Overview of Guillain-Barré syndrome 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].

Guillain-Barré syndrome (GBS) is a rare and severe neurological disorder. GBS is an umbrella term for multiple types of immune-mediated acute paralyzing neuropathies. The clinical presentation and disease course of GBS is heterogeneous with several clinical variants: demyelinating forms (Miller-Fisher and acute inflammatory demyelinating polyradiculoneuropathy [AIDP]) and axonal loss forms (acute motor axonal neuropathy [AMAN], and acute sensorimotor axonal neuropathy [AMSAN]). GBS often presents with progressive symmetrical muscle weakness with reduced and/or absent reflexes. The symptoms usually progress over a period of 2 weeks. Muscle weakness can vary from mild to severe, with respiratory failure requiring mechanical ventilation. In the vast majority of cases (>90%) the symptoms have reached their highest point by four weeks after onset [6]. If the symptoms persist for more than 8 weeks, the patient may be diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) instead of GBS. CIDP is an acquired, immune-medicated neuropathy which is characterized by a progressive course of symmetric weakness affecting peripheral nerves. Due to temporal overlap, it can be difficult to distinguish CIDP from GBS in practice. The cause of CIDP remains unknown, but there is evidence that immunologic triggers (T-cell activation and/or auto-antibodies) are involved [7]. With GBS, the disease is preceded by a respiratory-tract infection or gastroenteritis in approximately two-thirds of the cases. It is thought that the infection evokes an autoimmune response that targets peripheral nerve components. The first symptoms usually present 1-2 weeks after infection. GBS has been associated with vaccination as well (e.g., influenza vaccination, meningococcal vaccination, and recombinant zoster vaccination), but the associated risks appear small or negligible [6]. It is considered to be an Adverse Event of Special Interest (AESI) by the European Medicines Agency (EMA) [8]. An association of CIDP with vaccination remains unknown [7].

In July 2021 Pharmacovigilance Centre Lareb published a signal regarding Vaxzevria and GBS. A causal relationship between GBS and Vaxzevria seemed possible based on the 11 cases of GBS and the results of the observed over expected analysis [9]. In May 2021 the EMA Pharmacovigilance Risk Assessment Committee (PRAC) had started a review on Guillain-Barre syndrome with Vaxzevria. Based on all available information, the EMA decided to list GBS as an adverse drug reaction (ADR) for the adenovirus vector vaccines (Jcovden and Vaxzevria) in the product information [3, 4].

The current overview reviews all reports of GBS and CIDP associated with the COVID-19 vaccines. The number of GBS cases is compared to background incidence rates.

Reports

GBS reports

Until October 12th 2022, The Netherlands Pharmacovigilance Centre Lareb received 72 reports of GBS following COVID-19 vaccination. No duplicates were detected. The selected reports contained at least one coded reaction within the broad Standardised MedDRA Query (SMQ) for Guillain-Barre syndrome, Miller Fisher syndrome, Demyelinating polyneuropathy, and Acute motor sensory axonal neuropathy. An overview of the included reports is shown in table 1. Figure 1 shows the age distribution of the patients sorted by sex and vaccine, and figure 2 shows the distribution in time to onset (TTO) of GBS after COVID-19 vaccination clustered in 3 groups (<15 days, 15-42 days, and >42 days) sorted by type vaccine.

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

		Total	Pfizer (Comirnaty)	Moderna (Spikevax)	Vaxzevria (AstraZeneca)	Jcovden (Janssen)
Reports, n (%)		72 (100%)	30 (41.7%)	8 (11.1%)	18 (25%)	16 (22.2%)
Dose, n (%)	1	46 (63.9%)	11 (23.9%)	3 (6.5%)	16 (34.8%)	16 (34.8%)
	2	22 (30.6%)	16 (72.7%)	4 (18.2%)	2 (9.1%)	-
	3	4 (5.6%)	3 (75%)	1 (25%)	-	-
Reporter, n (%)	HCP	40 (55.6%)	16 (40%)	4 (10%)	13 (32.5%)	7 (17.5%)
	CONS	32 (44.4%)	14 (43.8%)	4 (12.5%)	5 (15.6%)	9 (28.1%)
Serious[1)], n (%)		65 (90.3%)	25 (38.5%)	7 (10.8%)	15 (23.1%)	18 (27.7%)
Outcome, n (%)	Recovered	4 (5.6%)	2 (50%)	-	-	2 (50%)
	Recovering	44 (61.1%)	18 (40.9%)	6 (13.6%)	9 (20.5%)	11 (25%)
	Not recovered	19 (26.4%)	9 (47.4%)	2 (10.5%)	5 (26.3%)	3 (15.8%)
	Fatal	1 (1.3%)	1 (100%)	-	-	-
	Unknown	4 (5.6%)	-	-	4 (100%)	-
Sex, n (%)	Male	42 (58.3%)	15 (35.7%)	6 (14.3%)	9 (21.4%)	12 (28.6%)
	Female	30 (41.7%)	15 (50%)	2 (6.7%)	9 (30%)	4 (13.3%)
Age (years)	Mean (range)	55 (18-89)	56 (25-89)	54 (18-87)	60 (40-65)	51 (23-76)
Time to onset (days)	Median (IQR)	13 (23)	13.5 (27.5)	26 (25)	11 (4)	16.5 (18.8)
Medical history	Previous SARS-CoV-2 infection	12 (16.7%)	5 (41.7%)	2 (16.7%)	3 (25%)	2 (16.7%)
	Infection[2)] ≤30 days prior	7 (9.7%)	4 (57.1%)	1 (14.3%)	-	2 (28.6%)
	GBS	1 (1.3%)	1 (100%)	-	-	-
Treatment	IVIG	46 (63.9%)				
	Corticosteroids	14 (19.4%)				

HCP = Health Care Professional, CONS = consumer, IVIG = intravenous immunoglobulin. [1)] Seriousness according CIOMS criteria: hospitalization, disabling/incapacitating, life threating, death, or other medically important condition. [2)] Infections include the following: SARS-CoV-2 infection, cytomegalovirus (CMV) infection, respiratory tract infection, Borrelia burgdorferi infection and gastroenteritis.

A majority of the patients in the reports (41.7%) received Comirnaty, which is the most commonly used vaccine, and most reports covered the first dose of vaccination with the COVID-19 vaccine (63.9%). Figure 1 displays the predominant use of Vaxzevria in the age group of 60-69 years old. During the vaccination campaign this age group was primarily exposed to this vaccine, which explains the portrayed age distribution. More than half of the reports were originated from health care professionals (HCPs) (55.6%). Due to the symptoms of GBS, most of the reports were marked as serious because it led to hospitalization and/or disability. 61.1% of the patients mentioned that they were recovering from the symptoms at time of reporting. GBS occurred within two weeks of vaccination in 56% and in 90% of the cases within 6 weeks (figure 2). Diagnostic certainty of GBS was difficult to obtain from all of the reports due to lack of detailed medical information. Performance of an electromyography (EMG) and/or lumbar puncture was frequently mentioned, but in a number of cases the results were doubtful or not reported. In 3 cases the diagnosis of the Miller Fisher Syndrome was made and in 1 case the COVID-19 vaccination aggravated an already existing GBS.

