Article

Demyelinating disorders following COVID-19 vaccines, a VAERS-based study

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Abstract: The rapid emergence of COVID-19 as a global crisis has led to the approval of many vaccinations, which were unfortunately associated with high complication rates due to a lack of sufficient safety studies. The following manuscript focuses on discussing the demyelinating disorders that were noticed after COVID vaccine administration. We conducted a retrospective study using anonymous medical records from the US vaccine adverse events reporting system, complications retrieved included Acute disseminated encephalomyelitis (ADEM), Guillain Barre syndrome (GBS), and Multiple sclerosis (MS), outcome parameters were age, sex and the dose after which this complication was observed. Patients younger than 18 years-old were excluded as some of the vaccines, namely Janssen (JNJ-78436735) is not yet approved below this age. Our analysis showed that demyelinating disorders were more likely to occur in patients over the age of 50 compared to other age groups, regardless of the type of vaccination, except for MS and ADEM occurrences after the Jansen vaccine. In addition, demyelinating complications were more likely to occur after the first dose of vaccination. Further research and observation of demyelinating diseases in different vaccinations, as well as additional in vitro studies, are recommended to further explain the pathogenesis of demyelinating disorder occurrence.

Keywords: COVID-19 vaccines; demyelinating disorders; PEG

1. Introduction

Health authorities all over the world have been forced to grant emergency authorization for various vaccines before full FDA (Food and Drug agency) approval owing to the COVID-19 global health pandemic. The emergence of unanticipated difficulties was a significant drawback of such emergency permission.1

Adenovirus-based vaccine recipients experienced a condition resembling HIT, whereas receivers of mRNA-based immunizations frequently experienced myocarditis.2

Myocarditis induced by mRNA vaccinations had a similar peak incidence to viral myocarditis, with 73% of reported cases in people under 30 years old, 33% occurring in people under 18, and the median age was 21.3

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The mechanism and age likelihood of myocarditis from mRNA vaccines is not fully understood yet. However, the trending hypothesis is that mRNA vaccines trigger an antibody response similar to Multi-System Inflammatory Syndrome in children. Another hypothesis is the molecular mimicry between SARS-CoV-2 (severe acute respiratory syndrome causing coronavirus-2) proteins and self-antigens, triggering an abnormal immune response reaction. 4

The latter explanation cannot be fully valid as inflammation and autoimmune processes are commoner with aging due to immune senescence, and loss of several checkpoints such as T-regulatory cells that tend to decrease uncontrolled inflammation. We presented in a comprehensive review a more valid approach, which attributes the development of myocarditis to dysregulation of certain miRNAs that tend to be upregulated in younger age groups and that explains the age likelihood of both viral and mRNA mediated myocarditis. 5

Few authors have reported the development of demyelinating disorders following different types of COVID-19 vaccines.6–8

Nevertheless, the likelihood of this complication following COVID-19 vaccinations based on age, sex, and other factors has not been thoroughly investigated in literature. So, our study's objective is to assess the age and sex chances of demyelinating disorders following COVID-19 vaccinations utilizing cases that were recorded in the United States of America's vaccine adverse event reporting system (USA).

2. Materials and Methods

2.1. Data Sources

An early warning system for probable vaccination adverse events, VAERS9 is considered a US spontaneous reporting (passive surveillance) system. VAERS, which is co-managed by the CDC and the US Food and Drug Administration, accepts reports about all adverse reactions post-vaccination from patients, parents, doctors, vaccine producers, and other parties, regardless of whether the reactions can be credibly linked to receiving the vaccine. Information regarding the vaccinated individual, the vaccine or vaccines delivered, and the adverse effects are all reported in reports to VAERS. Third-party professional coders who have received training in the assignment of Medical Dictionary for Regulatory Activities recommended terminology then analyze the reports submitted to VAERS. Based on the information in the reports, the coders then allocate the proper terms. The CDC reviewed this activity and validated that it was carried out to be consistent with CDC policy and any applicable federal laws. The activities herein were confirmed to be non-research under the Common Rule in accordance with institutional procedures and therefore were not subject to institutional review board requirements. The secondary use of already-existing data did not require obtaining an informed consent.

