Received: 7 January 2024 | Accepted: 25 March 2024

DOI: 10.1002/jmv.29591

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Global burden of vaccine-associated multiple sclerosis, 1967–2022: A comprehensive analysis of the international pharmacovigilance database

Ho Geol Woo[1] | Hyeon Jin Kim[2,3] | Jaeyu Park[2,3] | Jinseok Lee[4] | Hayeon Lee[2,4] | Min Seo Kim[5] | Ai Koyanagi[6] | Lee Smith[7] | Masoud Rahmati[8,9,10] | Seung Geun Yeo[11] | Dong Keon Yon[2,3,12]

[1]Department of Neurology, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea

[2]Center for Digital Health, Medical Science Research Institute, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea

[3]Department of Regulatory Science, Kyung Hee University, Seoul, South Korea

[4]Department of Biomedical Engineering, Kyung Hee University, Yongin, South Korea

[5]Medical and Population Genetics and Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

[6]Research and Development Unit, Parc Sanitari Sant Joan de Deu, Barcelona, Spain

[7]Centre for Health, Performance and Wellbeing, Anglia Ruskin University, Cambridge, UK

[8]CEReSS-Health Service Research and Quality of Life Center, Assistance Publique-Hôpitaux de Marseille (APHM), Aix-Marseille University, Marseille, France

[9]Department of Physical Education and Sport Sciences, Faculty of Literature and Human Sciences, Lorestan University, Khoramabad, Iran

[10]Department of Physical Education and Sport Sciences, Faculty of Literature and Humanities, Vali-E-Asr University of Rafsanjan, Rafsanjan, Iran

[11]Department of Otolaryngology—Head & Neck Surgery, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea

[12]Department of Pediatrics, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea

Correspondence

Seung Geun Yeo, Department of Otolaryngology—Head & Neck Surgery, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, South Korea.
Email: yeo2park@gmail.com

Ho Geol Woo, Department of Neurology, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, South Korea.
Email: nr85plasma@naver.com

Dong Keon Yon, Center for Digital Health, Medical Science Research Institute, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, South Korea.
Email: yonkkang@gmail.com

Abstract

Vaccine-associated multiple sclerosis (MS) is rare, with insufficient evidence from case reports. Given the scarcity of large-scale data investigating the association between vaccine administration and adverse events, we investigated the global burden of vaccine-associated MS and potential related vaccines from 1967 to 2022. Reports on vaccine-associated MS between 1967 and 2022 were obtained from the World Health Organization International Pharmacovigilance Database (total number of reports = 120 715 116). We evaluated global reports, reporting odds ratio (ROR), and information components (IC) to investigate associations between 19 vaccines and vaccine-associated MS across 156 countries and territories. We identified 8288 reports of vaccine-associated MS among 132 980 cases of all-cause MS. The cumulative number of reports on vaccine-associated MS gradually increased over time, with a substantial increase after 2020, owing to COVID-19 mRNA vaccine-associated MS. Vaccine-associated MS develops more frequently in males and adolescents. Nine vaccines were significantly associated with higher MS reporting, and the highest disproportional associations were observed for hepatitis B vaccines

Ho Geol Woo, Hyeon Jin Kim, and Jaeyu Park contributed equally to this study.

Funding information
National Research Foundation of Korea (NRF), Grant/Award Number: RS-2023-00239251; Korea Health Industry Development Institute (KHIDI), Grant/Award Number: HV22C0233

(ROR 19.82; IC_{025} 4.18), followed by encephalitis (ROR 7.42; IC_{025} 2.59), hepatitis A (ROR 4.46; IC_{025} 1.95), and papillomavirus vaccines (ROR 4.45; IC_{025} 2.01). Additionally, MS showed a significantly disproportionate signal for COVID-19 mRNA vaccines (ROR 1.55; IC_{025} 0.52). Fatal clinical outcomes were reported in only 0.3% (21/8288) of all cases of vaccine-associated MS. Although various vaccines are potentially associated with increased risk of MS, we should be cautious about the increased risk of MS following vaccination, particularly hepatitis B and COVID-19 mRNA vaccines, and should consider the risk factors associated with vaccine-associated MS.

KEYWORDS
global, vaccine-associated multiple sclerosis, vaccines, World Health Organization

1 | INTRODUCTION

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system.[1] The neuroinflammatory demyelination affecting the brain, spinal cord, and optic nerve leads to dysfunction of vision, sensory and motor disturbances, ataxia, and cognitive impairment.[1] These neurologic dysfunctions are reversible and predominantly present in individuals in early adulthood. However, after usually 10–20 years, progressive neurologic disability occurs in many affected individuals, and functional and financial burdens develop.[2]

The etiology and pathogenesis of MS are complex and remain uncertain, despite decades of research on both genetic and environmental factors.[1] Currently, genetically susceptible individuals and environmental triggers including smoking, obesity, vitamin D deficiency, autoimmune disorders, infections (e.g., Epstein-Barr virus, cytomegalovirus, and varicella-zoster virus), drugs, and alteration of the gut microbiota are known to aid in the development of MS.[3,4] Previous studies have suggested that immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS.[5] Furthermore, some reports suggest an association between influenza and human papillomavirus (HPV) vaccines with incident MS; however, it is important to recognize that some of these studies have been constrained by methodological limitations including limited sample sizes.[6,7]

Vaccination is an important public health intervention for preventing many life-threatening infectious diseases and ultimately early mortality.[8] The undeniable benefits of vaccines far outweigh the risks of potential adverse events (AEs).[9] This has been particularly highlighted during the COVID-19 pandemic, emphasizing the paramount importance of vaccination.[10–12] However, some AEs of vaccination, including MS, have been reported. As COVID-19 vaccines are urgently approved, MS associated with COVID-19 vaccines should be closely monitored.[13]

To better understand vaccine-associated MS on a global scale, further research is required to determine the burden, long-term trends, and related factors associated with MS. Using VigiBase, the World Health Organization (WHO) global pharmacovigilance database, we aimed to explore the burden and long-term trends of vaccine-associated MS and its related factors on a global scale.