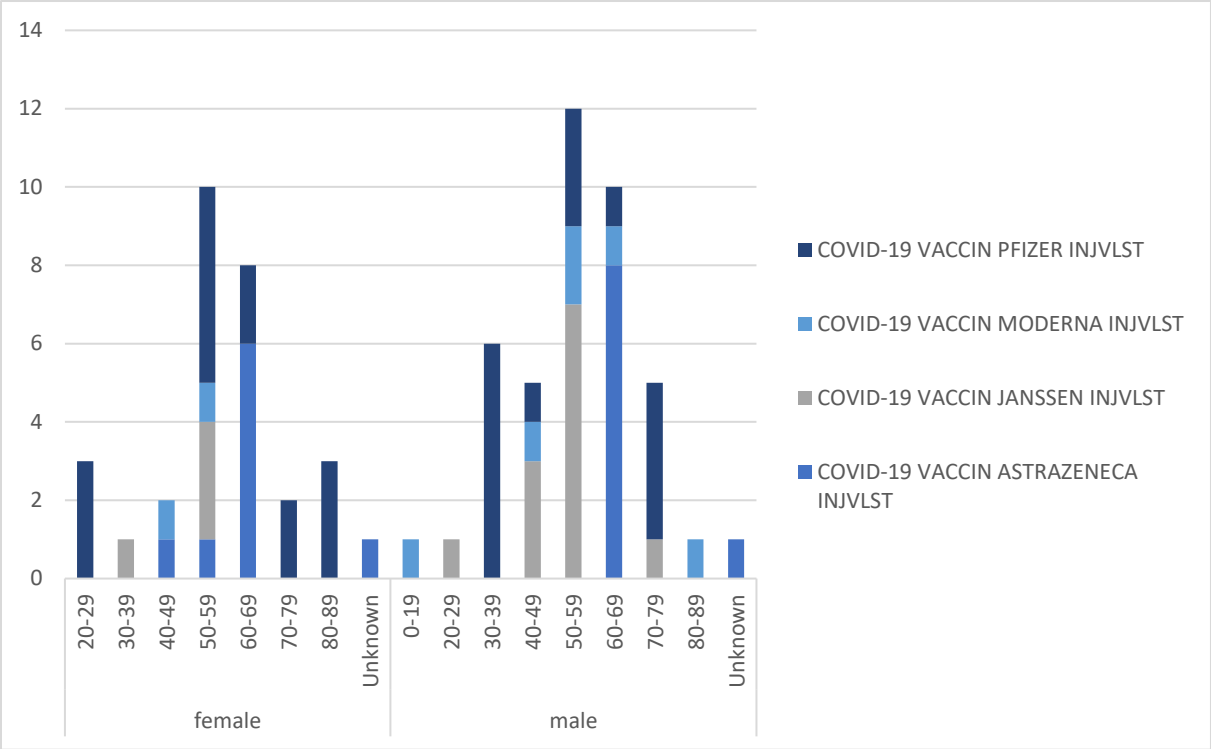

Figure 1: Age distribution of patients in the reports of GBS events with COVID-19 vaccines

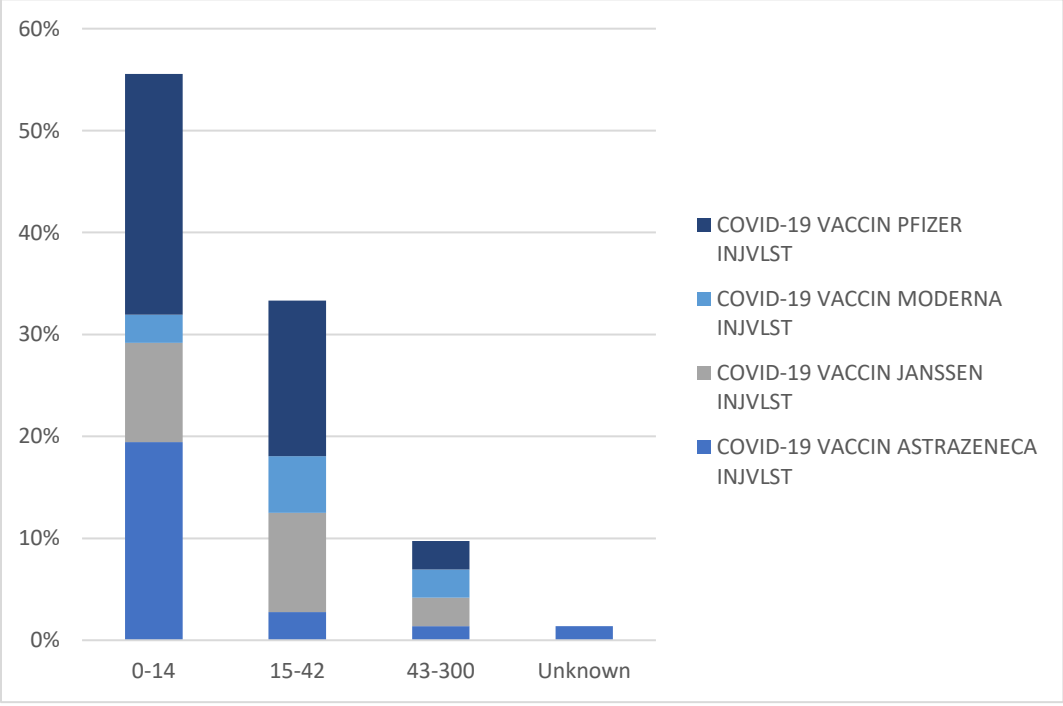

Figure 2: Distribution in time to onset of GBS event with COVID-19 vaccines clustered in 3 groups (<15 days, 15-42 days and >42 days)

CIDP reports

Until November 1st 2022, The Netherlands Pharmacovigilance Centre Lareb received 12 reports of CIDP following COVID-19 vaccination. Due to differences in disease pathogenesis and course compared to GBS, they are discussed separately. In Appendix A, the 12 reports of CIDP are listed. Of these 12 reports 5 patients received Spikevax, 4 Jcovden, 2 Vaxzevria, and 1 Comirnaty. 10 reports concerned the first dose of COVID-19 vaccination, 1 report the second dose, and 1 report the third

dose. In 7 reports new-onset of CIDP was mentioned, of which 4 reports were initially diagnosed as GBS and one had GBS in its medical history. In the other 5 cases aggravation of already existing CIDP was reported. The mean TTO was 26 days for new onset CIDP and 7 days for the reports concerning an aggravation of CIDP. In 5 out of 12 reports the patient was recovering and 2 were not recovered at time of reporting.

Comparison of reports with background incidence

For the comparison of the reported number of cases of GBS following COVID-19 vaccines with background incidence rates, data were obtained from the Dutch hospital and general practitioner registries based on ICD-10 coding selected by PHARMO institute. In figure 3 incidence rates (per 100,000 person-years) of GBS from 2017-2019 are shown and clustered by sex and age group.

