Overview of Sudden Sensorineural Hearing Loss associated with COVID-19 vaccines

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].

Sudden sensorineural hearing loss (SSNHL) is commonly defined as an acute onset (<72 hr) hearing loss of 30 dB or greater over at least three contingent audiometric frequencies. Possible causes of SSNHL are infections, autoimmune diseases, neoplasms, ototoxic drugs, trauma, vascular-, psychiatric-, metabolic- and neurologic disorders. Most cases however, remain idiopathic [6, 7]. SSHNL is commonly treated with corticosteroids. Prognosis of SSNHL depends on different factors including age, severity of the hearing loss, presence of vertigo, and shape of the audiogram [6].

The incidence of SSNHL is difficult to determine since affected people not always seek medical attention. The incidence is ranging from 11 to 77 per 100.000 people per year [8]. Idiopathic SSNHL can arise at any age but most commonly affects individuals 43 to 53 years old, with similar numbers of males and females affected [9, 10].

SSNHL is currently not labeled as an adverse reaction for any of the available COVID-19 vaccines in the Netherlands.

This overview summarizes cases of SSNHL reported in the Netherlands following vaccination with COVID-19 vaccines. In addition the number of SSNHL cases is compared to background incidence rates in an observed-over-expected analysis.

Reports

Until January 10th 2023 the Netherlands Pharmacovigilance Centre Lareb received 109 individual case safety reports of SSNHL following vaccination with COVID-19 vaccines. Table 1 summarizes the characteristics of these case reports.

Table 1: Report characteristics of sudden sensorineural hearing loss associated with COVID-19 vaccines in the Netherlands

Sudden hearing loss (PT)*	Total (n)	%	Pfizer	%	Moderna	%	Astra Zeneca	%	Janssen	%	Not Specified
Reports (N, %)	109	100	73	67.0	17	15.6	15	14.2	3	2.8	1
Reporters											
-Health care professional	16	14.7	10	13.7	3	17.6	2	13.3	-	-	1
-Consumer	93	85.3	63	86.3	14	82.4	13	86.7	3	100	-
Seriousness (N, %)**											
-Yes	21	19.3	12	16.4	3	17.6	6	40.0	-	-	-
-No	88	80.7	61	83.6	14	82.4	9	60.0	3	100	1
Sex (N, %)											
-Male	37	33.9	21	28.8	8	47.1	8	53.3	-		
-Female	72	66.1	52	71.2	9	52.9	7	46.7	3	100	1
Age (mean, range)											
-Male	56	(23-86)	55	(28-86)	52	(23-69)	66	(62-76)	-	-	-
-Female	53	(12-81)	53	(12-81)	52	(32-76)	56	(25-66)	47	(30-58)	78
Age (median, range)											
-Male	60	(23-86)	57	(28-86)	55,5	(23-69)	64,5	(62-76)	-	-	-
-Female	55	(12-81)	54.5	(12-81)	52	(32-76)	62	(25-66)	53	(30-58)	78
Dose											
-First	45	41.3	28	38.4	4	23,5	10	66.7	3	100	-

-Second	46	42.2	35	47.9	5	29.4	5	33.3	NA		1
-Third	18	16.5	10	13.7	8	47.1	-	-	NA		-
Uni- or bilateral hearing loss (N, %)											
-Unilateral	87	79.8	60	82.2	12	70.6	12	80.0	2	66.7	1
-Bilateral	6	5.5	4	5.5	1	5.9	1	6.7	-	-	-
-Unknown	16	14.7	9	12.3	4	23.5	2	13.3	1	33.3	-
Time to onset (mean day, range)											
- First dose	10.5	(0-42)	9.7	(0.9-34)	15.7	(1-29)	13.7	(1-42)	2.0	(0-4)	-
- Second dose	21.4	(0-131)	21.7	(0-122)	12.0	(0-28)	31.2	(1-131)	NA		7
- Third dose	9.7	(0-47)	9.0	(0.1-30)	10.5	(0.1-47)	-	-	NA		-
Time to onset (median day, range)											
- First dose	5.0	(0-42)	5.5	(0.9-34)	17.0	(1-29)	4.0	(1-42)	2	(0-4)	-
- Second dose	10.0	(0-131)	11.0	(0-122)	10.0	(0-28)	5.0	(1-131)	NA		7
- Third dose	3.6	(0-47)	1.8	(0.1-30)	6.4	(0.1-47)	-	-	NA		-
Outcome (N, %)											
- Not recovered	53	48.6	39	53.4	8	47.1	4	26.7	2	66.7	-
- Recovering	30	27.5	19	26.0	5	29.4	5	33.3	1	33.3	-
- Recovered	23	21.1	15	20.5	3	17.6	5	33.3	-		-
- Unknown	3	2.8	-	-	1	5.9	1	6.7	-		1
Duration* **											
- Mean days, range	24	(0.2-170)	25.5	(0.2-170)	4	(2-6)	30.8	(5-91)	-	-	-
- Median days, range	14.0	(0.2-170)	14	(0.2-170)	4	(2-6)	21.0	(5-91)	-	-	-
Tinnitus co-reported (N, %)											
- Yes	39	35.8	27	37.0	6	35.3	5	33.3	1	33.3	-
- No	70	64.2	46	63.0	11	64.7	10	66.7	2	66.7	1
Medical history of hearing loss (N, %)											
- Yes	7	6.4	5	6.8	2	11.8	-	-	-	-	
- No	102	93.6	68	93.2	15	88.2	15	100	3	100	1
Medical history of SARS-CoV-2 infection (N, %)											
- Yes	5	4.6	3	4.1	1	5.9	-	-	1	33.3	-
- No	104	95.4	70	95.9	16	94.1	15	100	2	66.7	-
Treatment (N, %)											
-Yes	82	75.2	57	78.1	11	64.7	11	73.3	2	66.7	1
-No or unknown	27	24.8	16	21.9	6	35.3	4	26.7	1	33.3	
Audiogram (N, %)											
-Yes	48	44.0	31	42.5	8	47.1	6	40.0	3	100	
-No	61	56.0	42	57.5	9	52.9	9	60.0	-	-	1
MRI (N, %)											
-Yes	31	28.4	23	31.5	3	17.6	5	33.3	-	-	-
-No	78	71.6	50	68.5	14	82.4	10	66.7	3	100	1
Relevant medical history											
- Autoimmune diseases	5	4.6	4	5.5	1	5.9	-	-	-	-	-
- Infections	2	1.8	2	2.7	-	-	-	-	-	-	-
- Cardiovascular risk factors	11	10.1	8	11.0	-	-	3	20.0	-	-	-