2.2. Exposure

The exposure of concern was vaccination with one of the three vaccines administered inside USA, namely, mRNA-based COVID-19 vaccines: the BNT162b2 vaccine (Pfizer-BioNTech) or the mRNA-1273 vaccine (Moderna) and Janssen vaccine.

During the analytic period, people aged 12 years of age or older were eligible to receive the BNT162b2 vaccine, while those who were 18 years of age or older could receive the mRNA-1273 vaccine. The CDC's COVID-19 Data Tracker was used to determine how many doses of the COVID-19 vaccination were given out throughout the analysis period.

2.3. Data search criteria

Using the CDC's WONDER system, nine spreadsheets were queried from VAERS, one for each combination of vaccine and symptom. In the "1. Organize Table Layout" step of WONDER, in order to retrieve the following selected fields from each patient record:

1. "VAERS ID": VAERS identification number
    a. "Sex": Sex

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2. "Vaccine Dose": Number of doses administered at time symptom occurred
3. "Recovered": Boolean representing the persistence or recovery from symptoms
4. "Adverse Event Description": Human written (but sometimes automated) description of the case

We did not select "Symptoms" as a field to ensure that each patient's record was output a single time regardless of the number of MedDRA codes present in their record. To filter the data based on the chosen combination of vaccine and symptom, the symptom was chosen in the "2. Select Symptoms" and the vaccine in the "3. Select Vaccine Characteristics" steps of WONDER, and a spreadsheet were developed for each vaccine combination and each disorder's corresponding MedDRA symptom codes. The following MedDRA codes and their associated descriptions were selected for each disorder:

- ADEM
  - o 10000709 (ACUTE DISSEMINATED ENCEPHALOMYELITIS)
- GBS
  - o 10018767 (GUILLAIN-BARRE SYNDROME)
- MS
  - o 10067067 (MARBURG'S VARIANT MULTIPLE SCLEROSIS)
  - o 10028245 (MULTIPLE SCLEROSIS)
  - o 10078558 (MULTIPLE SCLEROSIS PLAQUE)
  - o 10070716 (MULTIPLE SCLEROSIS PSEUDO RELAPSE)
  - o 10048393 (MULTIPLE SCLEROSIS RELAPSE)
  - o 10063401 (PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS)
  - o 10053395 (PROGRESSIVE MULTIPLE SCLEROSIS)
  - o 10067063 (PROGRESSIVE RELAPSING MULTIPLE SCLEROSIS)
  - o 10080700 (RELAPSING MULTIPLE SCLEROSIS)
  - o 10063399 (RELAPSING-REMITTING MULTIPLE SCLEROSIS)
  - o 10063400 (SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS)
  - o 10078556 (TUMEFACTIVE MULTIPLE SCLEROSIS)
  - o 10067485 (UHTHOFF'S PHENOMENON)

The following codes were selected for each vaccine:

- Janssen: 1203 (COVID19 (COVID19 (JANSSEN)))
- Moderna: 1201 (COVID19 (COVID19 (MODERNA)))
- Pfizer-BioNTech: 1200 (COVID19 (COVID19 (PFIZER-BIONTECH)))

All other filters were left as default (the default setting is to not filter) except "State/Territory" which was set to "The United States/Territories/Unknown". After all, mentioned filters were set, each spreadsheet was extracted from WONDER. Due to the limitations of WONDER, raw VAERS data for 2020 (first year of COVID-19 vaccine administration), 2021 and 2022 (until time of access) had to be downloaded to extract further data. The AGE_YRS (age in years) and DIED (Boolean value representing mortality status of patient at time of report submission) fields were automatically extracted from the raw data and added to each report present in the spreadsheets extracted from WONDER via a Python script. Finally, for each spreadsheet, another script extracted the patient's age (if mentioned) from the "Adverse Event Description" field by automatically checking for any sequence of words that matched common forms e.g. "X year old", "X y/o", "X yrs", "X decade old", extracting X, and adding it to a new field within the spreadsheet. This extraction was manually and meticulously checked for accuracy afterwards. Any ages of the form "X decade old" or "in their Xties" were rounded to the nearest decade. This was done as some patient ages were blank in the "AGE_YRS" field but were mentioned in the "Adverse Event Description" field. A new "Best Age" field was automatically computed containing the age in the "AGE_YRS" if present, the age in "Adverse Event Description" if not, and was left blank if neither were available. The data was up to date till November 7th, 2022