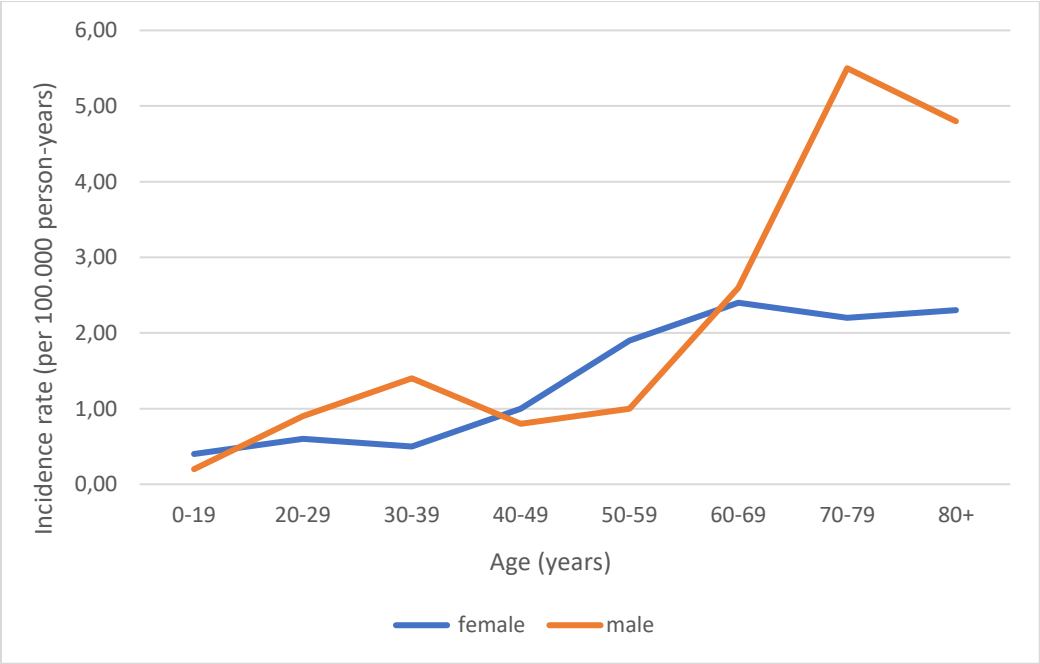

Figure 3: Background incidence rates of GBS in the Netherlands from 2017-2019
Data are stratified by age (decades) and sex (male/female) and counted per 100.000 person-years (10)

For calculating observed-over-expected ratios, the SMR (standardized morbidity rate) was used, which uses reported cases as observed (O) and background incidence rates applied to a certain vaccinated population as expected cases (E). 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 [10]. 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. For the calculations, reports received until October 12th with vaccination dates until September 28th (for risk period of 14 days) and August 30th (for risk period of 42 days) were taken into account, as well as times to onset up to 14 and 42 days respectively. Hence, cases with longer latencies were not included. 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: √((∑(O −/+1)2) / ∑ E; using Poisson distribution tables for low numbers of O (<10)*

The results are summarized in Figure 4.

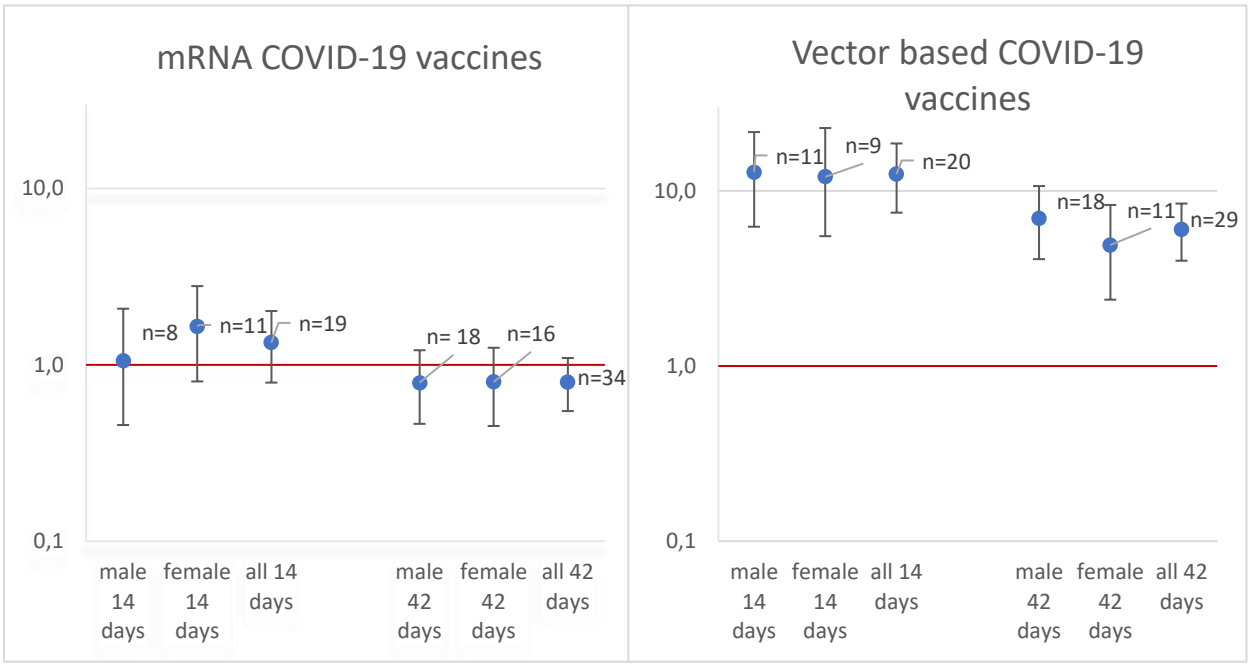

Figure 4: Observed over expected (OE) ratios of GBS reports for mRNA (Comirnaty and Spikevax) and vector based (Vaxzevria and Jcovden) COVID-19 vaccines for risk periods 14 and 42 days and male, female, and male + female.

The scale is semi-logarithmic. If OE 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. N= number of cases observed in the Lareb database. More details are available in Appendix B.

General-results

OE ratios exceeding 1.0 are seen with the vector based vaccines within any risk period. For the vector-based COVID-19 vaccines the OE ratios are as followed: 14 day risk period: male OE=12.79 [6.24-21.67], female OE=12.04 [5.51-22.85], and all OE=12.46 [7.51-18.85]; 42 days: male OE=6.98 [4.08-10.65], female OE=4.90 [2.39-8.31], and all OE=6.02 [3.99-8.46] (figure 4).

The results regarding the mRNA COVID-19 vaccines also show OE ratios above 1.0 for male, female, and all sexes for the 14 days risk period. However, all the lower limit confidence intervals are below 1.0: male OE=1.06 [0.46-2.08], female OE=1.65 [0.81-2.80], and all OE=1.34 [0.79-2.02] (figure 4). For the 42 days risk period the OE ratios for the mRNA vaccines are below 1.0: male OE=0.79 [0.46-1.21], female OE=0.80 [0.45-1.25], and all OE=0.80 [0.55-1.09] (figure 4).

Results per vaccine and dose

For the mRNA vaccines and the 14 day risk window, 17 out of 19 (89.5%) reports concern Comirnaty and 2 (10.5%) Spikevax; for the 42 days risk window 28 (82.4%) reports concern Comirnaty and 6 (17.6%) Spikevax (Appendix B). The second dose of mRNA vaccines showed a higher OE ratio compared to the first dose. In particular, the OE ratio for the 2nd dose of Comirnaty was 2.28 [1.10-4.20] in the risk window of 14 days (Appendix B).

For the vector-based vaccines the amount of reports of Jcovden and Vaxzevria was 7 (35%) and 13 (65%) respectively, for the risk period of 14 days (Appendix B). Looking at dose of vaccine, the first dose of the vector vaccines showed a higher OE ratio (OE=18.84 [11.19-28.48]) compared to the second dose (OE=1.67 [0.04-9.33]) for the risk period of 14 days. One report from Vaxzevria was observed for the second dose of vector vaccines in the risk period of 14 days (Appendix B).

