bijwerkingen centrumlareb

Overview of Transverse Myelitis after COVID-19 vaccination

Introduction

Various vaccines have been authorized and used for immunization against COVID-19 in The Netherlands: the mRNA vaccines Comirnaty® (Pfizer/BioNTech) [1] and Spikevax® (Moderna) [2], the adenovirus vector vaccines Vaxzevria® (Oxford/ AstraZeneca) [3] and Jcovden® (Janssen) [4], and the protein-based vaccine Nuvaxovid® (Novavax) [5].

Transverse myelitis (TM) is a rare neuro-immune spinal cord disorder presenting with acute onset of weakness, sensory alterations, and bladder or bowel dysfunction. It can occur independently or it can be part of other neuro-inflammatory disorders, such as acute disseminated encephalomyelitis, multiple sclerosis, myelin oligodendrocyte glycoprotein (MOG) antibody disease, neuromyelitis optica spectrum disorder (NMOSD), and acute flaccid myelitis (AFM). TM has been reported after infection and after vaccination (eg. Hepatitis B vaccination, Measles-Mumps-Rubella vaccination, and Diphtheria-Tetanus-Pertussis vaccination), although a causal relationship could not always be established [6-8]. TM is considered to be an Adverse Event of Special Interest (AESI) by the European Medicines Agency (EMA) [9].

The incidence of TM in literature is estimated to be 1-8 new cases per million per year [6]. However, registries used for estimating background incidence rates of AESI's in the ACCESS project (vACCine COVID-19 monitoring readinESS) vary from 0.02 to 1.79 per 100,000 person-years, depending on country, type of registry and age [10, 11].

In July 2021 Pharmacovigilance Centre Lareb published a signal regarding Vaxzevria® and TM. A causal relationship between TM and Vaxzevria seemed possible based on the 4 cases of TM and the results of the observed-over-expected analysis [12]. In January 2022 the EMA Pharmacovigilance Risk Assessment Committee (PRAC) had recommended a change to the Summary of Product Characteristics (SmPC) for Vaxzevria® and Jcovden® to include a warning to raise awareness of very rare cases of TM reported following vaccination [13]. TM has also been added as an adverse reaction of unknown frequency to the SmPC of Vaxzevria® and Jcovden® [3, 4]. Regarding Comirnaty®, Spikevax®, and Nuvaxovid® TM is not mentioned in the product information [1, 2, 5].

The current overview reviews all reports of TM associated with the COVID-19 vaccines used in the Netherlands. The number of TM cases is compared to background incidence rates in an observed-over-expected analysis.

Reports

Until January 16th 2023, The Netherlands Pharmacovigilance Centre Lareb received 48 reports of TM following COVID-19 vaccination. The selected reports contained at least one coded reaction within the broad Standardized MedDRA Query (SMQ) for 'Transverse Myelitis', 'Myelitis', 'Spinal cord injury', and 'Paraplegia'. The reports regarding 'Spinal cord injury' and 'Paraplegia' were screened and only the reports that could be a diagnosis of TM were included in this overview. In Table 1 the characteristics of the included reports is displayed. Figure 1 shows the distribution in time to onset (TTO) of TM after COVID-19 vaccination clustered in 3 groups (<15 days, 15-28 days, and >28 days) and sorted by vaccine brand.

Table 1: Report characteristics of Transverse Myelitis associated with COVID-19 vaccines in the Netherlands