2 | METHODS

2.1 | Data sources

We conducted a comprehensive analysis of international pharmacovigilance studies focusing on vaccine-associated MS reported in VigiBase, which is the global postmarketing pharmacovigilance database maintained by the Swedish WHO Collaborating Centre for International Drug Monitoring, branded as the Uppsala Monitoring Centre (UMC), and has accumulated individual case safety reports (ICSR).[14–16] Individual reports include basic health data of the patient, adverse effect data, and drug data. The database consists of ICSR from over 150 countries, involving 25 000 drugs and vaccines, and includes 120 715 116 reports submitted from national pharmacovigilance centers since 1967.[17] Physicians, healthcare professionals, pharmacists, pharmaceutical companies, and patients spontaneously notify the ICSR database, and they are checked for quality of report, regularly reviewed, and analyzed based on predefined criteria.[14,15] ICSR is coded into preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA).[18] The Institutional Review Boards of Kyung Hee University Medical Center (KHUH 2022-06-042) and the Uppsala Monitoring Centre (WHO Collaborating Center) approved the use of confidential and electronically processed patient data.

2.2 | Selection of cases

The study evaluated vaccine-associated MS between 1967 and 2022, and vaccines were classified into 19 categories, which include (1) anthrax, (2) cholera, (3) diphtheria, tetanus, acellular pertussis, polio,

and *Haemophilus influenzae* type b (DTaP-IPV-Hib), (4) meningococcal, (5) pneumococcal, (6) tuberculosis, (7) typhoid, (8) encephalitis, (9) influenza, (10) hepatitis A, (11) hepatitis B, (12) rotavirus diarrhea, (13) measles, mumps, and rubella (MMR), (14) varicella zoster, (15) HPV, (16) COVID-19 mRNA, (17) adenovirus type-5 (Ad5)-vectored COVID-19, (18) inactivated whole virus COVID-19, and (19) other (brucellosis, plague, typhus, leptospirosis, rabies, yellow fever, smallpox, Ebola, and dengue) vaccines.

Vaccines were categorized using the Level 4 Anatomical Therapeutic Chemical Code in the WHO drug classifications. All the MS cases were identified using MedDRA at the 25.0 preferred terms level (Supporting Information S1: Table 1). According to WHO causality assessment recommendations, vaccines are considered as "suspected" when calculating disproportional association with MS.

2.3 | Data collection

The study collected ICSR data where there was a suspicion of vaccine-associated MS for further description. The ICSR consists of administrative information (reporting region, year, reporter qualification, and reporting type) and patient characteristics (sex and age). The ICSR also included vaccine information (vaccine class and single vaccine suspected), information about AEs such as the time to onset (TTO) of the AEs, nature and severity of the AEs, and fatal outcome. TTO was defined as the number of days between the administration date of the vaccine and the date when MS was diagnosed. All spontaneous reports included at least one vaccine suspected to be involved in the occurrence of AEs following immunization. According to the WHO definition, each AE is characterized as "non-serious" or "serious."[14,15] Fatal outcome was defined as fatal or death among serious AE. Physicians who submitted the ICSR determined the severity of the MS. Concomitant AEs were reported with vaccine-associated MS. These concomitant AEs were classified using MedDRA terms, which are listed in Supporting Information S1: Table 2.[19] Given that ICSR was reported voluntarily based on anonymity and did not contradict patient consent, informed consent was not needed in this VigiBase study.

2.4 | Statistical analysis

The VigiBase data set was categorized into two groups (case and noncase), and disproportionality analysis was performed on each vaccine in the data set from 1967 to 2022 (Supporting Information S1: Tables 1 and 2). Disproportionality analysis involves comparison of the proportion of specific AEs reported for a single vaccine with the proportion of the same AEs for a control group of vaccines, which comprises the entire database of all vaccines.[14,15] The total number of reported AEs for each vaccine group was used as the denominator in these analyses. If the proportion of cases of AEs associated with a specific vaccine is greater than that of patients not experiencing them, a signal of disproportionality association (signal identification) between the vaccine and AE was identified.[14,15]

To investigate which vaccines were significantly associated with MS, two common pharmacovigilance measures of disproportionate analysis were used: information components (IC) and reporting odds ratio (ROR). The IC was calculated for case-non-case analysis using a Bayesian confidence propagation neural network, developed and validated by the Uppsala Monitoring Centre as the indicator value for disproportionate reporting.[20] The IC has been validated and its effectiveness to identify signals has been confirmed in several studies.[14,15] The statistical formula for calculating the IC is as follows: $IC = \log_2([N_{observed}+0.5]/[N_{expected}+0.5])$. $N_{expected}$ is the number of cases expected for the combination of vaccine and AEs and is calculated as $[N_{vaccine} \times N_{adverse\ event}]/N_{total}$; $N_{observed}$ refers to the number of case reports for a certain AE associated with a specific vaccine; $N_{vaccine}$ refers to the number of case reports for a specific vaccine regardless of AEs; $N_{adverse\ event}$ refers to the number of case reports for a given AE regardless of the vaccines; and N_{total} represents the total number of case reports in the database. IC_{025} is the lower limit of the 95% confidence interval (CI) for IC. A positive value of IC_{025} is the conventional threshold used to detect statistical signals.[18,21,22]

We also evaluated the disproportionality association using the ROR, which is a measure of the association derived from the number of AEs and the contingency table of the vaccine, and compared the number of specific AEs occurring with a targeted vaccine to the probability of the same event occurring with all other vaccines in the database. The ROR was calculated using a contingency table of the number of AEs. If the lower 95% CI of the ROR is greater than 1, it was considered a significant association between the vaccine and a certain AE.[23,24] The vaccine and all reported cases were compared using the unpaired Kruskal–Wallis test for continuous variables and the χ^2 test, or Fisher's exact test, for categorical variables.[25] A two-sided-value <0.05 was considered significant. All analyses were performed using SAS version 9.4 (SAS Inc.).[26–30]

3 | RESULTS

3.1 | Clinical characteristics of vaccine-associated MS

The number of reports for vaccine-associated MS was 9511 out of 141 935 MS reports in the full database. After excluding demographic information missingness vaccine-associated MS was 8288 (Supporting Information S1: Figure 1).