Information from literature

GBS

During a clinical trial for Jcovden two cases of GBS were reported: one in a 60-year-old vaccine recipient, and one in a 75-year-old placebo recipient occurring on days 16 and 10, respectively [11]. In de Food and Drug Administration (FDA) assessment it was stated that the GBS cases are unlikely related to the vaccine, but a causal relationship cannot be definitively excluded [12]. In a phase 3 trial of Vaxzevria one participant developed GBS after receiving the vaccine [13]. For the mRNA based COVID-19 vaccines no cases of GBS have been reported following vaccination in clinical trials [14, 15]. In July 2021 the EMA decided to list GBS as an adverse drug reaction for the adenovirus vector vaccines (Jcovden and Vaxzevria) in the product information [16].

Various studies have described the occurrence of GBS after COVID-19 vaccination [17-29]. In short, the vector based vaccines showed a higher incidence of GBS after vaccination compared to background incidence, whereas for the mRNA COVID-19 vaccines most studies found no increase [18, 20-22, 27, 28].

Studies based on spontaneous reporting showed higher reporting rates of GBS after vector vaccines compared to mRNA vaccines [18, 21]. The observed number of reports of GBS, extracted from VigiBase, was compared to the expected number of cases issued from published background rates for several countries. Overall, a higher frequency of GBS was found with adenovirus-vectored COVID-19 vaccines compared to mRNA-based COVID-19 vaccines: the OE ratio was consistently below 1.0 for mRNA based and above 2.0 for adenovirus vectored COVID-19 vaccines [18]. The OE ratio for the Dutch data within VigiBase for the mRNA vaccines was as followed: 0.88 [0.39-1.97] for a risk window of 21 days and 0.76 [0.42-1.37] for a risk window of 42 days. The vector vaccines showed a higher OE ratio: 7.22 [1.92-27.14] for a risk window of 21 days and 4.01 [1.50-10.67] for a risk window of 42 days [18] . Another study used the Vaccine Adverse Event Reporting System (VAERS) and showed that the reporting rate of GBS after COVID-19 vaccination was 4.97 per million and this number did not exceed the expected number of GBS in the general population in the United States (10-20 per million per year) [21]. However, the reporting rate of GBS within 6 weeks after vaccination was significantly higher compared to the incidence of GBS in the general population: 1.7 (95% CI 1.60–1.89) extra GBS reports per 1 million subjects vaccinated was found. When the cases were divided based on manufacturer of the COVID-19 vaccine, Jcovden had a significantly higher reporting rate than either Comirnaty or Spikevax. The reporting rates were 11.51 vs 1.23 vs 2.55 per million for the Jcovden, Spikevax, and Comirnaty respectively [21].

For the detection or confirmation of small risks following vaccination, such as GBS, large epidemiological studies are required [30]. A study performed in the United Kingdom (UK) used the English National Immunization (NIMS) Database to investigate the neurological adverse events associated with the first dose of Vaxzevria and Comirnaty, as well as SARS-CoV-2 infection [27]. By linking the NIMS database at individual patient level to national data for mortality, hospital admission and SARS-CoV-2 infection data, a possible association could be examined. There was an increased risk for GBS for Vaxzevria in the 1-28 days post vaccination period (IRR, 2.04; 95% CI: 1.60–2.60) and for Comirnaty no increased risk was found (IRR, 0.86; 95% CI: 0.54–1.36) [27]. Interestingly, after a SARS-Cov-2 infection the risk for GBS was higher compared to the COVID-19 vaccines (IRR, 5.25; 95% CI: 3.00–9.18) [27]. Another study used two large electronic health record databases from the UK and Spain [25]. The database from the UK was the Clinical Practice Research Datalink (CPRD) cohort, which is a subset of the larger UK dataset analyzed by Patone et al [27]. Neither Vaxzevria nor Comirnaty was associated with an increased risk of neurological adverse events. However, an increased risk of Bell's palsy, encephalomyelitis, and GBS was observed for people with SARS-CoV-2 infection [25].

CIDP

A few case reports have described the occurrence of CIDP after COVID-19 vaccination [31-39]. Whether COVID-19 vaccination can aggravate existing GBS or CIDP was investigated through a prospective multicenter cohort study in the Netherlands [40]. None of the 162 participants with a history of GBS had a recurrence after vaccination and of the 188 participants with CIDP, ten participants (5%) reported a worsening of symptoms within six weeks following vaccination. Of these 10 participants, 8 reported to

have a history of fluctuating symptoms prior to vaccination and 5 reported an alteration in their treatment regimen due to the symptoms [40].

GBS with COVID-19

A systematic review and meta-analysis of observational cohort and case series explored the occurrence, clinical characteristics, and outcomes of GBS associated with SARS-CoV-2 infection. The pooled prevalence of GBS in a SARS-CoV-2 positive population exceeded the corresponding average rate of GBS in the general population. On top of that, patients with a SARS-CoV-2 infection had increased odds for demyelinating GBS subtypes (OR 3.27, 95% CI 1.32%–8.09%; I2 = 0%) compared with non-infected contemporary or historical controls [41]. An epidemiological and cohort study from the UK showed that the incidence of GBS had reduced during the pandemic (March-May 2020), compared to the incidence of GBS in UK hospitals from 2016 to 2019. Hence, the influence of the lockdown measurement reducing the transmission of GBS inducing pathogens should be taken into account [42]. In contrast, an observational multicenter study from two Italian hotspot regions showed a 2.6-fold increase in the incidence of GBS in March and April 2020, when compared to the same months in 2019 [43].

In the reports of GBS Lareb received, 11 (15.9%) cases reported a history of a SARS-CoV-2 infection, of which only 2 (2.8%) had an active infection up to 30 days prior to the GBS symptoms.

Mechanism

A hypothesis for a pathophysiological mechanism for GBS following a COVID-19 vaccination is based on structural similarities between the SARS-CoV-2 spike protein and a myelin protein: molecular mimicry. By inducing immunization against the SARS-CoV-2 spike protein an antibody cross reaction can occur. [21, 44] Another approach for a potential mechanism suggest an immune-mediated cause rather than a structural resemblance of GBS in SARS-CoV-2 positive patients. A pro-inflammatory cytokine storm due to a SARS-CoV-2 infection could instigate GBS, since various cytokines have a potential role in the pathogenesis of GBS. In COVID-19 vaccines a homogeneous cytokine storm could attribute to the development of GBS [45].

Discussion

Our results showed a OE ratio above 1.0 for the risk period of 14 days, and a OE ratio below 1.0 for a risk period of 42 days, regarding the mRNA vaccines. Noteworthy, all the lower limit confidence intervals are below 1.0, which make the results not statically significant. This is in line with the results of Atzenhoffer et al., which shows OE ratios reaching 1.0 for the Dutch data, with lower limits below 1.0 and upper limits above 1.0 in the confidence intervals [18]. Regarding the vector-based COVID-19 vaccines Atzenhoffer et al. found a OE ration above 4 in the Netherlands, which is in line with our results [18]. On top of that, Jaffry et al. and Hanson et al. concluded that Jcovden had a significantly higher reporting rate than either Comirnaty or Spikevax, and Patone et al. showed an increased risk for GBS for Vaxzevria in the 1-28 days post vaccination [20, 21, 27]. On the other hand, Li et al. showed no increased risk of GBS for Vaxzevria, only a SARS-CoV-2 infection displayed a higher risk [25]. A smaller sample size and different measurement of outcomes could explain the difference in results when compared to Patone et al. [30].