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2.4. Data Cleaning

Due to human entry error, we found that some reports were erroneously duplicated in VAERS. These reports were manually checked and deleted from the spreadsheets. Additionally, any report for which a single age could not be found, whether in the "AGE_YRS" or in the "Adverse Event Description" fields, were manually checked and deleted. Also, all reports from literature describing more than one case fused into one report were deleted. All spreadsheets were rechecked manually before initiating the data analysis phase.

3. Results

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

We collected a total of 1210 cases that reported post-vaccination demyelinating events. Our analysis has proved a higher rate of occurrence among cases over 50 years of age, especially after receiving the first dose of the COVID-19 vaccine.

Of the total reported cases, 728 were above 50 years of age, comprising 60.1% and 711 cases of all cases (58.7%) were women. 537 cases (44.4%) reported symptoms after receiving only the first dose, 307 cases (25.4%) after the second dose, 97 cases (8%) after receiving more than two doses, and 267 cases (22%) did not report the time of symptom appearance.

Table 1. ADEM (Acute Demyelinating Encephalomyelitis).

Age (in years)	Pfizer	Moderna	Janssen
18-29 (N)	2	4	2
18-29 (%)	11.76%	28.57%	50.00%
30-50 (N)	5	2	2
30-50 (%)	29.41%	14.29%	50.00%
>50 (N)	10	8	0
>50 (%)	58.82%	57.14%	0.00%
Total Numbers	17	14	4
Sex data			
Male (N/%)	6 (35)	5 (35)	1 (25)
Female (N/%)	11 (65)	9(65)	3 (75)
F:M ratio	1.833	1.800	3.000
Unknown (N)	0	0	0
Total	17	14	4
Death data			
Deaths (N)	1	1	0
Deaths (%)	5.88%	7.14%	0.00%
Dose data:			
1 Dose (N/%)	7 (41)	5 (36)	3 (75)
2 Doses (N/%)	2 (12)	4 (29)	0 (0)
>2 Doses (N/%)	2 (12)	2 (14)	0 (0)
Unknown (N/%)	6 (35)	3 (21)	1 (25)
Total	17	14	4

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As shown in Table [1], A total of 35 cases were reported to have Acute Demyelinating Encephalomyelitis (ADEM) following the vaccine; 17 of which was after Pfizer, 14 after Moderna and 4 after Janssen. However, the number of deaths reported following Moderna (7.14%) was more than (5.88%). Most of the cases reported to have ADEM after the vaccines were female patients (65.7%) with a predominance of 65.7% aging over 50 years. 12 out of the 35 ADEM patients reported showed significant neurological symptoms following the first dose of vaccines while only 6 out of the 35 cases were affected after the second dose.

Table 2. GBS (Guillain-Bare Syndrome).

Age (in years)	Pfizer	Moderna	Janssen
18-29 (N)	28	18	9
18-29 (%)	8.51%	6.62%	4.29%
30-50 (N)	99	68	71
30-50 (%)	30.09%	25.00%	33.81%
>50 (N)	202	186	130
>50 (%)	61.40%	68.38%	61.90%
Total (N)	329	272	210
Sex data			
Male (N/%)	156 (47)	126 (46)	112 (53)
Female (N/%)	171 (52)	145 (53)	98 (47)
F:M ratio	1.096	1.151	0.875
Unknown (N/%)	2 (1)	1 (1)	0
Total (N)	329	272	210
Death data			
Deaths (N)	7	8	4
Deaths (%)	2.13%	2.94%	1.90%
Dose data			
1 Dose (N/%)	131 (40)	126 (46)	121 (58)
2 Doses (N/%)	104 (32)	77 (28)	1 (<1)
>2 Doses(N/%)	30 (9)	24 (9)	0
Unknown (N/%)	64 (19)	45 (17)	88(42)
Total	329	272	210

As shown in Table [2], A total of 811 cases developed Guillain-Barre Syndrome (GBS) after receiving COVID-19 vaccines; 329 of them after receiving Pfizer, 272 after Moderna and 210 after Janssen. The majority of the affected cases belonged to the over 50-year age group.