*Sudden hearing loss coding is based on the MedDRA terminology. Case reports in which a specific sudden onset of (severe) hearing loss/deafness was reported were included. This included the LLT coding's 'sudden deafness' and 'sudden hearing loss'.
**CIOMS criteria for seriousness are the following criteria: hospitalization, life threatening (leading to death without immediate

medically intervention), death, disabling, congenital anomaly or other medically relevant situation.
*** If recovered and the duration of the Sudden Hearing loss is reported: Pfizer n=13, Moderna n=2, AstraZeneca n=5

SSNHL is reported mostly after vaccination with mRNA vaccines Comirnaty® and Spikevax®, respectively in 73 (67.0%) and 17 (15.6%) cases. Almost 20% of case reports were classified as serious (other medically important condition) according to CIOMS criteria for seriousness.

Most of SSNHL cases concerned females (66.1%) with a median age of 55 years (12-81 years). In men median age was 60 years old (23-86 years). In 87 (79.8%) cases the deafness was unilateral, in 6 cases bilateral (5.5%), and in 16 cases it was unknown (14.7%). Treatment - mainly prednisone - was prescribed in 82 cases (75.2%), an audiogram was performed in 48 cases (44.0%), MRI in 31 cases (28.4%), and in 15 cases (13.8%) both an audiogram and MRI were performed. In 31 cases a MRI was performed in search of an underlying disease which showed no abnormalities in 18 cases and MS was diagnosed in 1 case. In 3 other cases inflammation in the ear canal and vestibular organ, a small tumor in the middle ear, and calcium on the ossicles was seen. In the remaining 9 cases the result of the MRI was unknown.

Time to onset of SSNHL after COVID-19 vaccination showed a wide range with a median time to onset for all vaccines and doses of 8.5 days. Figure 1 shows that most cases (46.2%) had a time to onset of SSHNL within one week after vaccination. In figure 2 the mean and median time to onset of SSHNL are visualized per vaccine brand and per dose. Median time to onset of SSNHL is below 10 days for all COVID-19 vaccines with the exception of the first dose of Spikevax® (n=4, median 17 days).

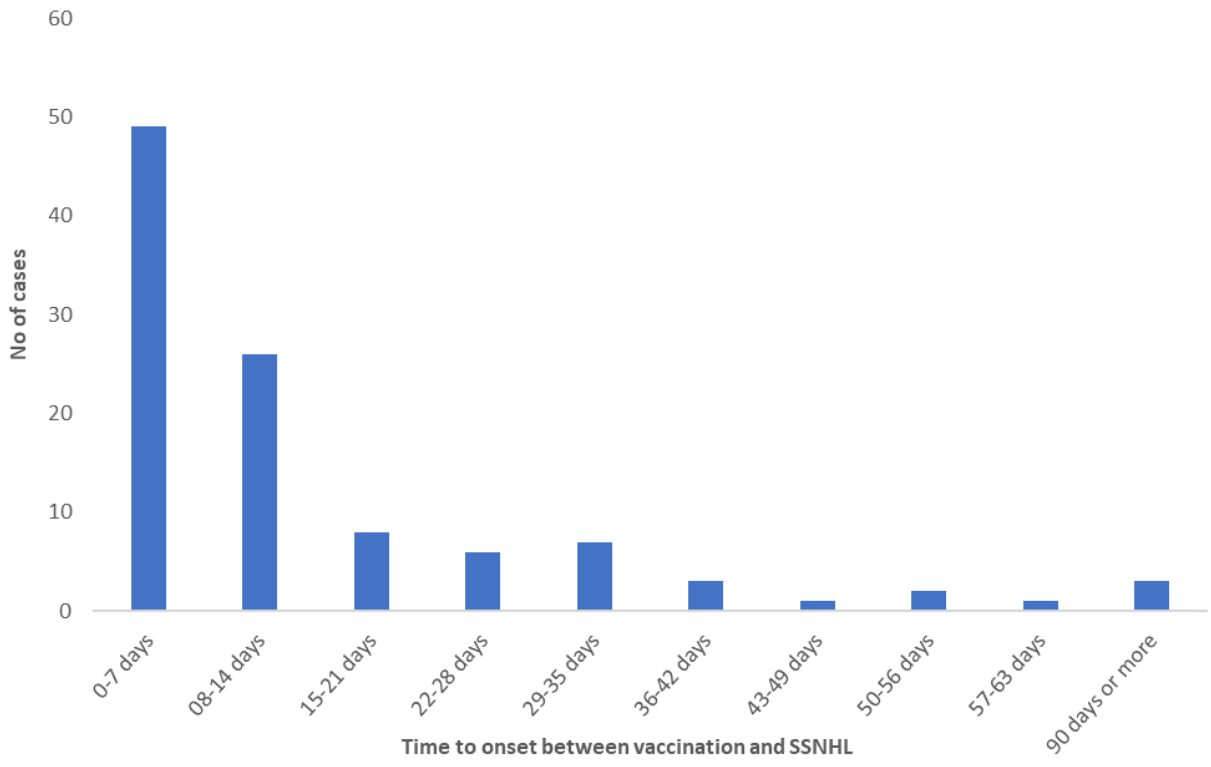

Figure 1:Distribution of number of cases per time to onset in days (n=106)