		Total	Pfizer (Comirnaty®)	Moderna (Spikevax®)	Vaxzevria (AstraZeneca®)	Jcovden (Janssen®)
Reports, n (%)		48 (100%)	24 (50%)	7 (14.6%)	12 (25%)	5 (10.4%)
Reporter, n (%)	HCP	16 (33.3%)	6 (37.5%)	3 (18.8%)	4 (25%)	3 (18.8%)
	CONS	32 (66.7%)	18 (56.3%)	4 (12.5%)	8 (25%)	2 (6.3%)
Serious[1)], n (%)		43 (89.6%)	20 (46.5%)	7 (16.3%)	12 (27.9%)	4 (9.3%)
Outcome, n (%)	Recovered	3 (6.3%)	3 (100%)	-	-	-
	Recovering	23 (47.9%)	11 (47.8%)	6 (26.1%%)	3 (13%)	3 (13%)
	Not recovered	20 (41.7%)	9 (45%)	1 (5%)	8 (40%)	2 (10%)
	Unknown	2 (4.2%)	1 (50%)	-	1 (50%)	-
Sex, n (%)	Male	18 (37.5%)	7 (38.9%%)	2 (11.1%)	5 (27.8%)	4 (22.2%)
	Female	30 (62.5%)	17 (56.7%)	5 (16.7%)	7 (23.3%)	1 (3.3%)
Age (years)	Mean (range)	53 (14-80)	50 (14-72)	55 (23-80)	61 (32-67)	48 (44-54)
Time to onset (days)	Median (IQR)	12.5 (35)	14.5 (85.5)	14 (13.5)	11.5 (17.5)	7 (22)
Other neurological co-reported reaction[2)]		8 (16.7%)	4 (50%)	1 (12.5%)	1 (12.5%)	2 (25%)
Medical history	TM	1 (2.1%)	-	-	1 (100%)	-
	Multiple sclerosis	2 (4.2%)	1 (50%)	-	1 (50%)	-
	Infection[3)] ≤30 days prior	4 (8.3%)	2 (50%)	-	2 (50%)	-
	Auto-immune disease	1 (2.1%)	-	1 (100%)	-	-
Treatment	Prednisone	23 (47.9%)	12 (52.2%)	3 (13%)	5 (21.7%)	3 (13%)
	Physiotherapy	3 (6.3%)	2 (66.7%)	-	1 (33.3%)	-

HCP = Health Care Professional, CONS = consumer. [1]) Seriousness according CIOMS criteria: hospitalization, disabling/incapacitating, life threating, death, or other medically important condition. [2]) Other neurological co-reported reactions include: Guillain-Barré Syndrome, Multiple Sclerosis, Clinically Isolated Syndrome, and MOG-antibody present. [3]) Infections include the following: bladder infection, otitis media, Varicella Zoster, and Staphylococcus aureus.

Half of the patients in the reports received Comirnaty®, which is the most commonly used vaccine in the Netherlands. Of the 7 reports receiving Spikevax®, 2 reports received Spikevax bivalent Original/Omicron BA.1.®. Two third of the reports were originated from consumers. Due to the symptoms of TM, most of the reports were marked as serious because it led to hospitalization and/or disability. 47.9% of the patients mentioned that they were recovering, and 41.7% were not recovered from the symptoms at time of reporting. In 32 of the reports TM occurred within 28 days after vaccination (figure 1). Diagnostic certainty of TM was difficult to obtain from all of the reports due to lack of detailed medical information. In 8 reports the following neurologic conditions were co-reported in addition to TM: Multiple Sclerosis (2), Guillain-Barré Syndrome (2), Clinically Isolated Syndrome (2), and in 2 reports MOG-antibodies were positive.