The reports of CIDP contain sometimes lack of information, with the consequence that diagnostics remain uncertain. For the reports with a new onset CIDP the diagnosis is plausible because the distinction with GBS is not always clear and it is known that CIDP is under/over diagnosed in practice. To contribute the aggravation of CIDP to the COVID-19 vaccines in the 5 reports is hard, since a relapse of the symptoms is also part of the natural progression of CIDP. One of the reports from Lareb describe a participant from the study from Baars et al., whether more reports are also part of the study remains unclear [40].

Spontaneous reporting

The presence of a prior infection reduces the chance of a potential relationship of GBS and vaccination. For previous SARS-CoV-2 infections, the Lareb reporting form had an obligatory question. However, asymptomatic infections may have been overlooked. In the reports received at Lareb, 16.7% of the patients reported to have a suspected or proven previous SARS-CoV-2 infection. For any other

infection, there was no standardized question in the reporting form. In 9.7% of the reports an infection up to 30 days prior to the GBS symptoms was identified. In one case the results regarding an existing Borrelia infection were doubtful, however the patient was treated with both IVIG and doxycycline.

The TTO of GBS following vaccination in literature varies, however latencies of several weeks have been often mentioned. The average TTO in our reports was 25 days with 90% of the cases where GBS occurred within 6 weeks. Based on previous vaccine safety studies a time frame from 1-42 days to develop GBS post vaccination is considered most plausible [46].

Limitations OE method
Underreporting is a common feature of voluntary reporting systems. Since the extent of underreporting is unknown, the number of observed cases can be underestimated. With respect to the OE analysis we compared an 'observed' number based on spontaneous reporting with an 'expected' number from healthcare registries. The Dutch background incidence rates were based on the average incidence of GBS from 2017 to 2019. As a consequence, the effect of SARS-CoV-2 infections during the COVID-19 pandemic, which is potentially associated with GBS, was not taken into account. Otherwise, the total amount of infections as a background incidence may have been reduced by measurements like social distancing. Since the 'observed' number is likely to be underestimated, OE ratios reaching 1.0 should give rise to an alert as well.

Compared to the OE analysis of Atzenhoffer et al. [18], our results do show OE ratios exceeding 1.0 for vector based vaccines, and also for mRNA vaccines within the 14 days risk period. The relatively high OE ratios with mRNA vaccines in our results are inconclusive, due to the small lower limits of the confidence intervals. However, for the second dose of Comirnaty, the OE ratio including the confidence interval exceeded 1.0, indicating a potential association as well.

Conclusion
The results of the observed over expected analysis show that GBS has been reported more frequently than expected following the first dose of vector based vaccines (Vaxzevria and Jcovden), for which this reaction is labelled in the SmPC. For the mRNA vaccines a tendency of a OE ratio greater than 1.0 is seen with the second dose, however, due to broad confidence intervals these results remain inconclusive. For mRNA vaccines the potential association cannot be ruled out using merely data from a spontaneous case reporting system. Additional research is needed to elucidate the risks with more certainty.

The association of CIDP with COVID-19 vaccines remains uncertain. Although CIDP is a rare disease, the number of reports per vaccine is low and good clinical documentation for both diagnostic and causality assessment is limited. Furthermore, no support in literature was found.

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This signal has been raised on February 28, 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

Supplementary

Appendix A: Reports from CIPD associated with COVID-19 vaccines in the Netherlands

No.	ID, sex, age, primary source	Drug, dose	Medical history + Concomitant medication	Reported ADRs	Latency after start	Outcome	Clinical information
1.	NL-LRB-00450234, female, 50-60 Years, Consumer or other non health professional	COVID-19 Vaccin Moderna Injvlst 0,5Ml Dose 1	Chronic inflammatory demyelinating polyneuropathy Immunoglobulin normal Injv 200Mg/Ml	Chronic inflammatory demyelinating polyradiculoneuropathy	2 Days	Recovering	2 days after vaccination serious deterioration of the muscle disease CIDP happened. Muscle disease worsened sharply. Pain in nerve roots, neuropathic pains, loss of strength. First week severe, second week somewhat better. Expert opinion: insufficient data on objectification of the aggravation/treatment/course surrounding vaccination/other factors (infection, other health problems)
2.	NL-LRB-00521078, female, 20-30 Years, Physician	COVID-19 Vaccine Moderna Injvlst 0,5Ml Dose 1	Guillain barre syndrome Tacrolimus Caps1Mg; Mycophenolate Mofetil Tabl 500Mg; Cotrimoxazole 480 Tabl 80/400Mg; Calciumcarb/Colecalc 2,5G/800Ie; Pantoprazole Tabl Msr 40Mg	Chronic inflammatory demyelinating polyneuropathy; Myocarditis; Respiratory insufficiency	1 Days; 19 Days; 19 Days	Recovering	1 day after vaccination the patient collapsed in the lower legs and was unable to mobilize independently. The patient was hospitalized and the diagnosis of CIDP was made. Subsequently also myocarditis and respiratory insufficiency occurred for which intubation and IC admission. Diagnostic certainty: EMG, nerve ultrasound, blood test, CT chest (results not stated) Expert opinion: insufficient data to confirm diagnosis
3.	NL-LRB-00540781, female, 70 Years and older, Consumer or other non health professional	COVID-19 Vaccin Pfizer Injvlst 0,3Ml Dose 1	Chronic inflammatory demyelinating polyneuropathy Immunoglobuline Normaal Infvlst 50Mg/Ml	Chronic inflammatory demyelinating polyneuropathy; Headache; Fatigue; Disease aggravation	2 Days	Recovering	CIDP attack: All night long tingling, cramps and stiffness that went through arms and legs in violent waves. Then weeks of great difficulty with walking and balance, headache and fatigue was experienced. Infusion with IVIG already worn off after 10 days, patient can't walk more than 10 meters. Second vaccination has been postponed 14 months later: disease has stabilized after an increase in dose and frequency of IVIG in a period of more than 1 year, but new level is worse than before vaccination. Neurologist has attributed worsening complaints to vaccination. Expert opinion: insufficient data to confirm exacerbation