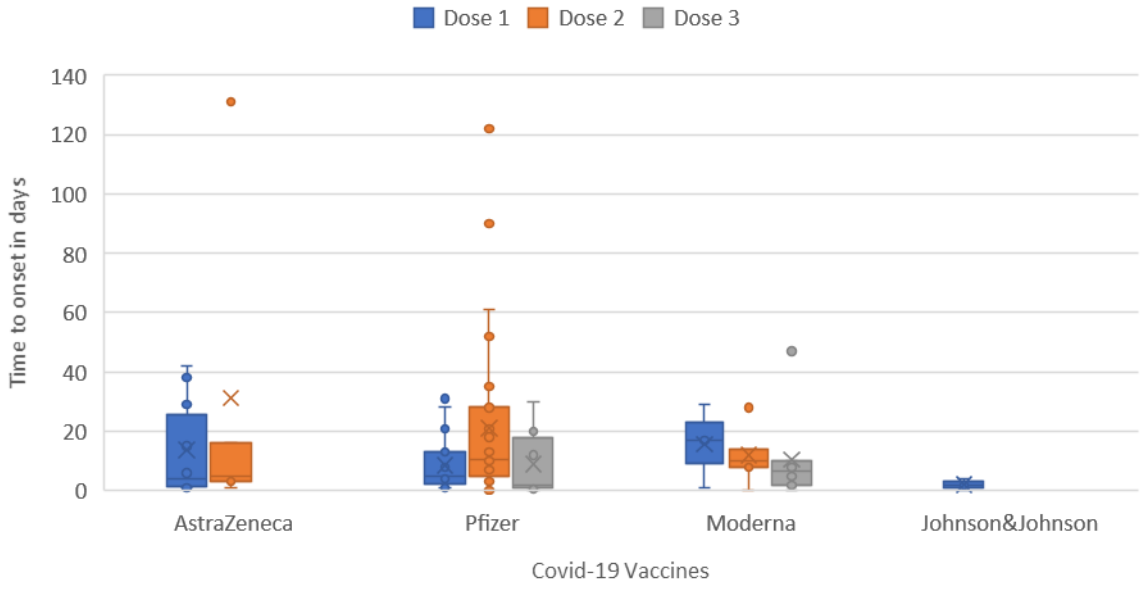

Figure 2: Mean and median time to onset of the SSNHL per dose per vaccine brand

In 48.6% of cases the patient was not recovered from SSNHL that at time of reporting. 27.5% of patients was recovering, and 21.1% was recovered. For recovered patients, median time of SSNHL duration was 14 days and 69.5% received treatment. Figure 3 shows the time to onset and duration of SSNHL in days per case report. As shown, most of the SSNHL started within 20 days after vaccination and recovered within 30 days.

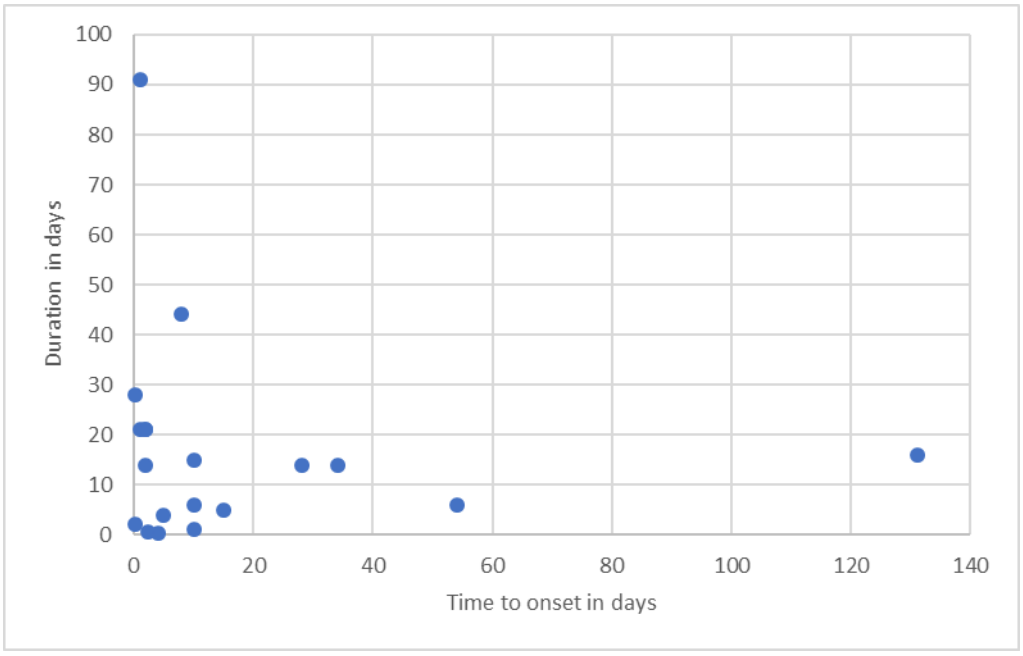

Figure 3: Time to onset and duration of the hearing loss in days per report (n=19)

Observed over Expected analysis

For calculating observed-over-expected ratios, the SMR (standardized morbidity rate) was used, which uses the received cases as the observed (O) number of cases. For the calculation of the amount of expected cases (E), background incidence rates of the natural occurrence of SSNHL are used as well as the total person-time at risk applied to a certain vaccinated population.

Representative background incidence rates for SSNHL are not easily established since incidence rates of SSNHL vary in literature. The incidence rate of SSNHL in the United States (US) in 2006-2007 was calculated as 27 per 100.000 person years [8]. In this study stratified data was presented as well showing higher incidence rates of SSHNL with aging and in men. In Japan similar numbers were seen [11]. Although a German study showed higher incidence rates of SSHNL, it is unknown whether a broader definition of hearing loss was used in this study [12]. In the Netherlands, the Dutch society for general practitioners estimated incidence rates of 5-20 per 100,000 person years [13]. These numbers are, however, based on visits to the general practitioner (GP). As patients with temporary hearing loss will not always visit their GP, these numbers are probably an underestimation of the actual incidence rate of SSNHL. Because of the presence of stratified data from the US, these background incidence numbers are used in this overview to calculate the number of expected cases [8].

Stratified vaccine exposure data until April 18th 2022 were obtained from the COVID-vaccination Information- and Monitoring system (CIMS) database of RIVM for men and women per vaccine, dose and age [14]. Since the vaccination dates of the reports are all before April 18th 2022, the missing vaccine exposure data from after this date are allowed for performing the analysis. Since there is no standardized at risk period for onset of SSNHL after vaccination, the risk periods were determined based on the pattern of latencies observed in the received cases. Figure 1 shows that SSNHL occurred in the majority of the cases in the first week following vaccination, therefor a risk period of 7 days was applied in this overview.

The following equations were used in calculating SMR:

- *E = (IR per 100,000 person years in Alexander TH et al. [8])* (risk period (days)/365)*Nvaccine exposure/100,000*
- *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 time period/ with corresponding given time-to-onset. The results are summarized in Figure 4.