The age of onset of MS was most prevalent between 18 and 64 years, with females representing 72.1% of the cases. Health professionals contributed to over 50.8% of the reported cases of MS. The median time to onset was 2.0 days for MS. Fatal clinical outcomes were reported in only 0.3% (21/8288) of all cases of vaccine-associated MS (Table 1).

TABLE 1 Patient characteristics of reports on vaccine-associated multiple sclerosis (n = 8288).

Variables		Number (%)
Region reporting	African Region	7 (0.1)
	Region of the Americas	3746 (45.2)
	South-East Asia Region	1 (0.0)
	European Region	4355 (52.6)
	Eastern Mediterranean Region	7 (0.1)
	Western Pacific Region	172 (2.1)
Reporting year	1967–1979	0 (0.0)
	1980–1989	8 (0.1)
	1990–1999	165 (2.0)
	2000–2009	689 (8.3)
	2010–2019	3146 (38.0)
	2020–2022	4280 (51.6)
Reporter qualification	Health professional	4212 (50.8)
	Nonhealth professional	4076 (49.2)
Studies	Study related	7829 (94.5)
	Nonstudy related	459 (5.5)
Sex	Male	2104 (25.4)
	Female	5974 (72.1)
	Unknown	210 (2.5)
Age	12–17 years	554 (6.7)
	18–64 years	5366 (64.7)
	≥65 years	273 (3.3)
	Unknown	2095 (25.3)
Delay (TTO), days	Median days (IQR)	2.0 (2.0–2.0)
Vaccine class	Anthrax vaccines	39 (0.5)
	Cholera vaccines	5 (0.1)
	DTaP-IPV-Hib	299 (3.6)
	Meningococcal vaccines	67 (0.8)
	Pneumococcal vaccines	41 (0.5)
	Tuberculosis vaccines	6 (0.1)
	Typhoid vaccines	51 (0.6)
	Encephalitis vaccines	162 (2.0)
	Influenza vaccines	360 (4.3)
	Hepatitis A vaccines	296 (3.6)
	Hepatitis B vaccines	2301 (27.8)
	Rotavirus diarrhea vaccines	0 (0.0)
	MMR vaccines	116 (1.4)
	Zoster vaccines	97 (1.2)
	Papillomavirus vaccines	629 (7.6)
	COVID-19 mRNA vaccines	3113 (37.6)
	Ad5-vectored COVID-19 vaccines	426 (5.1)
	Inactivated whole-virus COVID-19 vaccines	0 (0.0)
	Others	280 (3.4)
Outcomes	Alive	5034 (60.7)
	Fatal	21 (0.3)
	Unknown	3233 (39.0)
Single vaccine suspected		8288 (100.0)

Abbreviations: DTaP-IPV-Hib, diphtheria, tetanus toxoids, pertussis, polio, and Hemophilus influenza type b; IQR, interquartile range; MMR, measles, mumps, and rubella; TTO, time to onset; WHO, World Health Organization.

The temporal changes in the reported cases of vaccine-associated MS are illustrated (Figures 1 and 2). The number of vaccine-associated MS cases gradually increased over time. The proportion of vaccine-associated MS cases among all vaccine-related MS cases also increased. There was a sharp increase in the number and proportion of vaccine-associated MS cases since 2020. European regions had the highest number of reported cases of vaccine-associated MS, followed by America.

3.2 | Cumulative report analysis of vaccine-associated MS

The cumulative number of vaccine-associated MS cases evaluated for different vaccines is shown in Figure 3. Vaccine-associated MS has been reported for 17 vaccines. Before 2020, hepatitis B vaccines had the highest cumulative counts of MS, whereas after 2020, COVID-19 mRNA vaccines were most commonly reported for MS, followed by hepatitis B, HPV, influenza, DTaP-IPV-Hib, and hepatitis A vaccines.

3.3 | Disproportionality analysis of vaccine-associated MS

Nine out of 17 vaccines were significantly associated with MS. Among them, the highest disproportional association with MS was hepatitis B vaccines (ROR 19.82, 95% CI 19.02–20.67; IC_{025} 4.18). In the age-specific subgroup analysis, disproportionate signals of hepatitis B vaccine-associated MS were significant in individuals aged 12–64 years (Table 2). A significant disproportionality in MS reporting was also found for encephalitis vaccines (ROR 7.42, 95% CI 6.38–8.66; IC_{025} 2.59), hepatitis A vaccines (ROR 4.46, 95% CI