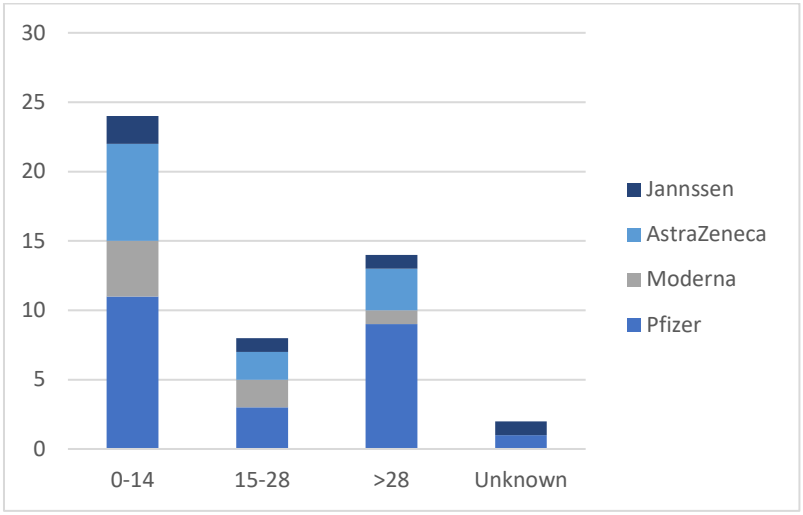

Figure 1: Distribution in time to onset of TM events with COVID-19 vaccines clustered in 3 groups (<15 days, 15-28 days, >28 days)

Comparison of reports with background incidence

Since TM is a rare disease, the observed number of reported cases was compared to the expected number based on background incidence rates. To define the numerator for the expected cases, vaccine exposure data until April 18th 2022 were used from the COVID-vaccination Information- and Monitoring system (CIMS) database of RIVM. For the reports receiving Spikevax bivalent Original/Omicron BA.1.®, vaccine exposure data from 19-09-2023 until 16-01-2023 were used for the risk period of 14 days, and data until 19-12-2022 for the risk period of 28 days. Background rates for TM were provided by the ACCESS project [11]. The background rates varied considerately among different European countries [11]. The biggest difference was observed between The Netherlands and Denmark, which is unexpected based on similar population characteristics in these countries. Therefore, background rates from The Netherlands (lowest rate) and Denmark (highest rate) were used in order to establish if in both scenarios the observed amount of TM cases exceeds the expected amount. The following formulas were used in calculating SMRs:

- *E = (Nevents in PHARMO / Nperson years in PHARMO)*(risk period (days)/365)*Nvaccine exposure*
- *SMR = O / E*
- *95% confidence intervals: $\sqrt{((\sum(O -/+1)2) / \sum E}$; using Poisson distribution tables for low numbers of O (<10)*

An O/E ratio of > 1 means that more cases were observed (reported) than were expected based on background incidence in a given period/ with corresponding given time-to-onset. The results are summarized in Figure 2.