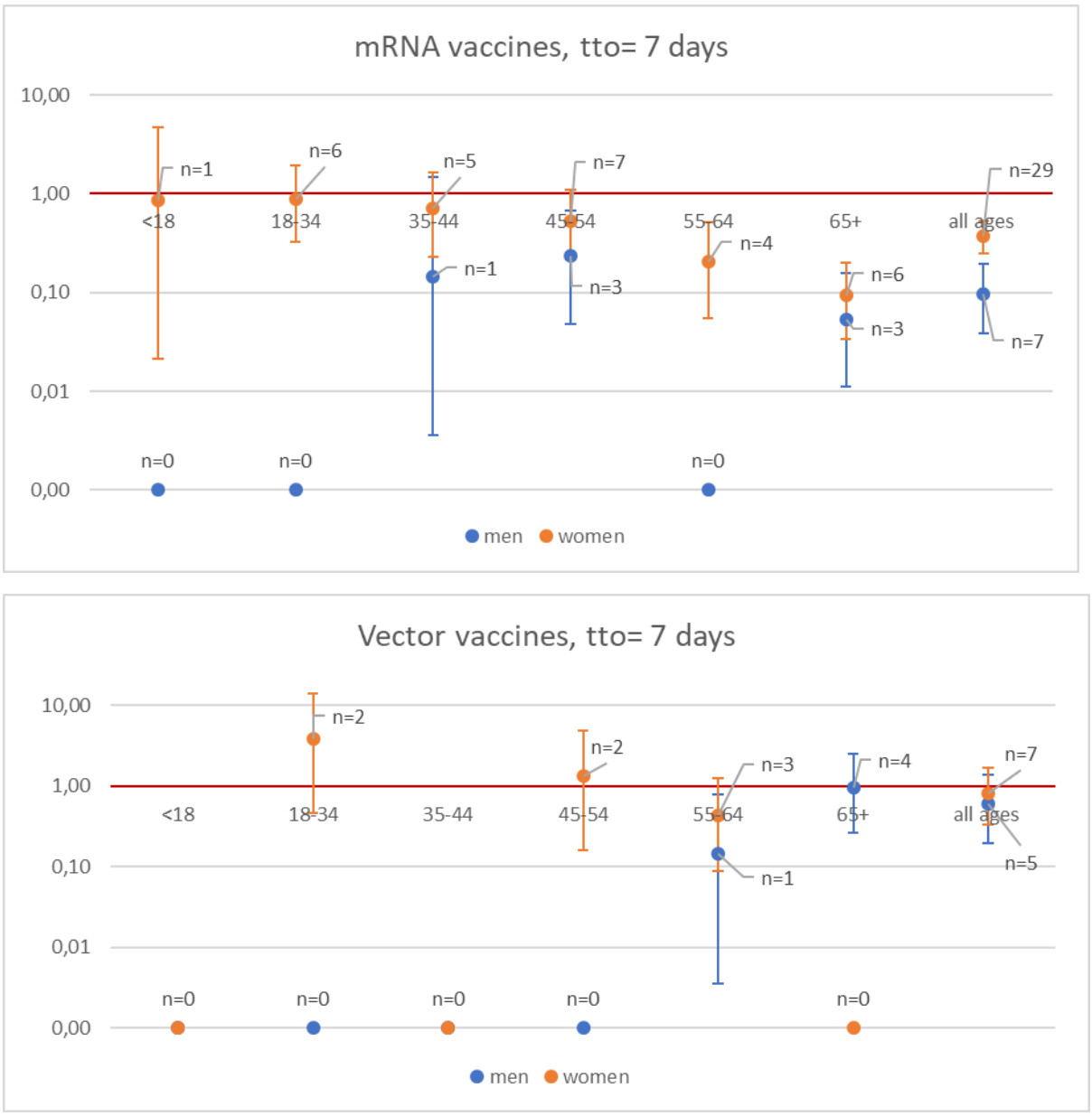

Figure 4: Observed-over-expected (O/E) ratios of SSNHL reports. Above for the mRNA based (Spikevax® and Comirnaty®) and below for the vector based (Vaxzevria® and Jcovden®) COVID-19 vaccines for risk period of 7 days, male and female in the following age categories: <18, 18-34, 35-44, 45-54, 55-64, 65+, and all ages.
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.

Regarding the mRNA based COVID-19 vaccines a decrease in O/E ratio is observed for increasing age in women. The O/E ratio for women below 45 years of age was 0.70 (Figure 4). However, due to low numbers of observed cases (n<10) the confidence intervals are broad with the lower limits below 1.0. For the first dose of Comirnaty® in women aged 18-34 years the result is statistically significant: O/E= 2.36 (1.15-3.99) (appendix A). For the men the O/E ratios are below 0.30 in all the age categories.

For the vector based COVID-19 vaccines the O/E ratio exceed 1.0 for women in the age categories 18-34 and 45-54 years old: O/E = 3.90 (95% CI: 0.47-14.06) for 18-34 years and O/E=1.35 (95% CI: 0.16-4.88) for 45-54 years old. Nevertheless, the results are not statistically significant because the lower limits of the confidence intervals are below 1.0. Interestingly, for men in the age above 65 years old the O/E approaches 1.0: O/E=0.97 (0.26-2.49).

Information from literature

A study in which 555 cases from the Vaccine Adverse Event Reporting System (VAERS) were included, over the first 7 months of the vaccination campaign, showed no increased incidences of SSNHL after COVID-19 vaccination. The incidences of SSNHL were as followed: 0.16 cases per 100.000 doses for both Spikevax® and Comirnaty®, and 0.22 cases per 100.000 doses for Jcovden®. This represents an annualized incidence estimate of 0.6 to 28.0 cases of SSNHL per 100.000 people per year [15].

An Israeli study showed a slight increased risk of SSNHL after vaccination with Comirnaty®. This retrospective population-based cohort study compared observed cases of SSNHL (occurring within 21 days after vaccination) with the expected cases based on the experience of the population in 2018 and 2019. After the first dose with Comirnaty®, the estimated standardized incidence ratios (SIR) were more pronounced in female patients aged 16-44 years (SIR, 1.92; 95% CI, 0.98-3.43), and female patients 65 years or older (SIR, 1.68; 95% CI, 1.15-2.37). After the second Comirnaty® dose, the highest estimated SIR was observed in male patients 16-44 years (SIR, 2.45; 95% CI, 1.36-4.07) [16].