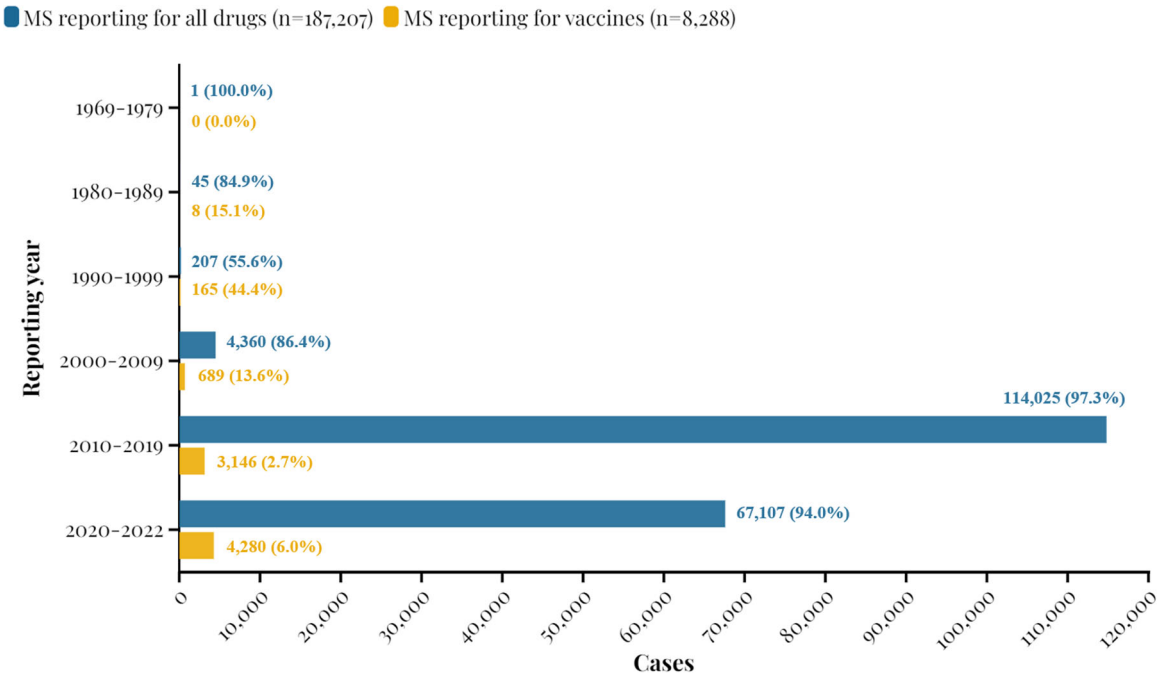

FIGURE 1 Temporal changes of reported cases of vaccine-associated multiple sclerosis. Absolute reported counts of multiple sclerosis according to the reporting year. The proportions of relevant adverse reactions among all drug- or vaccine-related adverse reactions are indicated.

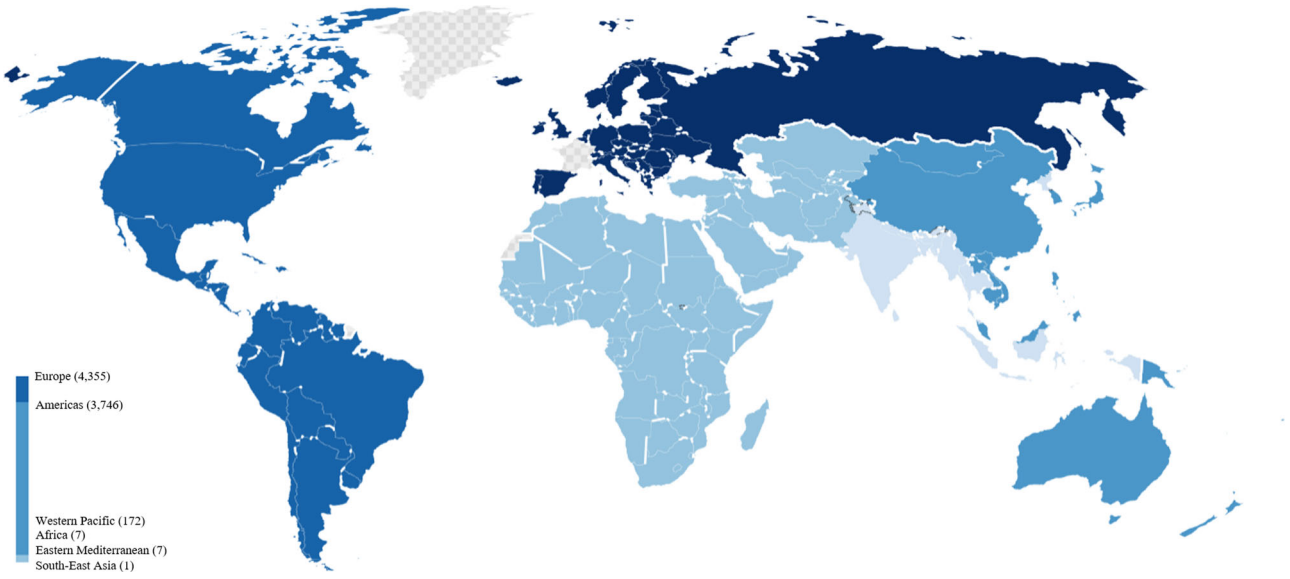

FIGURE 2 World map of reported cases of vaccine-associated multiple sclerosis by continent. Global reported counts based on the continent.

3.98–5.00; IC_{025} 1.95), HPV vaccines (ROR 4.45, 95% CI 4.11–4.81; IC_{025} 2.01), anthrax vaccines (ROR 3.58, 95% CI 2.61–4.90; IC_{025} 1.26), typhoid vaccines (ROR 2.80, 95% CI 2.13–3.68; IC_{025} 0.99), COVID-19 mRNA vaccines (ROR 1.55, 95% CI 1.49–1.60; IC_{025} 0.52), other vaccines (ROR 1.42, 95% CI 1.26–1.60; IC_{025} 0.31), and MMR vaccines (ROR 1.33, 95% CI 1.11–1.60; IC_{025} 0.11).

From an age-specific perspective, the 12–17 years age group had the highest risk of developing vaccine-associated MS (IC_{025} 7.33). Regarding individual vaccines, age-specific top disproportionality was found in DTaP-IPV-Hib, encephalitis, hepatitis A, and HPV vaccines for 12–64 years, anthrax and typhoid vaccines for 18–64 years, and COVID-19 mRNA and Ad5-vectored COVID-19 vaccine for ≥65 years (Table 2). Concurrent AEs in vaccines with significantly disproportionate signals of vaccine-associated MS showed similar patterns. Neurological events were the most frequently reported concurrent manifestations, followed by muscular and psychiatric events (Supporting Information S1: Table 3).