4.	NL-LRB-00547285, male, 60-70 Years, Consumer or other non health professional	COVID-19 Vaccin Astrazeneca Injvlst Dose 1	Myocardial infarction, atrial fibrillation Rivaroxaban Tablet 10Mg, Bisoprolol Fumaraat, Ramipril Tablet 10Mg	Chronic inflammatory demyelinating polyneuropathy	14 Days	Recovering	Reported as GBS, IVIG infusion 5 days, started with muscle pain/nerve pain that got worse with paralysis in legs and later arms. Nerve test and epidural done that confirmed diagnosis. 4 months later chronic variant CIDP was diagnosed, already had a 3rd relapse, now receives an IVIG infusion and methylprednisolone once every 3 weeks. After 1 year still chronic complaints of foot drop, trembling hands, little energy, balance disorder, numb hands and feet. IVIG course is being phased out; a lot of physiotherapy. Second opinion academic hospital diagnosis confirmed. Expert opinion: insufficient data to confirm diagnosis
5.	NL-LRB-00668287, male, 40-50 Years, Physician	COVID-19 Vaccin Janssen Injvlst 0,5Ml Dose 1	No medical history / concomitant medication	Chronic inflammatory demyelinating polyneuropathy; Facial paresis	1 Weeks	Recovering	Diagnostic certainty: EMG, nerve ultrasound, lumbar puncture progressive motor and sensory complaints in extremities in a non-length dependent distribution. Based on EMG there is demyelinating neuropathy, fits CIDP (meets criteria based on the EFNS, no indications in the other direction). Echo supports this. Expert opinion: based on this data it is not a typical CIDP. Possibly multifocal CIDP.
6.	NL-LRB-00669375, male, 60-70 Years, Consumer or other non health professional	COVID-19 Vaccin Astrazeneca Injvlst Dose 1	Polyneuropathy (3 weeks prior to vaccination), talipes equinovarus	Chronic inflammatory demyelinating polyneuropathy; Aggravation of Polyneuropathy; Monoclonal gammopathy of unknown significance	3 Months, 2 Weeks, 2 Weeks	Not Recovered	Reinforcement of polyneuropathy (onset 3 weeks before vaccination): Can hardly walk, loss of strength in lower legs and hands, almost disabled; Diagnosis Chronic inflammatory demyelinating polyneuropathy has been established Diagnostic procedures: MRI, blood test, bone marrow biopsy, abdominal wall fat biopsy (all with no abnormalities), EMG (slow nerve conduction in hands feet and lower legs; demyelinisation), lumbar puncture (presence of proteins). Expert opinion: after exclusion of hematological disease, this could be CIDP
7.	NL-SA-2021SA345413, male, 70 Years and older, Other health professional	COVID-19 Vaccin Moderna Injvlst 0,5Ml Dose 1	Chronic inflammatory demyelinating polyneuropathy, coronary artery disease, coronary artery stents and a dual-chamber pacemaker for sick sinus syndrome	Chronic inflammatory demyelinating polyradiculoneuropathy; Acute inflammatory demyelinating polyradiculopathy; Muscle weakness Aggravated; Numbness in leg; Paraesthesia lower limb,	21 Days	Recovering	In 2017 after influenza vaccination GBS -> CIDP develops. Incomplete recovery after 5x plasmapheresis. On an unknown date in 2017, the relevant laboratory test included thyroid function tests, hemoglobin A1c (HbAc1), serum protein electrophoresis, syphilis and Lyme titers with result as unremarkable. 21 days after COVID vaccination in March 2021 again the same complaints. Patient had onset over twelve hours of significantly worse weakness (muscular weakness), numbness in his legs (hypoaesthesia) and paresthesia of bilateral lower extremities (paraesthesia). All these events were assessed as medically significant. The relevant laboratory data included physical examination with result as notable for normal strength in the upper extremities, with diminished but present reflexes and lower extremity exam revealed bilateral weakness in the hip, distal extremities and feet. Ankle and knee reflexes were absent. The relevant

							laboratory data included cerebrospinal fluid contained elevated protein and electromyography revealed F-waves in the lower extremities. The patient was treated with a more intensive course of plasmapheresis consisting four treatments over ten days. Patient strength and sensation improved to baseline over this period. Expert opinion: unknown whether it is a Dutch case, insufficient information to assess causality
8.	NL-LRB-00746389, male, 60-70 years, Consumer or other non health professional	COVID-19 Vaccin Moderna Injvlst 0,5Ml Dose 3 (1st two were AZ)	Chronic inflammatory demyelinating polyneuropathy	Chronic inflammatory demyelinating polyneuropathy; Condition aggravated	3 Days	Recovering	I have CIPD, and after the Moderna vaccination I had a relapse. Loss of strength in arms and legs. The complaints lasted 1.5 weeks. There is no change in diagnosis, disease or treatment. During the complaints period he received the regular IVIG treatment, which may have contributed to recovery. Expert opinion: insufficient data to assess causality
9.	NL-LRB-00806928, male, 70 Years and older, Consumer or other non health professional	COVID-19 Vaccin Janssen Injvlst 0,5Ml Dose 1	Edoxaban Tablet 60Mg, Metoprolol Tablet 50Mg, Amlodipine Tablet 5Mg, Simvastatine Tablet Fo 20Mg	Chronic inflammatory demyelinating polyneuropathy; Guillain Barre syndrome	23 Days	Recovering, Recovering	Guillain barre, turned into CIDP General paralysis occurred. Progressive sensory and motor deficit in GBS, treatment with IVIG but 1st line physiotherapy treatment. 5 months after start treatment diagnosis of CIDP is made After 2 months: Patient is recovering, can do things again. There has been no change of diagnosis or disease, still the same 4-week treatment schedule with IVIG. Lareb opinion: causality is possible due to long course of disease
10.	NL-LRB-00703048, male, 30-40, Consumer	COVID-19 vaccin Janssen, dose 1	No medical history / concomitant medication	Chronic inflammatory demyelinating polyneuropathy; Guillain Barre syndrome	24 Days	Not recovered	First diagnosed as GBS, later changed to CIDP Complaints started with muscle paralysis in the face, painful tingling in limbs, double vision and severe muscle pain. Complaints initially decreased. First conclusion neurology: image appropriate to immune-mediated polyradiculoneuropathy D.D idiopathic Guillain Barre syndrome. Six months later: diagnosed with CIDP. This was established after an epidural and an extensive EMG. IVIG for the first time. Symptoms have also gotten a bit worse. I walk more difficult and have severely reduced muscle strength in my legs. In addition, there have been research performed in which was shown that the nerves in my arms are also affected, not had any trouble with this so far was experienced. Lareb opinion: possible causality due to new onset CIDP (initial diagnosis GBS), supported by EMG/spinal puncture
11.	NL-JNJFOC-20220908718, male, 30-40,	COVID-19 vaccin Janssen, dose 1	No medical history / concomitant medication	Chronic inflammatory demyelinating polyneuropathy, Guillain Barre syndrome, Vaccination failure, COVID 19	3 weeks	Unknown	About 3 weeks later of vaccine administration, patient started to suffer from various complaints. Patient saw double, facial muscles were weakened, limbs were tingling and had severe muscle pain. After neurological examination, GBS was diagnosed. Patient went to the neurologist (physician office visit) again because patient was deteriorating. After another neurological examination, patient

							was diagnosed with CIDP. Patient was on further treatment with intravenous immunoglobulin therapy. Patient's life had been greatly affected by illness. Patient was less strong and mobile than before and this also had an impact mentally. Patient took three electromyogram test for which result was not reported, and lumbar puncture (result not reported). Lareb/MAH opinion: The event has a compatible/suggestive temporal relationship, is unlabeled, and has unknown scientific plausibility. There is no information on any other factors potentially associated with the event(s). Therefore, this event(s) is considered un-assessable.
12.	NL-MODERNATX, INC.-MOD-2022-670532, female, 50-60, Consumer	COVID-19 Vaccin Moderna Injvlst 0,5Ml Dose 2	Chronic inflammatory demyelinating polyneuropathy	Chronic inflammatory demyelinating polyneuropathy, pneumonia, condition aggravated	3-7 days	Recovering	This is a literature non-study case concerning a 55 year-old, female patient with a history of Chronic inflammatory demyelinating polyradiculoneuropathy with fluctuating course of the disease without any maintenance treatment Patient reported the worsening of CIDP with the following symptoms: weakness of legs, sensory symptoms, fatigue, and muscle aches Expert opinion: The fluctuating course of disease might be another possible cause.