A recent article showed no increased risk of diagnoses of SSNHL after COVID-19 vaccination in a large retrospective cohort (5.5 million Finns). For Comirnaty®, Spikevax®, and Vaxzevria®, the adjusted incidence rate ratios (aIRR) were less than 1, indicating no increased risk of SSNHL after the first vaccination: 0.8 (0.6-1.0), 0.8 (0.5-1.4) and 0.4 (0.2-0.8), respectively. The study accounted for previous hearing problems and other possible confounders. However, a long risk period (up to 55 days after vaccination) was chosen [17].

Based on spontaneous reports of SSNHL received in France, the occurrence of SSNHL as an adverse event after COVID-19 mRNA vaccination was rare. The incidence of SSNHL after COVID-19 mRNA vaccination was estimated to be <2 per 1 million injections for both mRNA vaccines (Comirnaty® and Spikevax®). In total, 108 cases of SSNHL after Comirnaty® and 26 cases of SSNHL after Spikevax® were received within 20 days after vaccination. The hearing loss and assessment of hearing recovery outcomes were performed according to a grading system modified from the Siegel criteria. In 5 cases of Comirnaty® and 3 Spikevax® cases positive rechallenge was documented [18].

In September 2021 tinnitus was added as an adverse event in the product information of the COVID-19 vaccine Jcovden® [19]. Later on, in June 2022, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) discussed the occurrence of hearing loss following vaccination with Comirnaty®. It was concluded that the marketing authorization holder should provide a cumulative review of cases of SSNHL following vaccination with Comirnaty® and should propose an update of the product information as warranted [20].

SSNHL with SARS-CoV-2 infection

A retrospective analysis performed in Italy investigated the impact of the COVID-19 pandemic on the incidence of acute hearing and vestibular disorders. The amount of patients evaluated in an audiology tertiary referral center between March 2020 and February 2021 were compared to patients presenting with the same disorders during two previous time periods (March 2019 to March 2020 and March 2018 to March 2019). The incidence of SSNHL was slightly increased during the COVID-19 pandemic period compared to the previous periods: 0.68% incidence during pandemic, 0.49% incidence in first period, and 0.53% in second period. However, the results are not statistically significant ($p>0.05$) [21]. In addition, a Turkish study found an increased incidence of SSNHL during the COVID-19 pandemic. In 2019, 9.8% of the patients seen at the otolaryngology clinic presented with active or recent symptoms consistent with SARS-CoV-2 infection. In 2020 this percentage increased to 60.3% [22]. However, Niemen et al. concluded that there was no strong evidence of an increased risk of SSNHL following SARS-CoV-2 infection. The aIRR for the main risk period 0 to 54 days following infection was 1.1 (95% CI, 0.7-1.8), and the aIRR for the secondary risk period 55 days onwards from infection was 1.1 (95% CI, 0.7-1.6), both suggesting no significant change in the incidence of SSNHL compared with the uninfected time [17].

In the reports of SSNHL received by Lareb, 5 (4.6%) cases reported a history of a SARS-CoV-2 infection, of which 3 (2.8%) had an active infection up to 30 days prior to the SSNHL symptoms.

Mechanism

A hypothesis for a pathophysiological mechanism for audio vestibular adverse events following immunization is based on structural similarities between anti-spike SARS-CoV-2 antibodies and ear antigens: molecular mimicry. By inducing immunization against the SARS-CoV-2 spike protein an antibody cross reaction can occur [23]. Regarding the SARS-CoV-2 virus, the neurotropic aspects of the virus could instigate an immune reaction causing cranial neuropathy [21, 22].

Discussion

Our results showed O/E ratios below 1.0 for the mRNA based COVID-19 vaccines. However, for women aged below 45 years the O/E ratio approached 1.0 (O/E>0.70). This is in line with the results of Yanir et al., which showed high incidence ratios of SSNHL after the first dose of Comirnaty® in women aged 16-44 years [16]. In addition, our results show a significant result for the O/E ratio for women in the age of 18-34 years after the first dose of Comirnaty®: O/E= 2.36 (95% CI; 1.15-3.99). In contrast, Yanir et al. showed a high incidence of SSNHL in women aged 65 years or older after Comirnaty® [16]. In our results the O/E ratio decreases with the increase of age in women. Regarding the vector based COVID-19 vaccines we found an O/E ratio above 1.0 for women in the age categories 18-34 and 45-54 years old. However, the confidence intervals are very broad. Besides case reports, literature does not find an association between SSNHL and the vector based COVID-19 vaccines. A review from Pisani et al. indicates that no study has been done so far in which a causal relationship has been found between hearing disorders (audiovestibular side effects) and the COVID-19 vaccinations [23]. It is stated that more case reports of better quality/similar data are needed in able to aggregate cases. An increase in the number of case reports is seen, but for causality assessment is it necessary that these cases are of good quality.

Overall, the majority of cases have a plausible time to onset (<15 days) and 75% of cases received treatment for their SSNHL. Only 7 cases describe a history of hearing loss and in 13 cases a potential alternative cause is identified (3 previous SARS-Cov-2 infections, 5 with a medical history of an autoimmune disease, 2 infections in the medical history and 1 MS diagnosis after a MRI scan). Of the 6 bilateral SSNHL cases an underlying autoimmune disease was reported in 2 patients (both thyroid disorders) and 1 patient was diagnosed with MS based on MRI results. In 11 cases cardiovascular risk factors were identified, such as hypertension and diabetes. Although this number could be higher since not all reports provided information about medical history. Furthermore, 19 reports were identified with comprehensive documentation on diagnosis and exclusion of alternative causes. In all of these reports the hearing loss started within 2 weeks and the age of the patient was below 54 years. In 4 of the reports an audiogram was performed confirming the sudden hearing loss, a MRI was performed, and treatment was prescribed. In 12 of these 19 reports only an audiogram or MRI was performed and 11 of them received treatment. In another three reports no tests were reported, although treatment was prescribed.

Spontaneous reports

The presence of a prior infection serves as a potential confounder in the causality assessment of SSNHL and COVID-19 vaccination. For previous SARS-CoV-2 infections, the Lareb reporting form had an obligatory question. Three of the reports of SSNHL in this overview reported a SARS-CoV-2 infection 30 days prior to the occurrence of SSNHL. However, asymptomatic infections may have been overlooked. For any other infection, there was no standardized question in the reporting form. Only a few reports (6.4%) indicated hearing problems before vaccination. In 35.8% of reports tinnitus is co-reported as a reaction. In more than half of the reports (56%) no hearing test was performed and only in 28.4% of reports a MRI was done. However, only the cases with a valid description of a sudden onset of hearing loss were included.