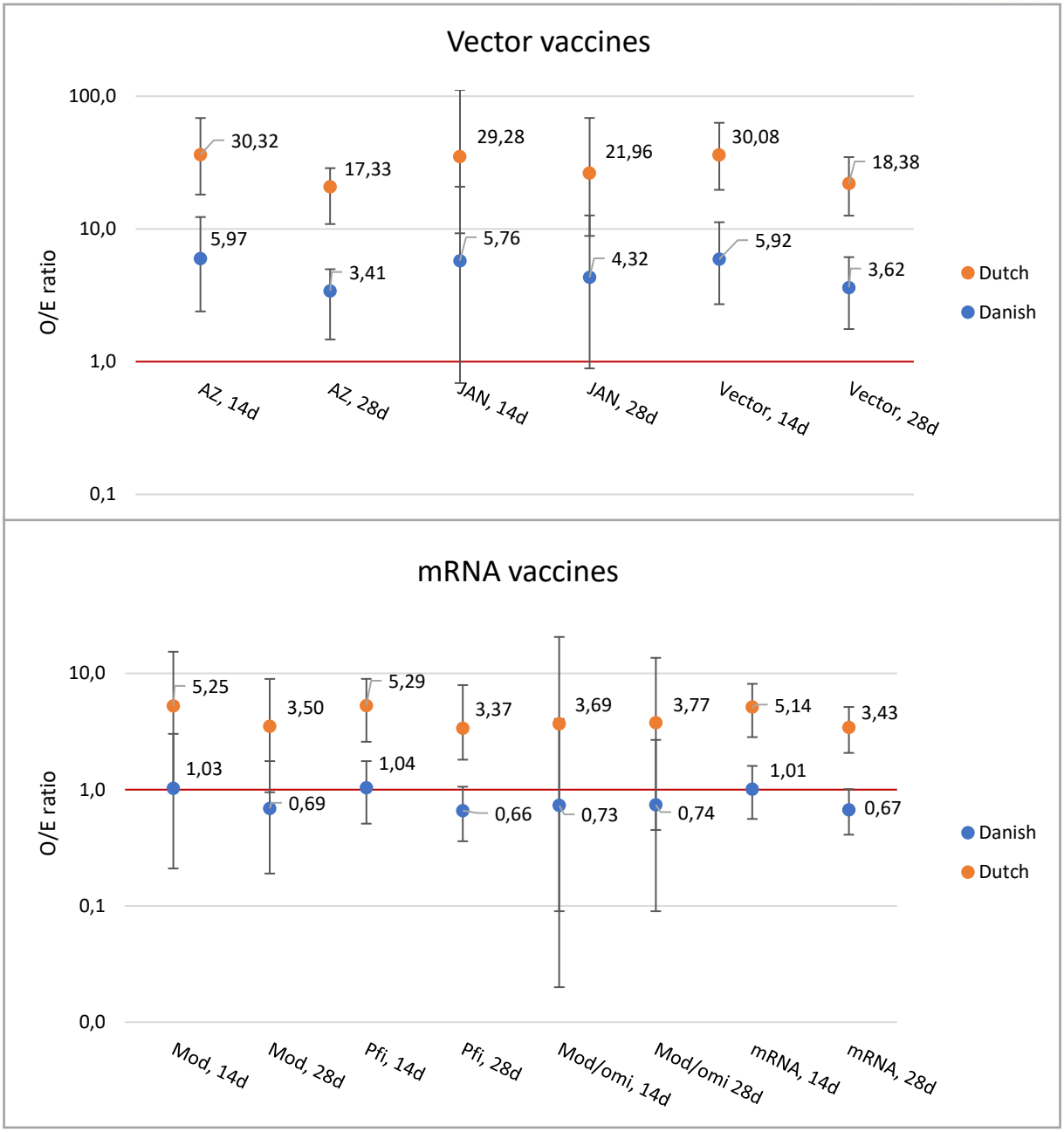

Figure 2: Observed-over-expected (O/E) ratios of TM reports. Above for the vector based vaccines: Vaxzevria, Jcovden, and all vector vaccines together and below for the mRNA vaccines: Spikevax, Comirnaty, Spikevax Original/Omicron and all mRNA vaccines together for risk periods 14 and 28 days and two different background incidence rates: Danish (blue) and Dutch (orange).
The scale is semi-logarithmic. If O/E ratio >1, the number of reported cases exceeds the expected number based on background incidence. The error bars show the range of the lower and upper limits of the 95% confidence intervals. More details are available in Appendix A.

The O/E ratios for the vector based COVID-19 vaccines exceed 1.0 at every risk period and for both the lowest (Dutch) and highest (Danish) estimated background incidence. For Vaxzevria® all O/E ratios show a significant result; the lower limits of the confidence intervals are all above 1.0. Regarding Jcovden® the confidence intervals of the O/E are very broad due to a low number of observed cases (n<4). For the mRNA vaccines, the O/E ratios at the highest estimated background incidence are around or below 1.0 with a lower limit of the confidence interval below 1 (all mRNA vaccines: TTO 14 days: O/E=1.01 (0.56-1.60), TTO 28 days: O/E= 0.67 (0.41- 1.01)). With the lowest estimated background incidence, the O/E ratios for the mRNA vaccines exceed 1.0 with a significant result (all mRNA vaccines: TTO 14 days: O/E= 5.14 (2.83-8.13), TTO 28 days: O/E= 3.43 (2.07-5.14)).

Information from literature

During phase III clinical trials with Vaxzevria® three people developed TM, of which one was possibly vaccination related and occurred 14 days after the second dose [14, 15]. The trial was put on hold for a short period. Two other cases were considered unlikely to be related to the vaccination, since one (also in vaccine group) could be attributed to pre-existing multiple sclerosis and the other occurred in the control group after 68 days of the intervention, receiving the MeningococcalACWY vaccine. In this trial 12,021 subjects out of 23,745 participants received at least one dose of Vaxzevria®, based on the interim analysis [14].