Appendix B:

Risk period / TTO 14 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
PFIZER - dose 1										
Male 0-19	0	552082	2	1327124	0,03	0,00				
Male 20-29	0	559248	6	662716	0,19	0,00				
Male 30-39	1	640358	10	713006	0,34	**2,90**				
Male 40-49	0	634057	7	856751	0,20	0,00				
Male 50-59	0	771953	8	837899	0,28	0,00				
Male 60-69	1	440043	18	682041	0,45	**2,24**				
Male 70-79	0	729404	21	384552	1,53	0,00				
Male 80+	0	328142	6	124569	0,61	0,00				
Male all age	**2**	**4655287**	**78**	**5588658**	**3,63**	**0,55**	**0,55**	**0,07**	**1,99**	*
Female 0-19	0	552082	5	1304761	0,08	0,00				
Female 20-29	2	559248	4	715268	0,12	**16,67**				
Female 30-39	0	640358	4	770452	0,13	0,00				
Female 40-49	0	634057	9	882174	0,25	0,00				
Female 50-59	1	771953	16	850091	0,56	**1,79**				
Female 60-69	0	440043	17	708276	0,41	0,00				
Female 70-79	0	729404	10	457900	0,61	0,00				
Female 80+	1	328142	5	213046	0,30	**3,39**				
Female all age	**4**	**4655287**	**70**	**5901968**	**2,45**	**1,64**	**1,64**	**0,45**	**4,19**	*
Male/ female al	**6**	**9310574**	**148**	**11490626**	**4,60**	**1,30**	**1,30**	**0,48**	**2,84**	*
PFIZER - dose 2										
Male 0-19	0	466103	2	1327124	0,03	0,00				
Male 20-29	0	488118	6	662716	0,17	0,00				
Male 30-39	4	585590	10	713006	0,32	**12,70**				
Male 40-49	0	587130	7	856751	0,18	0,00				
Male 50-59	1	723595	8	837899	0,26	**3,77**				
Male 60-69	0	435714	18	682041	0,44	0,00				
Male 70-79	1	713236	21	384552	1,49	0,67				
Male 80+	0	321325	6	124569	0,59	0,00				
Male all age	**6**	**4320811**	**78**	**5588658**	**3,49**	**1,72**	**1,72**	**0,63**	**3,74**	*
Female 0-19	0	451154	5	1304761	0,07	0,00				
Female 20-29	0	511244	4	715268	0,11	0,00				
Female 30-39	0	577263	4	770452	0,11	0,00				
Female 40-49	0	588013	9	882174	0,23	0,00				
Female 50-59	2	707212	16	850091	0,51	**3,92**				
Female 60-69	0	487589	17	708276	0,45	0,00				
Female 70-79	1	760902	10	457900	0,64	1,57				
Female 80+	1	461552	5	213046	0,42	2,41				
Female all age	**4**	**4544929**	**70**	**5901968**	**2,53**	**1,58**	**1,58**	**0,43**	**4,04**	*
Male/ female al	**10**	**8865740**	**148**	**11490626**	**4,38**	**2,28**	**2,28**	**1,10**	**4,20**	*
PFIZER - dose 3										
Male 0-19	0	81098	2	1327124	0,00	0				
Male 20-29	0	407402	6	662716	0,14	0				
Male 30-39	0	464646	10	713006	0,25	0				
Male 40-49	0	361976	7	856751	0,11	0				
Male 50-59	0	255798	8	837899	0,09	0				
Male 60-69	0	210440	18	682041	0,21	0				
Male 70-79	0	155497	21	384552	0,33	0				
Male 80+	0	114884	6	124569	0,21	0				
Male all age	**0**	**2051741**	**78**	**5588658**	**1,35**	**0**	**0**	**0,74**	**0,74**	*
Female 0-19	0	87453	5	1304761	0,01	0,00				
Female 20-29	1	435116	4	715268	0,09	**10,71**				
Female 30-39	0	476113	4	770452	0,09	0,00				
Female 40-49	0	405583	9	882174	0,16	0,00				
Female 50-59	0	331559	16	850091	0,24	0,00				
Female 60-69	0	243743	17	708276	0,22	0,00				
Female 70-79	0	174925	10	457900	0,15	0,00				
Female 80+	0	193653	5	213046	0,17	0,00				
Female all age	**1**	**2348145**	**70**	**5901968**	**1,14**	**0,87**	**0,87**	**0,02**	**4,87**	*
Male/ female al	**1**	**4399886**	**148**	**11490626**	**2,17**	**0,46**	**0,46**	**0,01**	**2,56**	*
PFIZER - dose 1-2-3										
MALE	8	11027839	78	5588658	5,90	1,36	**1,36**	**0,58**	**2,67**	*
FEMALE	9	11548361	70	5901968	5,25	1,71	**1,71**	**0,78**	**3,25**	*
ALL	17	22576200	148	11490626	11,15	1,52	**1,52**	**0,87**	**2,35**	*