Nearly half of the cases involved patients with an age under 54 years old. Literature indicates that idiopathic SSNHL can arise at any age but most commonly affects individuals 43 to 53 years old [9]. This could explain the age distribution in our received cases. However, it could be possible that elderly people do not make the connection between their COVID-19 vaccination and SSNHL because hearing problems are more common in this population. As a possible consequence, less elderly people report about the occurrence of SSNHL after COVID-19 vaccination. In addition, women in the age of 18-34 tend to report more often at a spontaneous reporting system. As a result a high number of observed cases is expected and this could contribute to the significant result of the O/E in this group.

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. The background incidence rates calculated with data from the United Stated were collected from 2006 to 2007. As a consequence, the effect of SARS-CoV-2 infections during the COVID-19 pandemic, which is potentially associated with SSNHL, was not taken into account.

Conclusion

The results of the observed-over-expected analysis showed that SSNHL has not been reported more frequently than expected following the COVID-19 vaccines when all age categories are analysed together. However, for mRNA COVID-19 vaccines high O/E ratios were found for women aged under 45 years, especially for women between 18 and 34 years of age, and this result was also significant. Therefore, mRNA COVID-19 vaccination could be associated with an increased risk of SSNHL. For the vector based COVID-19 vaccines, O/E ratios were above 1.0 for women aged 18-34 and 45-54 years, although this results was not significant. It remains important to monitor cases of SSNHL after COVID-19 vaccination and epidemiological research would be desirable in order to further evaluate this risk, especially in young women receiving mRNA COVID-19 vaccines.

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This signal has been raised on November 21, 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

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Supplementary

Appendix A:

Highlight: OE and/or ll 95% CI > 0.8 (USA IR's only) between 0.5 and 0.8 If n > 5 and OE > 0.5

Note: none of the ll 95% CI is > 1 and numbers are relatively low

			Agegroups (men and women together)																									
			N; O/E (95% CI)																									
Vaccine	Dose	TTO	<18				18-34				35-44				45-54				55-64				65+				total			
			n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul
mRNA	all	7d	1	0,41	0,01	2,31	6	0,45	0,17	0,99	6	0,43	0,16	0,94	10	0,39	0,19	0,71	4	0,10	0,03	0,26	9	0,07	0,03	0,14	36	0,24	0,17	0,33
mRNA	D1	7d	0	0,00	0,00	2,84	4	0,77	0,21	1,97	3	0,56	0,12	1,64	2	0,22	0,03	0,80	2	0,17	0,02	0,60	4	0,10	0,03	0,25	15	0,28	0,15	0,44
mRNA	D2	7d	1	0,91	0,02	5,09	1	0,22	0,01	1,20	1	0,20	0,01	1,13	5	0,59	0,19	1,39	1	0,09	0,00	0,48	2	0,05	0,01	0,18	11	0,22	0,11	0,37
mRNA	D3	7d	0	0,00	0,00	174,07	1	0,30	0,01	1,66	2	0,54	0,06	1,94	3	0,36	0,07	1,04	1	0,06	0,00	0,35	3	0,07	0,02	0,22	10	0,22	0,11	0,41
vector	all	7d	0	0,00	0,00	5052,71	2	1,89	0,23	6,83	0	0,00	0,00	8,05	2	0,73	0,09	2,63	4	0,29	0,08	0,74	4	0,51	0,14	1,30	12	0,73	0,37	1,21
vector	D1	7d	0	0,00	0,00	7053,05	2	2,22	0,27	7,22	0	0,00	0,00	7,73	1	0,44	0,01	2,44	3	0,41	0,08	1,19	3	0,73	0,15	2,13	9	0,85	0,39	1,62
vector	D2	7d	0	0,00	0,00	17815,48	0	0,00	0,00	23,62	0	0,00	0,00	19,67	1	2,18	0,05	12,15	1	0,15	0,00	0,85	1	0,26	0,01	1,47	3	0,48	0,10	1,40
Pfizer	all	7d	1	0,41	0,01	2,31	5	0,41	0,13	0,96	6	0,48	0,18	1,05	7	0,40	0,16	0,82	4	0,16	0,04	0,41	7	0,08	0,03	0,16	30	0,25	0,17	0,36
Pfizer	D1	7d	0	0,00	0,00	2,84	3	0,65	0,13	1,89	3	0,65	0,14	1,91	2	0,27	0,03	0,96	2	0,20	0,02	0,71	4	0,10	0,03	0,26	14	0,28	0,15	0,46
Pfizer	D2	7d	1	0,91	0,02	5,09	1	0,24	0,01	1,35	1	0,24	0,01	1,32	4	0,57	0,16	1,46	1	0,10	0,00	0,56	2	0,05	0,01	0,19	10	0,22	0,10	0,40
Pfizer	D3	7d	0	0,00	0,00	174,72	1	0,30	0,01	1,66	2	0,54	0,07	1,96	1	0,33	0,01	1,84	1	0,20	0,00	1,11	1	0,09	0,00	0,50	6	0,26	0,10	0,57
Moderna	all	7d	0	0,00	0,00	5117,21	1	0,92	0,02	5,15	0	0,00	0,00	2,47	3	0,36	0,07	1,05	0	0,00	0,00	0,26	2	0,06	0,01	0,23	6	0,19	0,07	0,41
Moderna	D1	7d	0	0,00	0,00	11965,62	1	1,76	0,04	9,81	0	0,00	0,00	4,88	0	0,00	0,00	2,43	0	0,00	0,00	2,15	0	0,00	0,00	3,73	1	0,20	0,00	1,10
Moderna	D2	7d	0	0,00	0,00	11083,36	0	0,00	0,00	7,26	0	0,00	0,00	5,25	1	0,71	0,02	3,93	0	0,00	0,00	2,28	0	0,00	0,00	3,98	1	0,21	0,01	1,18
Moderna	D3	7d	0	0,00	0,00	46251,72	0	0,00	0,00	573,66	0	0,00	0,00	113,67	2	0,37	0,04	1,34	0	0,00	0,00	0,34	2	0,07	0,01	0,25	4	0,18	0,05	0,46
AZ	all	7d	0	0,00	0,00	8620,39	1	3,08	0,08	17,13	0	0,00	0,00	9,45	1	1,05	0,03	5,85	3	0,22	0,05	0,64	4	0,51	0,14	1,31	9	0,69	0,32	1,32
AZ	D1	7d	0	0,00	0,00	15417,24	1	5,89	0,15	32,80	0	0,00	0,00	18,15	0	0,00	0,00	7,45	2	0,28	0,03	1,02	3	0,74	0,15	2,18	6	0,89	0,33	1,94
AZ	D2	7d	0	0,00	0,00	19553,57	0	0,00	0,00	23,76	0	0,00	0,00	19,73	1	2,19	0,05	12,19	1	0,15	0,00	0,85	1	0,26	0,01	1,47	3	0,48	0,10	1,40
Janssen	all	7d	0	0,00	0,00	12208,58	1	1,37	0,03	7,62	0	0,00	0,00	54,28	0	0,00	0,00	2,06	1	3,54	0,09	19,73	0	0,00	0,28	63,28	3	0,78	0,16	2,28
Janssen	D1	7d	0	0,00	0,00	13000,48	1	1,37	0,03	7,63	0	0,00	0,00	13,46	0	0,00	0,00	2,06	1	3,57	0,09	19,86	0	0,00	0,29	64,09	3	0,78	0,16	2,29