The highest percentage was in Moderna recipients comprising of 186 cases above 50 years of age (68.38%), while Pfizer had 202 cases (61.4%) and Janssen 130 cases (61.90%). Females were more highly affected after Pfizer and Moderna vaccines, showing a female:

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male ratio of 1.096 and 1.151 respectively. In contrast, a larger number of males were affected after Janssen vaccines with a female: male ratio of 0.875. The death rates were highest after receiving the first dose of all vaccine types. It's important to note that death rates were higher after receiving Moderna and Pfizer, with and 8 and 7 cases reported respectively, as opposed to only 4 reported deaths after Janssen.

Table 3. MS (Multiple Sclerosis).

Age (in years)	Pfizer	Moderna	Janssen
18-29 (N)	18	15	5
18-29 (%)	10.98%	8.62%	19.23%
30-50 (N)	62	59	13
30-50 (%)	37.80%	33.91%	50.00%
>50 (N)	84	100	8
>50 (%)	51.22%	57.47%	30.77%
Total	164	174	26
Sex Data			
Male (N/%)	41 (25)	38 (22)	8 (31)
Female (N/%)	122 (74)	134 (77)	18 (69)
F:M ratio	2.976	3.526	2.250
Unknown (N/%)	1 (1)	2 (1)	0 (0)
Total	164	174	26
Death data			
Deaths (N)	3	1	0
Deaths (%)	1.83%	0.57%	0.00%
Dose data			
1 Dose (N/z%)	53 (32)	74 (43)	17 (65)
2 Doses (N/%)	62 (38)	58 (33)	1 (4)
>2 Doses (N/%)	21 (13)	18 (10)	0 (0)
Unknown (N/%)	28 (17)	24 (14)	8 (31)
Total	164	174	26

As shown in table [3], Of the total of 364 reported cases of Multiple Sclerosis (MS) post-vaccination, 192 (52.7%) were above 50 years, the majority of which (57.47%) had received Moderna vaccination. The female to male ratio was high in all vaccines, with the highest ratio of 3.5 reported in Moderna as well.

There were no deaths reported in Multiple sclerosis following Janssen, while only death was reported post Moderna and 3 in Multiple sclerosis cases post Pfizer. There is no solid conclusion on when MS developed however larger number of people developed MS after 1doses in both Moderna and Janssen while after 2nd dose in those who took Pfizer The majority of Multiple sclerosis arose after the first dose (39.5%), most commonly after Moderna vaccine (74 reported cases). It is worth noting that 14% were of unknown timing.

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4. Discussion

Age signatures of post infectious disorders are poorly understood. For instance, myocarditis, is commoner in infants and children. Several explanations have been postulated to explain this age predilection, the theory that is most accepted to date, is the susceptibility of this age to coxsackie-virus, and the development of immunologic memory with advancing age later.10 Despite the validity of this explanation in post infectious myocarditis, it cannot explain the same age likelihood of myocardial inflammation occurring as a post vaccination sequela from mRNA vaccines. Another explanation has been proposed by our team, suggesting that some miRNAs are upregulated by higher muscle mass, encountered in childhood, and are implicated in induction of myocarditis, whether post-viral or post vaccination. 5

After the extensive use of mRNA vaccines, and the emergence of myocarditis as a potential complication from this specific type of vaccines, there was a false impression, that the use of mRNA complication should be avoided in children and young adolescents, as most of the affected cases were among these age groups. Our current research excludes this false impression, and rather proves that age signature, of post-vaccination complications is closely related to the nature of this complication and to the affected tissue rather than the type of the used vaccine.

