assessment of prevalence, incidence and regional distribution of multiple sclerosis in Bavaria from 2006 to 2015. Front Neurol 2018;9:871.
6. Swart E, Gothe H, Geyer S, et al. Gute Praxis Sekundärdatenanalyse (GPS): Leitlinien und Empfehlungen. Gesundheitswesen 2015;77:120–126.
7. Kuo C-L, Duan Y, Grady J. Unconditional or conditional logistic regression model for age-matched case-control data? Front Public Health 2018;6:57.
8. Disanto G, Zecca C, MacLachlan S, et al. Prodromal symptoms of multiple sclerosis in primary care. Ann Neurol 2018;83:1162–1173.
9. Högg T, Wijnands JMA, Kingwell E, et al. Mining healthcare data for markers of the multiple sclerosis prodrome. Mult Scler Relat Disord 2018;25:232–240.
10. Wijnands JMA, Kingwell E, Zhu F, et al. Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study. Lancet Neurol 2017;16:445–451.
11. Wijnands JMA, Zhu F, Kingwell E, et al. Five years before multiple sclerosis onset: phenotyping the prodrome. Mult Scler J 2018;25:1092–1101.
12. Amini Harandi A, Pakdaman H, Sahraian MA, Hosseini SK. Infectious diseases, related vaccinations, and risk of multiple sclerosis later in life: a case-control study (P03.242). Neurology 2012;78:P03.242.
13. Ascherio A, Zhang SM, Hernán MA, Olek PM, Brodovicz K, Walker AM Hepatitis B vaccination and the risk of multiple sclerosis. N Engl J Med 2001;344:327–332.
14. Baumhackl U, Franta C, Retzl J, Salomonowitz E, Eder G. A controlled trial of tick-borne encephalitis vaccination in patients with multiple sclerosis. Vaccine 2003;21 Suppl 1:S56–S61.
15. DeStefano F, Verstraeten T, Jackson LA, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. Arch Neurol 2003;60:504–509.
16. Eftekharian MM, Mousavi M, Hormoz MB, Roshanaei G, Mazdeh M. Multiple sclerosis and immunological-related risk factors: results from a case–control study. Hum Antibodies 2014;23:31–36.
17. Grimaldi-Bensouda L, Rossignol M, Koné-Paut I, et al. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: six years of case-referent surveillance. J Autoimmun 2017;79:84–90.
18. Hernán MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurology 2004;63:838–842.
19. Kurtzke JF, Hyllested K, Arbuckle JD, et al. Multiple sclerosis in the Faroe Islands: 7: results of a case control questionnaire with multiple controls. Acta Neurol Scand 1997;96:149–157.
20. Lai YC, Yew YW. Severe autoimmune adverse events post herpes zoster vaccine: a case-control study of adverse events in a national database. J Drugs Dermatol 2015;14:681–684.
21. Langer-Gould A, Qian L, Tartof SY, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseasesvaccines and the risk of multiple sclerosis vaccines and the risk of multiple sclerosis. JAMA Neurol 2014;71:1506–1513.
22. Mahmud SM, Bozat-Emre S, Mostaço-Guidolin LC, Marrie RA. Registry cohort study to determine risk for multiple sclerosis after vaccination for pandemic influenza A(H1N1) with Arepanrix, Manitoba, Canada. Emerging Infect Dis 2018;24:1267–1274.
23. McNicholas N, Chataway J. Relapse risk in patients with multiple sclerosis after H1N1 vaccination, with or without seasonal influenza vaccination. J Neurol 2011;258:1545–1547.
24. Miller AE, Morgante LA, Buchwald LY, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. Neurology 1997;48:312–314.
25. Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. Mult Scler 1997;3:243–247.
26. Ramagopalan SV, Valdar W, Dyment DA, et al. Association of infectious mononucleosis with multiple sclerosis. Neuroepidemiology 2009;32:257–262.
27. Scheller NM, Svanström H, Pasternak B, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015;313:54–61.
28. Zorzon M, Zivadinov R, Nasuelli D, et al. Risk factors of multiple sclerosis: a case–control study. Neurol Sci 2003;24:242–247.
29. Landfeldt E, Castelo-Branco A, Svedbom A, Löfroth E, Kavaliunas A, Hillert J. Sick leave and disability pension before and after diagnosis of multiple sclerosis. Mult Scler 2016;22:1859–1866.
30. Marrie RA, Yu N, Wei Y, Elliott L, Blanchard J. High rates of physician services utilization at least five years before multiple sclerosis diagnosis. Mult Scler J 2012;19:1113–1119.
31. Ristori G, Buzzi MG, Sabatini U, et al. Use of Bacille Calmette-Guérin (BCG) in multiple sclerosis. Neurology 1999;53:1588.
32. Ristori G, Romano S, Cannoni S, et al. Effects of Bacille Calmette-Guérin after the first demyelinating event in the CNS. Neurology 2014;82:41–48.

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