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			Agegroups (men)																										
			N; O/E (95% CI)																										
Vaccine	Dose	TTO	<18				18-34				35-44				45-54				55-64				65+				total			
			n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul
mRNA	all	7d	0	0,00	0,00	2,98	0	0,00	0,00	0,57	1	0,14	0,00	1,48	3	0,23	0,05	0,68	0	0,00	0,00	0,19	3	0,05	0,01	0,16	7	0,10	0,04	0,20
mRNA	D1	7d	0	0,00	0,00	5,53	0	0,00	0,00	1,44	0	0,00	0,00	1,39	1	0,22	0,01	1,24	0	0,00	0,00	0,61	2	0,11	0,01	0,38	3	0,11	0,06	0,44
mRNA	D2	7d	0	0,00	0,00	6,56	0	0,00	0,00	1,62	0	0,00	0,00	1,50	1	0,24	0,01	1,33	0	0,00	0,00	0,64	1	0,05	0,00	0,30	2	0,08	0,01	0,24
mRNA	D3	7d	0	0,00	0,00	351,67	0	0,00	0,00	2,25	1	0,55	0,01	3,07	1	0,24	0,01	1,34	0	0,00	0,00	0,46	0	0,00	0,00	0,20	2	0,09	0,07	0,53
vector	all	7d	0	0,00	0,00	9776,79	0	0,00	0,00	6,81	0	0,00	0,00	14,38	0	0,00	0,00	2,92	1	0,14	0,00	0,80	4	0,97	0,26	2,49	5	0,60	0,19	1,40
vector	D1	7d	0	0,00	0,00	13071,14	0	0,00	0,00	7,40	0	0,00	0,00	18,12	0	0,00	0,00	3,25	1	0,27	0,01	1,52	3	1,40	0,76	5,44	4	0,74	0,20	1,91
vector	D2	7d	0	0,00	0,00	38791,76	0	0,00	0,00	84,48	0	0,00	0,00	69,60	0	0,00	0,00	28,82	0	0,00	0,00	1,12	1	0,51	0,01	2,82	1	0,34	0,01	1,89
Pfizer	all	7d	0	0,00	0,00	2,65	0	0,00	0,00	0,62	1	0,16	0,00	0,90	2	0,23	0,03	0,85	0	0,00	0,00	0,27	3	0,06	0,01	0,18	6	0,11	0,04	0,24
Pfizer	D1	7d	0	0,00	0,00	4,92	0	0,00	0,00	1,60	0	0,00	0,00	1,61	1	0,27	0,01	1,49	0	0,00	0,00	0,64	2	0,09	0,01	0,34	3	0,13	0,03	0,38
Pfizer	D2	7d	0	0,00	0,00	5,84	0	0,00	0,00	1,81	0	0,00	0,00	1,74	1	0,29	0,01	1,60	0	0,00	0,00	0,66	1	0,05	0,00	0,27	2	0,09	0,01	0,34
Pfizer	D3	7d	0	0,00	0,00	313,74	0	0,00	0,00	2,25	1	0,56	0,01	3,10	0	0,00	0,00	2,79	0	0,00	0,00	1,48	0	0,00	0,00	0,65	1	0,10	0,00	0,54
Moderna	all	7d	0	0,00	0,00	8834,12	0	0,00	0,00	7,23	0	0,00	0,00	5,11	1	0,23	0,01	1,30	0	0,00	0,00	0,43	0	0,00	0,00	0,22	1	0,06	0,00	0,36
Moderna	D1	7d	0	0,00	0,00	19613,37	0	0,00	0,00	13,73	0	0,00	0,00	10,11	0	0,00	0,00	4,87	0	0,00	0,00	3,61	0	0,00	0,00	6,83	0	0,00	0,00	1,53
Moderna	D2	7d	0	0,00	0,00	19794,97	0	0,00	0,00	15,47	0	0,00	0,00	10,85	0	0,00	0,00	5,20	0	0,00	0,00	3,82	0	0,00	0,00	7,23	0	0,00	0,00	1,65
Moderna	D3	7d	0	0,00	0,00	85514,29	0	0,00	0,00	1134,74	0	0,00	0,00	219,91	1	0,35	0,01	1,97	0	0,00	0,00	0,56	0	0,00	0,00	0,23	1	0,09	0,00	0,51
AZ	all	7d	0	0,00	0,00	15055,33	0	0,00	0,00	40,28	0	0,00	0,00	33,45	0	0,00	0,00	13,88	1	0,13	0,00	0,72	4	0,85	0,23	2,17	5	0,85	0,28	1,98
AZ	D1	7d	0	0,00	0,00	26723,21	0	0,00	0,00	77,00	0	0,00	0,00	64,39	0	0,00	0,00	26,79	1	0,25	0,01	1,39	3	1,24	0,26	3,62	4	1,31	0,36	3,36
AZ	D2	7d	0	0,00	0,00	34481,57	0	0,00	0,00	84,48	0	0,00	0,00	69,60	0	0,00	0,00	28,82	0	0,00	0,00	0,99	1	0,44	0,01	2,44	1	0,35	0,01	1,96
Janssen	all	7d	0	0,00	0,00	20556,32	0	0,00	0,00	8,19	0	0,00	0,00	25,21	0	0,00	0,00	3,70	0	0,00	0,00	26,61	0	0,00	0,00	64,11	0	0,00	0,00	1,74
Janssen	D1	7d	0	0,00	0,00	20556,32	0	0,00	0,00	8,19	0	0,00	0,00	25,21	0	0,00	0,00	3,70	0	0,00	0,00	26,61	0	0,00	0,00	64,11	0	0,00	0,00	1,74