Various case studies describe the occurrence of TM after COVID-19 vaccination [16-24]. A large self-controlled case series study performed in the United Kingdom investigated the potential association of COVID-19 vaccination and three acute neurological events: Guillain-Barré Syndrome, Bell's Palsy, and TM [24]. The incidence rate ratio (RR) for each outcome in the period following vaccination (4–28 days for TM) was compared to a within-person baseline, using conditional Poisson regression [25]. No clear association with TM was found for both Vaxzevria® (N = 199; RR=1.51 (0.96–2.37) and Comirnaty® (N = 109; RR=1.62 (0.86–3.03). The outcome of TM remained too rare and too low a relative risk for the association to be detected among the general adult population in the study [25]. In addition, a population based cohort and self-controlled case series analysis was not able to ascertain the association of TM and COVID-19 vaccination due to the low number of TM events in all the vaccinated reports (n<5) [26].

TM with SARS-CoV-2 infection
Acute TM is associated with a SARS-CoV-2 infection as well, as was described by Roman et al. in a review of 43 case reports [24]. Both a post-infectious neurological complication mediated by the immune response as well as a direct neurotropic effect of SARS-CoV-2 were postulated mechanisms [24]. Besides, a systematic review showed the occurrence of TM in 9 cases after a SARS-CoV-2 infection [27]. However, none of our reports mentioned a concurrent SARS-CoV-2 infection.

Mechanism
Post-vaccination TM may be caused by different types of immune pathways. It is thought that infectious agents and vaccine adjuvants may evoke autoimmunity in several ways: molecular mimicry, epitope spreading, upregulation of cytokines, and polyclonal activation of B and T lymphocytes, which may induce immune reactions associated with TM [28]. For the vector based COVID-19 vaccines it is suggested that the use of chimpanzee adenovirus vectors play role in causing autoimmunity [24]. For mRNA based COVID-19 vaccines an immunological reaction between the SARS-CoV-2 spike protein antibody and tissue proteins may be a plausible cause for the occurrence of demyelinating autoimmune diseases [29]. Furthermore, the interaction between spike proteins and angiotensin-converting enzyme 2 (ACE2) receptors, present in the endothelial cells of the blood–brain barrier or spinal neurons, may be another possible mechanism of demyelination [30].

Discussion

Spontaneous reports
The presence of a prior infection serves as a potential confounder in the causality assessment of TM and COVID-19 vaccination. For previous SARS-CoV-2 infections, the Lareb reporting form had an obligatory question. None of the reports of TM in this overview reported a SARS-CoV-2 infection 30 days prior to the occurrence of TM. However, asymptomatic infections may have been overlooked. For any other infection, there was no standardized question in the reporting form. In 8.3% of the reports an infection up to 30 days prior to the TM symptoms was identified. Furthermore, TM can occur as part of other neuro-inflammatory disorders and in 2 cases received at Lareb a history of multiple sclerosis was present. In 16.7% of the cases another neurological disease was reported as an reaction next to TM, which makes the occurrence of TM due to the COVID-19 vaccines less plausible. An underlying other neurological disease could have attributed to the occurrence of TM in these cases.

Limitations observed-over-expected method
The occurrence of underreporting is inevitable in a spontaneous reporting system and cannot be corrected for in observed-over-expected calculations. However, considering the seriousness and designation of TM as an AESI, the amount of underreporting of TM is expected to be little. The

background incidence rates extracted from the ACCSESS project were collected from 2017 to 2020. As a consequence, the effect of SARS-CoV-2 infections during the COVID-19 pandemic, which is potentially associated with TM, was only partly taken into account. On the other hand, the total amount of infections as a background incidence may have been reduced by measurements like social distancing.