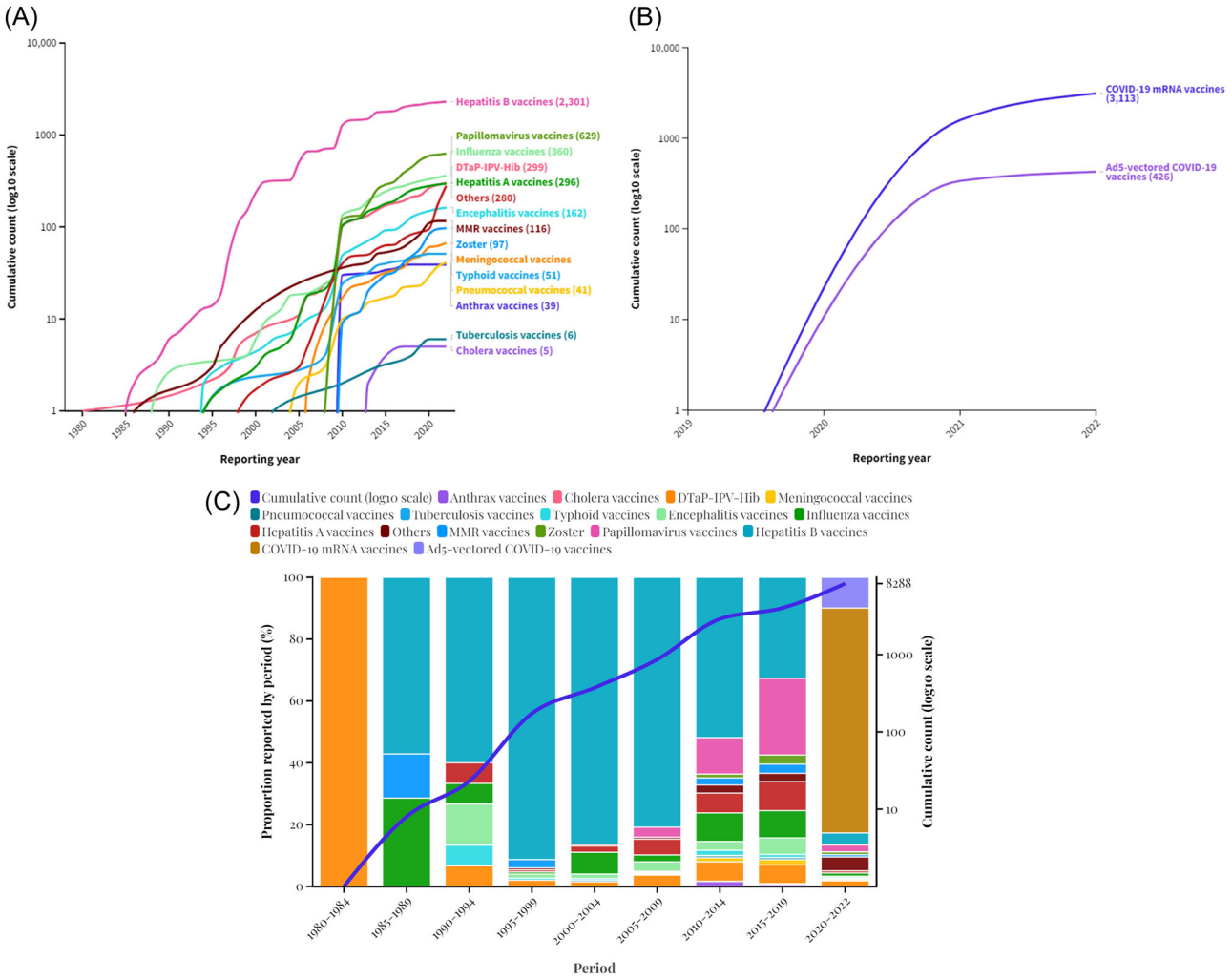

FIGURE 3 Cumulative number of reports of multiple sclerosis per year in association with different vaccines. (A–C) Cumulative counts of multiple sclerosis according to the reporting year. Other vaccines included brucellosis, plague, typhus, leptospirosis, rabies, yellow fever, smallpox, Ebola, and dengue vaccines. Ad5, adenovirus type-5; COVID, coronavirus disease 2019; DTaP-IPV-Hib, diphtheria, tetanus, acellular pertussis, polio, and *Hemophilus influenzae* type b; HPV, human papillomavirus; MMR, measles, mumps, and rubella.

4 | DISCUSSION

This global pharmacovigilance data set, consisting of almost 120 million reports between 1967 and 2022, was analyzed for a comprehensive investigation of vaccine-associated MS. We observed a gradual increase in the number of cases of vaccine-associated MS over the years, with a substantial increase observed after 2020 due to COVID-19 mRNA vaccine-associated MS. Vaccine-associated MS develops more frequently in males and adolescents. Nine vaccines were significantly associated with higher MS reporting, and the highest disproportional associations were observed for hepatitis B vaccines, followed by encephalitis, hepatitis A, and papillomavirus vaccines. In addition, MS showed a significantly disproportionate signal for COVID-19 mRNA vaccines (ROR 1.55; IC_{025} 0.52). These results imply that vaccines are emerging as an important potential cause of MS and suggest the importance of continuous pharmacovigilance monitoring for vaccine AEs.[31,32]

Our analysis revealed nine vaccines with significant disproportionality in MS reporting. Our study clearly suggests that COVID-19 mRNA vaccines had the highest number of vaccine-associated MS reports, which was significantly disproportionate to vaccine-associated MS reporting. COVID-19 vaccines were granted with emergency use authorization, and several case reports of vaccine-associated MS pointed out safety concerns.[6,33–38] Moreover, Ad5-vectored COVID-19 vaccines and inactivated whole-virus COVID-19 vaccines did not exhibit disproportionate MS signals among the various vaccines analyzed.[39] It is also unclear how COVID-19 mRNA vaccines could trigger the immunologic processes that lead to MS. COVID-19 mRNA vaccine-associated MS may develop via an overactive immune system response, including a self-reactive T-cell response, through exposure of dendritic cells to exogenous mRNA.[37,38,40,41] However, these findings suggest that COVID-19 mRNA vaccines have the greatest potential for vaccine-associated MS. Additionally, the risk of MS in the context of COVID-19 mRNA

TABLE 2 Disproportionality analysis of vaccine-associated multiple sclerosis and relevant subgroups analysis.