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			Agegroups (women)																									
			N; O/E (95% CI)																									
Vaccine	Dose	TTO	<18				18-34				35-44				45-54				55-64				65+				total			
			n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul	n	OE	ll	ul
mRNA	all	7d	1	0,85	0,02	4,74	6	0,89	0,33	1,94	5	0,71	0,23	1,66	7	0,54	0,22	1,11	4	0,20	0,06	0,52	6	0,09	0,03	0,20	29	0,38	0,25	0,53
mRNA	D1	7d	0	0,00	0,00	5,83	4	1,52	0,41	3,88	3	1,12	0,23	3,28	1	0,22	0,01	1,23	2	0,34	0,04	1,22	2	0,09	0,01	0,33	12	0,43	0,22	0,72
mRNA	D2	7d	1	1,88	0,05	10,47	1	0,42	0,01	2,36	1	0,41	0,01	2,27	4	0,94	0,26	2,42	1	0,17	0,00	0,97	1	0,05	0,00	0,26	9	0,35	0,16	0,66
mRNA	D3	7d	0	0,00	0,00	344,67	1	0,58	0,01	3,23	1	0,53	0,01	2,93	2	0,47	0,06	1,70	1	0,13	0,00	0,70	3	0,14	0,03	0,41	8	0,34	0,15	0,68
vector	all	7d	0	0,00	0,00	11032,52	2	3,90	0,47	14,06	0	0,00	0,00	9,05	2	1,35	0,16	4,88	3	0,43	0,09	1,26	0	0,00	0,00	0,98	7	0,82	0,33	1,69
vector	D1	7d	0	0,00	0,00	15319,04	2	4,98	0,60	17,97	0	0,00	0,00	13,49	1	0,87	0,54	7,63	2	0,54	0,07	1,97	0	0,00	0,00	1,87	5	0,96	0,31	2,25
vector	D2	7d	0	0,00	0,00	39427,69	0	0,00	0,00	33,06	0	0,00	0,00	27,54	1	3,04	0,08	16,93	1	0,31	0,01	1,71	0	0,00	0,00	2,04	2	0,60	0,07	2,18
Pfizer	all	7d	1	0,97	0,02	5,42	5	0,75	0,24	1,75	5	0,80	0,26	1,86	5	0,54	0,17	1,25	4	0,35	0,09	0,89	4	0,09	0,03	0,24	24	0,41	0,26	0,59
Pfizer	D1	7d	0	1,47	0,72	2,49	3	2,36	1,15	3,99	3	0,59	0,29	1,00	1	0,45	0,22	0,77	2	0,00	0,00	6,67	2	1,18	0,24	3,46	11	0,45	0,22	0,77
Pfizer	D2	7d	1	2,15	0,05	11,97	1	0,44	0,01	2,46	1	0,48	0,01	2,66	3	0,82	0,17	2,41	1	0,23	0,01	1,26	1	0,05	0,00	0,30	8	0,35	0,15	0,70
Pfizer	D3	7d	0	0,00	0,00	395,44	1	0,54	0,01	2,99	1	0,53	0,01	2,96	1	0,57	0,01	3,17	1	0,40	0,01	2,22	1	0,18	0,00	1,00	5	0,43	0,14	1,00
Moderna	all	7d	0	0,00	0,00	12055,59	1	1,61	0,04	8,99	0	0,00	0,00	4,80	2	0,48	0,06	1,74	0	0,00	0,00	0,61	2	0,14	0,02	0,51	5	0,32	0,10	0,76
Moderna	D1	7d	0	0,00	0,00	29876,89	1	3,09	0,08	17,20	0	0,00	0,00	9,44	0	0,00	0,00	4,70	0	0,00	0,00	5,12	0	0,00	0,00	7,97	1	0,40	0,01	2,24
Moderna	D2	7d	0	0,00	0,00	25217,19	0	0,00	0,00	12,63	0	0,00	0,00	10,19	1	1,37	0,03	7,61	0	0,00	0,00	5,43	0	0,00	0,00	8,57	1	0,44	0,01	2,43
Moderna	D3	7d	0	0,00	0,00	101802,72	0	0,00	0,00	1070,95	0	0,00	0,00	235,29	1	0,38	0,01	2,11	0	0,00	0,00	0,80	2	0,15	0,00	0,42	3	0,28	0,06	0,82
AZ	all	7d	0	0,00	0,00	20063,31	1	3,95	0,10	22,02	0	0,00	0,00	13,18	1	1,41	0,04	7,85	2	0,33	0,04	1,19	0	0,00	0,00	1,11	4	0,60	0,16	1,55
AZ	D1	7d	0	0,00	0,00	36166,76	1	7,57	0,19	42,19	0	0,00	0,00	25,28	0	0,00	0,00	9,98	1	0,32	0,01	1,77	0	0,00	0,00	2,16	2	0,58	0,07	2,10
AZ	D2	7d	0	0,00	0,00	45060,22	0	0,00	0,00	30,52	0	0,00	0,00	27,54	1	2,94	0,07	16,39	1	0,34	0,01	1,91	0	0,00	0,00	2,30	2	0,63	0,08	2,27
Janssen	all	7d	0	0,00	0,00	33934,24	1	3,30	0,08	18,37	0	0,00	0,00	28,90	1	1,22	0,03	6,81	1	7,11	0,18	39,60	0	0,00	0,00	112,68	3	1,91	0,40	5,59
Janssen	D1	7d	0	0,00	0,00	33934,24	1	3,30	0,08	18,37	0	0,00	0,00	28,90	1	1,22	0,03	6,81	1	7,11	0,18	39,60	0	0,00	0,00	112,68	3	1,91	0,40	5,59