Our study proves that the three studied demyelinating disorders, are more likely to occur above the age of fifty years, regardless of the type or subtype of the vaccine used. With the exception of the multiple sclerosis and ADEM developing after Janssen vaccination, the commonest age developing peripheral or central demyelination from mRNA or the adenovirus-based vaccines is above 50 years. Unlike, the misconception that GBS and ADEM are disorders of infancy or childhood, several studies have proven the reverse. For instance, a study by Li and colleagues of 437 ADEM patients, they reported that ADEM could occur in any age group, with a mean age of 37.1 years. 11

Another study by McGrogan et al concerning GBS showed increasing rates above the age of 50 years. Variations in severity did not account for such differences in incidence. However, there is evidence of an increase in rates across the surveyed timeframe.12

A retrospective study on the age incidence of multiple sclerosis by Cheraghmakani Et al, showed that the age group 60–64, the incidence of MS is 1.5 times higher than the baseline age group of 10–15 years. 13

Aging is associated with brain iron accumulation, these age-related increases in brain iron concentration are associated with the disruption of WM. While myocarditis post-COVID vaccines, tend to occur after the second dose, demyelinating disorders are mostly occurring after the first dose. 14

No clear explanation why demyelination is more likely after the first dose, yet myocardial involvement needs priming of the immune system with one dose, then becomes initiated after second dose. The antigen itself, whether in the form of a protein or an mRNA, as well as several adjuvants, most notably Polyethylene Glucose (PEG), have all been linked to the emergence of post-vaccination immunological problems. PEG presentation employs Cluster of Differentiation 1 (CD1) antigen presentation, which is a non-MHC novel route. A protein (family) called CD1 is connected to MHC class I and non-polymorphic molecules. T cells can be exposed to both native and foreign lipid antigens by CD1 proteins. On the cell surface, CD1 proteins from groups 1 (CD1a-c) and 2 (CD1d) are expressed and serve as antigen-presenting molecules. Group 3 (CD1e), which is solely produced extracellularly, is involved in modifying and digesting lipids so that the other CD1 isoforms can deliver them. 15–17

Although similar structure, MHC class I and CD1 vary in that CD1's inner surface is coated with hydrophobic residues, and the helices are also different. The antigen-binding groove in CD1 is deeper (which differs per CD1 isoform). However, PEG can stimulate Toll-like receptor 9, which triggers innate immunity and demyelination by stimulating the transcription of a variety of pro-inflammatory cytokines.

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In addition, it has been found that many people have pre-existing anti-peg antibodies, which might also explain, why PEG related autoimmunity can occur after first dose of vaccination without the need of priming of the immune system by a first dose. The validity of this hypothesis remains elusive and needs in-vitro testing to confirm it or exclude it. 16

5. Conclusions

Our manuscript concluded that the rate of complications different vaccinations can be linked to demographic factors such as age and sex. We conclude a higher occurrence rate of demyelinating disorders after the first dosage of vaccinations and in patients aged above the ages of 50. We, therefore, recommend further in-vitro and clinical studies to evaluate the safety of different COVID vaccines and the predictability of complications, which will help determine the potential for preventive measures that can be taken in the future.

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"CDC WONDER is a public service developed and operated by the Centers for Disease Control and Prevention, an agency of United States federal government. The public web site at http://wonder.cdc.gov is in the public domain, and only provides access to public use data and information. You may access the information freely, and use, copy, distribute or publish this information without additional or explicit permission."

Informed Consent Statement: The data obtained from CDC WONDER system are anonymous and can be accessed and used freely without additional permission

Data Availability Statement: The original data that were used to implement this work are freely available in the WONDER VAERS SYSTEM.

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Conflicts of Interest: The authors declare no conflict of interest.

List of Abbreviations:

Abbreviation	Definition
ADEM	Acute disseminated encephalomyelitis
Anti-PEG antibodies	Immunoglobulins against polyethylene glycol
CD1	Cluster of differentiation 1
CDC	Center for disease control and prevention
COVID	Coronavirus disease
COVID-19	Coronavirus disease of 2019

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FDA	Food and drug agency
GBS	Guillain-Barre syndrome
HIT	Heparin induced thrombocytopenia
MEDdra	Medical dictionary for regulatory activities
MHC	Major histocompatibility index
mRNA	Messenger ribonucleic acid
MS	Multiple sclerosis
SARS-CoV-2	Severe acute respiratory syndrome causing coronavirus-2
VAERS	Vaccine adverse event reporting system
WONDER	Wide-range online data for epidemiologic research
Yrs	Years
WM	White Matter

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