		Multiple sclerosis			IC (IC_{025}) based on age, years		
	Total	Observed	ROR (95% CI)	IC (IC_{025})	12–17 years	18–64 years	≥65 years
Total							
IC (IC_{025})					**7.48 (7.33)**	**1.22 (1.18)**	**2.91 (2.71)**
ROR (95% CI)					**8.08 (7.13–9.15)**	**1.07 (1.04–1.10)**	**1.59 (1.41–1.80)**
Sex difference							
Male	2 533 435	2104	**1.19 (1.14–1.25)**	**0.24 (0.17)**	**1.89 (1.52)**	**0.46 (0.37)**	**1.01 (0.64)**
Female	4 283 879	5974	1.01 (0.98–1.04)	0.01 (−0.03)	**2.18 (2.02)**	−0.04 (−0.10)	**0.46 (0.22)**
Anthrax vaccines	9923	39	**3.58 (2.61–4.90)**	**1.79 (1.26)**	−0.01 (−10.34)	**1.30 (0.72)**	−0.01 (−10.33)
Cholera vaccines	2310	5	1.97 (0.82–4.73)	0.85 (−0.71)	−0.10 (−10.42)	0.77 (−1.00)	−0.06 (−10.39)
DTaP-IPV-Hib vaccines	777 222	299	0.35 (0.31–0.39)	−1.52 (−1.71)	**0.88 (0.13)**	**0.85 (0.61)**	1.36 (−0.06)
Meningococcal vaccines	144 492	67	0.42 (0.33–0.53)	−1.24 (−1.65)	0.42 (−0.40)	0.36 (−0.27)	−0.29 (−10.61)
Pneumococcal vaccines	264 284	41	0.14 (0.10–0.19)	−2.81 (−3.33)	0.35 (−3.43)	−0.91 (−1.57)	−1.07 (−2.64)
Tuberculosis vaccines	33 415	6	0.16 (0.07–0.36)	−2.52 (−3.94)	−1.49 (−11.81)	0.89 (−0.87)	−0.52 (−10.85)
Typhoid vaccines	16 578	51	**2.80 (2.13–3.68)**	**1.46 (0.99)**	−0.62 (−10.95)	**1.36 (0.84)**	−0.32 (−10.65)
Encephalitis vaccines	19 976	162	**7.42 (6.36–8.66)**	**2.85 (2.59)**	**3.16 (1.95)**	**3.16 (2.85)**	−0.60 (−10.92)
Influenza vaccines	346 453	360	0.94 (0.85–1.05)	−0.08 (−0.26)	0.16 (−1.26)	0.18 (−0.02)	0.48 (−0.25)
Hepatitis A vaccines	60 558	296	**4.46 (3.98–5.00)**	**2.14 (1.95)**	**2.27 (1.37)**	**2.79 (2.56)**	−0.62 (−10.94)
Hepatitis B vaccines	109 304	2301	**19.82 (19.02–20.67)**	**4.25 (4.18)**	**5.09 (4.82)**	**4.77 (4.69)**	−0.58 (−10.90)
MMR vaccines	78 971	116	**1.33 (1.11–1.60)**	**0.41 (0.11)**	−3.01 (−13.33)	−6.08 (−16.41)	−0.17 (−10.49)
Zoster vaccines	203 900	97	0.43 (0.35–0.53)	−1.21 (−1.54)	1.14 (−0.17)	−0.67 (−1.18)	0.83 (−0.01)
Papillomavirus vaccines	129 318	629	**4.45 (4.11–4.81)**	**2.14 (2.01)**	**3.11 (2.89)**	**2.46 (2.23)**	−0.04 (−10.37)
COVID-19 mRNA vaccines	3 230 266	3113	**1.55 (1.49–1.60)**	**0.58 (0.52)**	−0.47 (−1.14)	−0.62 (−0.70)	**0.72 (0.46)**
Ad5-vectored COVID-19 vaccines	1 073 625	426	0.61 (0.56–0.67)	−0.70 (−0.86)	−1.62 (−11.94)	−1.81 (−1.99)	**0.76 (0.30)**
Others[a]	178 902	280	**1.42 (1.26–1.60)**	**0.51 (0.31)**	−0.41 (−4.20)	0.07 (−0.17)	0.35 (−1.21)

Note: Bold style indicates when the value of IC025 is greater than 0.0 or the lower end of the ROR 95% CI is greater than 1.0. This means it is statistically significant. Numbers in bold indicate statistical significance.

Abbreviations: CI, confidence interval; DTaP-IPV-Hib, diphtheria, tetanus toxoids, pertussis, polio, and Hemophilus influenza type b; IC, information component; MMR, measles, mumps, and rubella; ROR, reported odds ratio.

[a]Others include brucellosis, plague, typhus, leptospirosis, rabies, yellow fever, smallpox, Ebola, and dengue vaccines.

vaccinations should be emphasized, and importance of monitoring and managing these risks should be stressed.

We also confirmed several significant signals between different vaccines and higher reporting of MS. Previous pooled analyses suggested that there is no evidence that vaccination with tuberculosis, hepatitis B, influenza, MMR, DTaP-IPV-Hib, or typhoid vaccines is associated with an increased risk of developing MS.[42,43] However, in the present study, hepatitis B vaccines exhibited the strongest disproportionate signal for MS among the various vaccines analyzed. These were the commonly reported vaccine-associated MS cases before 2020. The potential link between hepatitis B vaccines and an increased risk of MS has been evaluated in several previous studies.[44–46] In addition to previous studies,[42,46,47] our findings showed significant disproportionality for vaccine-associated MS in recipients of encephalitis, HPV, hepatitis A, anthrax, typhoid, and MMR vaccines. Our findings provide valuable insights into associations between specific vaccines and MS occurrence in different age subgroups.