Conclusion

The results of the observed-over-expected analysis show that TM has been reported more frequently than expected following the vector based COVID-19 vaccines (Vaxzevria® and Jcovden®), for which this reaction is labelled in the SmPC. Assuming little underreporting no significant increase in TM can be observed after vaccination with the mRNA COVID-19 vaccines, when compared to the highest estimated background incidence. However, compared to the lowest estimated background incidence from the Netherlands, a significant increase in TM reports is noticeable. Due to the low occurrence of TM events published papers were not able to establish a potential association between TM and COVID-19 vaccination. Epidemiological research would be desirable in order to rule out this risk.

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This signal has been raised on June 2, 2023. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

Addendum 1. Detailed results observed-over-expected TM events for COVID-19 vaccines

Vaccine	At risk period / TTO	Number of reports (O)	Number of vaccinations	Incidence rate (per 100,000 person-years)		Expected cases (E)	O/E
	Days			Source	IR		(95% CI)
Pfizer	14	11	22576200	NL_PHARMO_HOSP	0.24	2.08	**5.29** (2.58-8.97)
		11	22576200	DK_DCE_PC	1.22	10.56	**1.04** (0.51-1.76)
	28	14	22576200	NL_PHARMO_HOSP	0.24	4.16	**3.37** (1.81-7.93)
		14	22576200	DK_DCE_PC	1.22	21.13	0.66 (0.36-1.06)
Moderna	14	3	6209718	NL_PHARMO_HOSP	0.24	0.57	**5.25** (1.08-15.34)*
		3	6209718	DK_DCE_PC	1.22	2.91	**1.03** (0.21-3.02)*
	28	4	6209718	NL_PHARMO_HOSP	0.24	1.14	**3.50** (0.95-8.96)*
		4	6209718	DK_DCE_PC	1.22	5.81	0.69 (0.19-1.76)*
Moderna/ omicron	14	1	2941865	NL_PHARMO_HOSP	0.24	0.27	**3.69** (0.09-20.57)*
			2941865	DK_DCE_PC	1.22	1.38	0.73 (0.02-4.05)*
	28	2	2882638	NL_PHARMO_HOSP	0.24	0.53	**3.77** (0.45-13.60)*
			2882638	DK_DCE_PC	1.22	2.70	0.74 (0.09-2.68)*
mRNA vaccines	14	15	31727783	NL_PHARMO_HOSP	0.24	2.92	**5.14** (2.83-8.13)
		15	31727783	DK_DCE_PC	1.22	14.85	**1.01** (0.56-1.60)
	28	20	31668556	NL_PHARMO_HOSP	0.24	5.83	**3.43** (2.07-5.14)
		20	31668556	DK_DCE_PC	1.22	29.64	0.67 (0.41-1.01)
AstraZeneca	14	7	2507681	NL_PHARMO_HOSP	0.24	0.23	**30.32** (12.17-62.47)*
		7	2507681	DK_DCE_PC	1.22	1.17	**5.97** (2.39-12.29)*
	28	8	2507681	NL_PHARMO_HOSP	0.24	0.46	**17.33** (7.47- 25.28)*
		8	2507681	DK_DCE_PC	1.22	2.53	**3.41** (1.47- 4.97)*
Janssen	14	2	742134	NL_PHARMO_HOSP	0.24	0.07	**29.28** (3.51-105.68)*
		2	742134	DK_DCE_PC	1.22	0.35	**5.76** (0.69-20.79)*
	28	3	742134	NL_PHARMO_HOSP	0.24	0.14	**21.96** (4.54-64.19)*
		3	742134	DK_DCE_PC	1.22	0.69	**4.32** (0.89-12.63)*
Vector vaccines	14	9	3249815	NL_PHARMO_HOSP	0.24	0.30	**30.08** (13.77-57.09)*
		9	3249815	DK_DCE_PC	1.22	1.52	**5.92** (2.71-11.23)*
	28	11	3249815	NL_PHARMO_HOSP	0.24	0.60	**18.38** (8.97-31.14)
		11	3249815	DK_DCE_PC	1.22	3.04	**3.62** (1.76-6.13)

* O<10, Confidence interval calculated with Poisson table