To the best of our knowledge, this is the first comprehensive study to investigate the global trends of vaccine-associated MS and identify which of them have significant signals. Despite this, our study has several limitations. First, the database (VigiBase) lacks clinical information, including neurological symptoms or signs, laboratory findings, or radiological features needed to diagnose MS. Second, the ICSR of suspected vaccine-associated MS uses a passive reporting method with the potential for reporting bias, such as

underreporting, and the sources of reports are also heterogeneous. Third, we conducted our analysis using MedDRA codes, which have limitations in appropriately mapping to ICD codes. This could affect the reproducibility. Nevertheless, VigiBase collects ICSR data from more than 150 countries spanning 50 years, which guarantees the generalizability of our findings. Third, the exact denominator of recipients exposed to the vaccines could not be determined. In this study, the total number of ICSRs was used as a denominator for the disproportionality analysis, which has been validated in pharmacovigilance studies of signals. Finally, a causal relationship between COVID-19 mRNA vaccinations and the risk of MS cannot be determined. Therefore, it is important that further research be conducted to provide the necessary evidence to support this result.

In conclusion, using the global pharmacovigilance database, we found that the number of vaccine-associated MS cases substantially increased after 2020. Vaccine-associated MS develops more frequently in males and adolescents. A total of nine vaccines were significantly associated with higher MS reporting, and the highest disproportionate associations were observed for hepatitis B vaccines, followed by encephalitis, hepatitis A, papillomavirus, anthrax, typhoid, COVID-19 mRNA, and MMR vaccines. We should be cautious about the increased risk of MS following vaccination and its risk factors, and further studies are needed to inform the early diagnosis and treatment of vaccine-associated MS.

AUTHOR CONTRIBUTIONS

Study concept and design: Ho Geol Woo, Hyeon Jin Kim, Jaeyu Park, and Dong Keon Yon. *Acquisition, analysis, or interpretation of data*: Ho Geol Woo, Hyeon Jin Kim, Jaeyu Park, and Dong Keon Yon. *Drafting of the manuscript*: Ho Geol Woo, Hyeon Jin Kim, Jaeyu Park, and Dong Keon Yon. *Critical revision of the manuscript for important intellectual content*: Ho Geol Woo, Hyeon Jin Kim, Jaeyu Park, Jinseok Lee, Hayeon Lee, Min Seo Kim, Ai Koyanagi, Lee Smith, Masoud Rahmati, Seung Geun Yeo, Dong Keon Yon. *Statistical analysis*: Ho Geol Woo, Hyeon Jin Kim, Jaeyu Park, and Dong Keon Yon. *Study supervision*: Ho Geol Woo, Hyeon Jin Kim, Jaeyu Park, and Dong Keon Yon. Ho Geol Woo, Seung Geun Yeo, and Dong Keon Yon contributed equally as corresponding authors. Ho Geol Woo, Hyeon Jin Kim, and Jaeyu Park contributed equally as first authors. Dong Keon Yon supervised the study and were guarantors. The corresponding authors attest that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. Ho Geol Woo and Dong Keon Yon had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the manuscript before submission.

ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT; RS-2023-00239251) and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HV22C0233). The funders played no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on reasonable request. Study protocol, statistical code: available from DKY (email: yonkkang@gmail.com). Data set: available from the Uppsala Monitoring Centre or World Health Organization through a data use agreement.

ORCID

Masoud Rahmati http://orcid.org/0000-0003-4792-027X
Dong Keon Yon http://orcid.org/0000-0003-1628-9948

REFERENCES

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. *N Engl J Med*. 2018;378(2):169-180.
2. Bebo B, Cintina I, LaRocca N, et al. The economic burden of multiple sclerosis in the United States: estimate of direct and indirect costs. *Neurology*. 2022;98(18):e1810-e1817.
3. Rimkus CM, Schoeps VA, Boaventura M, et al. Drug-related demyelinating syndromes: understanding risk factors, pathophysiological mechanisms and magnetic resonance imaging findings. *Mult Scler Relat Disord*. 2021;55:103146.
4. Zarghami A, Li Y, Claflin SB, van der Mei I, Taylor BV. Role of environmental factors in multiple sclerosis. *Expert Rev Neurother*. 2021;21(12):1389-1408.
5. Hernán MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis. A prospective study. *Neurology*. 2004;63(5):838-842.
6. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. *Autoimmun Rev*. 2014;13(3):215-224.
7. Huynh W, Cordato DJ, Kehdi E, Masters LT, Dedousis C. Post-vaccination encephalomyelitis: literature review and illustrative case. *J Clin Neurosci*. 2008;15(12):1315-1322.
8. The Lancet Infectious Diseases D. The imperative of vaccination. *Lancet Infect Dis*. 2017;17(11):1099.
9. Nanni A, Meredith S, Gati S, Holm K, Harmon T, Ginsberg A. Strengthening global vaccine access for adolescents and adults. *Vaccine*. 2017;35(49 Pt B):6823-6827.
10. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis*. 2022;22(9):1293-1302.
11. Shin YH, Shin JI, Moon SY, et al. Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: a nationwide cohort study. *Lancet Rheumatol*. 2021;3(10):e698-e706.
12. Lee SW, Kim SY, Moon SY, et al. Estimating COVID-19 infection and severity risks in patients with chronic rhinosinusitis: a Korean nationwide cohort study. *J Allergy Clin Immunol Pract*. 2021;9(6):2262-2271.
13. Hosseini R, Askari N. A review of neurological side effects of COVID-19 vaccination. *Eur J Med Res*. 2023;28(1):102.
14. Min C. The importance of a world health organization international pharmacovigilance database (VigiBase): novel methods for safety monitoring and surveillance of medical products. *Life Cycle*. 2022;2:e13.

15. Kim MS, Jung SY, Lee SW, et al. Hepatobiliary adverse drug reactions associated with remdesivir: the WHO international pharmacovigilance study. *Clin Gastroenterol Hepatol*. 2021;19(9):1970-1972.
16. Smith L, Shin JI, Hwang SY, et al. Global burden of disease study at the World Health Organization: research methods for the most comprehensive global study of disease and underlying health policies. *Life Cycle*. 2022;2:e8.
17. Kyung S, Woo S, Kim M, et al. Global burden of vaccine-associated alopecia, 1979-2023: a comprehensive analysis of the international pharmacovigilance database. *Br J Dermatol*. 2024. https://doi.org/10.1093/bjd/ljae055
18. Lee K, Lee H, Kwon R, et al. Global burden of vaccine-associated anaphylaxis and their related vaccines, 1967-2023: a comprehensive analysis of the international pharmacovigilance database. *Allergy*. 2024;79(3):690-701.
19. Nguyen LS, Cooper LT, Kerneis M, et al. Systematic analysis of drug-associated myocarditis reported in the World Health Organization pharmacovigilance database. *Nat Commun*. 2022;13(1):25.
20. Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018;19(12):1579-1589.
21. Lee HJ, Choi Y, Park J, Choi YS, Yon DK, Kim DH. National trends in rotavirus enteritis among infants in South Korea, 2010-2021: a nationwide cohort. *Children*. 2023;10(9):1436.
22. Choi Y, Kim HJ, Park J, et al. National prevalence and trends in food labeling awareness, comprehension, usage, and COVID-19 pandemic-related factors in South Korea, 2014-2022. *Sci Rep*. 2024;14(1):2617.
23. Salem JE, Nguyen LS, Moslehi JJ, et al. Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study. *Eur Heart J*. 2021;42(38):3915-3928.
24. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. *J Am Coll Cardiol*. 2019;74(13):1667-1678.
25. Lee SW. Methods for testing statistical differences between groups in medical research: statistical standard and guideline of Life Cycle Committee. *Life Cycle*. 2022;2:e1.
26. Lee H, Cho JK, Park J, et al. Machine learning-based prediction of suicidality in adolescents with allergic rhinitis: derivation and validation in 2 independent nationwide cohorts. *J Med Internet Res*. 2024;26:e51473.
27. Cho JK, Yang H, Park J, et al. Association between allergic rhinitis and despair, suicidal ideation, and suicide attempts in Korean adolescents: a nationally representative study of one million adolescents. *Eur Rev Med Pharmacol Sci*. 2023;27(19):9248-9256.
28. Kim MS, Lee H, Lee SW, et al. Long-term autoimmune inflammatory rheumatic outcomes of COVID-19: a binational cohort study. *Ann Intern Med*. 2024;177:291-302.
29. Yoo HW, Jin HY, Yon DK, et al. Non-alcoholic fatty liver disease and COVID-19 susceptibility and outcomes: a Korean nationwide cohort. *J Korean Med Sci*. 2021;36(41):e291.
30. Yon DK, Hwang S, Lee SW, et al. Indoor exposure and sensitization to formaldehyde among inner-city children with increased risk for asthma and rhinitis. *Am J Respir Crit Care Med*. 2019;200(3):388-393.
31. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet*. 2018;391(10130):1622-1636.
32. Wallin MT, Culpepper WJ, Nichols E, et al. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(3):269-285.
33. Kelly H, Sokola B, Abboud H. Safety and efficacy of COVID-19 vaccines in multiple sclerosis patients. *J Neuroimmunol*. 2021;356:577599.
34. Allen-Philbey K, Stennett A, Begum T, et al. Experience with the COVID-19 AstraZeneca vaccination in people with multiple sclerosis. *Mult Scler Relat Disord*. 2021;52:103028.
35. Frahm N, Fneish F, Ellenberger D, et al. Frequency and predictors of relapses following SARS-CoV-2 vaccination in patients with multiple sclerosis: interim results from a longitudinal observational study. *J Clin Med*. 2023;12(11):3640.
36. Alluqmani M. New onset multiple sclerosis post-COVID-19 vaccination and correlation with possible predictors in a case-control study. *Cureus*. 2023;15(3):e36323.
37. Khayat-Khoei M, Bhattacharyya S, Katz J, et al. COVID-19 mRNA vaccination leading to CNS inflammation: a case series. *J Neurol*. 2022;269(3):1093-1106.
38. Havla J, Schultz Y, Zimmermann H, Hohlfeld R, Danek A, Kümpfel T. First manifestation of multiple sclerosis after immunization with the Pfizer-BioNTech COVID-19 vaccine. *J Neurol*. 2022;269(1):55-58.
39. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA*. 2021;326(14):1390-1399.
40. Savarin C, Bergmann CC. Viral-induced suppression of self-reactive T cells: lessons from neurotropic coronavirus-induced demyelination. *J Neuroimmunol*. 2017;308:12-16.
41. Dessau RB, Lisby G, Frederiksen JL. Coronaviruses in brain tissue from patients with multiple sclerosis. *Acta Neuropathol*. 2001;101(6):601-604.
42. Farez MF, Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. *J Neurol*. 2011;258(7):1197-1206.
43. Zipp F, Weil JG, Einhäupl KM. No increase in demyelinating diseases after hepatitis B vaccination. *Nature Med*. 1999;5(9):964-965.
44. Ascherio A, Zhang SM, Hernán MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med*. 2001;344(5):327-332.
45. Sadovnick AD, Scheifele DW. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. *Lancet*. 2000;355(9203):549-550.
46. DeStefano F. Vaccinations and risk of central nervous system demyelinating diseases in adults. *Arch Neurol*. 2003;60(4):504-509.
47. Guarnaccia J, Creed M, Muriel S. Transverse myelitis as a first event of multiple sclerosis precipitated by Pfizer-BioNTech COVID-19 vaccination. *Neuroimmunol Rep*. 2022;2:100074.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Woo HG, Kim HJ, Park J, et al. Global burden of vaccine-associated multiple sclerosis, 1967–2022: a comprehensive analysis of the international pharmacovigilance database. *J Med Virol*. 2024;96:e29591. doi:10.1002/jmv.29591