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Risk period / TTO 42 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp (# O > E=0)	SMR	95% CI SMR (* O<10 with poisson table)		
PFIZER - dose 1										
Male 0-19	0	552082	2	1327124	0,10	0,00				
Male 20-29	0	559248	6	662716	0,58	0,00				
Male 30-39	1	640358	10	713006	1,03	0,97				
Male 40-49	1	634057	7	856751	0,60	**1,68**				
Male 50-59	1	771953	8	837899	0,85	**1,18**				
Male 60-69	1	440043	18	682041	1,34	0,75				
Male 70-79	1	729404	21	384552	4,58	0,22				
Male 80+	0	328142	6	124569	1,82	0,00				
Male all age	**5**	**4655287**	**78**	**5588658**	**10,89**	**0,46**	**0,46**	**0,15**	**1,07**	*
Female 0-19	0	552082	5	1304761	0,24	0,00				
Female 20-29	2	559248	4	715268	0,36	**5,56**				
Female 30-39	0	640358	4	770452	0,38	0,00				
Female 40-49	0	634057	9	882174	0,74	0,00				
Female 50-59	1	771953	16	850091	1,67	0,60				
Female 60-69	1	440043	17	708276	1,22	0,82				
Female 70-79	1	729404	10	457900	1,83	0,55				
Female 80+	1	328142	5	213046	0,89	**1,13**				
Female all age	**6**	**4655287**	**70**	**5901968**	**6,35**	**0,94**	**0,94**	**0,35**	**2,06**	*
Male/ female al	**11**	**9310574**	**148**	**11490626**	**13,80**	**0,80**	**0,80**	**0,39**	**1,35**	
PFIZER - dose 2										
Male 0-19	0	466103	2	1327124	0,08	0,00				
Male 20-29	0	488118	6	662716	0,51	0,00				
Male 30-39	5	585590	10	713006	0,95	**5,29**				
Male 40-49	0	587130	7	856751	0,55	0,00				
Male 50-59	2	723595	8	837899	0,79	**2,52**				
Male 60-69	0	435714	18	682041	1,32	0,00				
Male 70-79	2	713236	21	384552	4,48	0,45				
Male 80+	0	321325	6	124569	1,78	0,00				
Male all age	**9**	**4320811**	**78**	**5588658**	**6,94**	**1,30**	**1,30**	**0,59**	**2,46**	*
Female 0-19	0	451154	5	1304761	0,20	0,00				
Female 20-29	0	511244	4	715268	0,33	0,00				
Female 30-39	0	577263	4	770452	0,34	0,00				
Female 40-49	0	588013	9	882174	0,69	0,00				
Female 50-59	2	707212	16	850091	1,53	**1,31**				
Female 60-69	1	487589	17	708276	1,35	0,74				
Female 70-79	1	760902	10	457900	1,91	0,52				
Female 80+	1	461552	5	213046	1,25	0,80				
Female all age	**5**	**4544929**	**70**	**5901968**	**6,20**	**0,81**	**0,81**	**0,26**	**1,88**	*
Male/ female al	**14**	**8865740**	**148**	**11490626**	**13,14**	**1,07**	**1,07**	**0,57**	**1,71**	
PFIZER - dose 3										
Male 0-19	0	81098	2	1327124	0,01	0,00				
Male 20-29	0	407402	6	662716	0,42	0,00				
Male 30-39	0	464646	10	713006	0,75	0,00				
Male 40-49	0	361976	7	856751	0,34	0,00				
Male 50-59	0	255798	8	837899	0,28	0,00				
Male 60-69	0	210440	18	682041	0,64	0,00				
Male 70-79	0	155497	21	384552	0,98	0,00				
Male 80+	0	114884	6	124569	0,64	0,00				
Male all age	**0**	**2051741**	**78**	**5588658**	**3,30**	**0,00**	**0,00**	**0,30**	**0,30**	*
Female 0-19	0	87453	5	1304761	0,04	0,00				
Female 20-29	1	435116	4	715268	0,28	3,57				
Female 30-39	0	476113	4	770452	0,28	0,00				
Female 40-49	0	405583	9	882174	0,48	0,00				
Female 50-59	1	331559	16	850091	0,72	1,39				
Female 60-69	0	243743	17	708276	0,67	0,00				
Female 70-79	0	174925	10	457900	0,44	0,00				
Female 80+	1	193653	5	213046	0,52	1,91				
Female all age	**3**	**2348145**	**70**	**5901968**	**3,20**	**0,94**	**0,94**	**0,19**	**2,74**	*
Male/ female al	**3**	**4399886**	**148**	**11490626**	**6,52**	**0,46**	**0,46**	**0,10**	**1,34**	*
PFIZER - dose 1-2-3										
MALE	14	11027839	78	5588658	17,71	0,79	**0,79**	**0,42**	**1,27**	
FEMALE	14	11548361	70	5901968	15,76	0,89	**0,89**	**0,48**	**1,43**	
ALL	28	22576200	148	11490626	33,46	0,84	**0,84**	**0,55**	**1,18**	

Risk period / TTO 14 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
MODERNA - dose 1										
Male 0-19	0	11934	2	1327124	0,00069	0				
Male 20-29	0	70138	6	662716	0,024356	0				
Male 30-39	0	76000	10	713006	0,040884	0				
Male 40-49	0	122638	7	856751	0,038433	0				
Male 50-59	0	153155	8	837899	0,056087	0				
Male 60-69	0	29318	18	682041	0,029678	0				
Male 70-79	0	15800	21	384552	0,033095	0				
Male 80+	0	5370	6	124569	0,009921	0				
Male all age	**0**	**484353**	**78**	**5588658**	**0,233144**	**0**	**0,00**			
Female 0-19	0	12185	5	1304761	0,001791	0				
Female 20-29	0	78661	4	715268	0,016873	0				
Female 30-39	0	84513	4	770452	0,01683	0				
Female 40-49	0	126547	9	882174	0,049519	0				
Female 50-59	1	142131	16	850091	0,102607	9,75				
Female 60-69	0	25970	17	708276	0,023909	0,00				
Female 70-79	0	13500	10	457900	0,011308	0,00				
Female 80+	0	14358	5	213046	0,012925	0,00				
Female all age	**1**	**497865**	**70**	**5901968**	**0,235762**	**4,24**	**4,24**	**0,11**	**23,63**	*
Male/ female al	1	982218	148	11490626	0,49	2,06	**2,06**	**0,05**	**11,48**	*
MODERNA - dose 2										
Male 0-19	0	10097	2	1327124	0,00	0,00				
Male 20-29	0	61686	6	662716	0,02	0,00				
Male 30-39	0	69987	10	713006	0,04	0,00				
Male 40-49	0	114841	7	856751	0,04	0,00				
Male 50-59	0	143985	8	837899	0,05	0,00				
Male 60-69	0	27717	18	682041	0,03	0,00				
Male 70-79	0	15066	21	384552	0,03	0,00				
Male 80+	0	4827	6	124569	0,01	0,00				
Male all age	**0**	**448206**	**78**	**5588658**	**0,22**	**0,00**	**0,00**			
Female 0-19	0	10545	5	1304761	0,00	0,00				
Female 20-29	0	70777	4	715268	0,02	0,00				
Female 30-39	0	77806	4	770452	0,02	0,00				
Female 40-49	1	117723	9	882174	0,05	**21,71**				
Female 50-59	0	133463	16	850091	0,10	0,00				
Female 60-69	0	24451	17	708276	0,02	0,00				
Female 70-79	0	12739	10	457900	0,01	0,00				
Female 80+	0	12901	5	213046	0,01	0,00				
Female all age	**1**	**460405**	**70**	**5901968**	**0,22**	**4,56**	**4,56**	**0,11**	**25,38**	*
Male/ female al	1	908611	148	11490626	0,45	2,23	**2,23**	**0,06**	**12,41**	*
MODERNA - dose 3										
Male 0-19	0	151	2	1327124	0,00	0				
Male 20-29	0	805	6	662716	0,00	0				
Male 30-39	0	1208	10	713006	0,00	0				
Male 40-49	0	210162	7	856751	0,07	0				
Male 50-59	0	601915	8	837899	0,22	0				
Male 60-69	0	649045	18	682041	0,66	0				
Male 70-79	0	535009	21	384552	1,12	0				
Male 80+	0	179998	6	124569	0,33	0				
Male all age	**0**	**2178142**	**78**	**5588658**	**2,40**	**0**	**0,00**			
Female 0-19	0	185	5	1304761	0,00	0				
Female 20-29	0	789	4	715268	0,00	0				
Female 30-39	0	1103	4	770452	0,00	0				
Female 40-49	0	193495	9	882174	0,08	0				
Female 50-59	0	529095	16	850091	0,38	0				
Female 60-69	0	618205	17	708276	0,57	0				
Female 70-79	0	558610	10	457900	0,47	0				
Female 80+	0	239265	5	213046	0,22	0				
Female all age	**0**	**2140747**	**70**	**5901968**	**1,71**	**0**	**0,00**			
Male/ female al	0	4318889	148	11490626	2,13	0,00	**0,00**	**0,00**	**1,73**	
MODERNA - dose 1-2-3										
MALE	0	3110701	78	5588658	1,67	0,00				
FEMALE	2	3099017	70	5901968	1,41	1,42	**1,42**	**0,17**	**5,12**	*
ALL	2	6209718	148	11490626	3,07	0,65	**0,65**	**0,08**	**2,35**	*

Risk period / TTO 42 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
MODERNA - dose 1										
Male 0-19	0	11934	2	1327124	0,00	0,00				
Male 20-29	0	70138	6	662716	0,07	0,00				
Male 30-39	0	76000	10	713006	0,12	0,00				
Male 40-49	0	122638	7	856751	0,12	0,00				
Male 50-59	1	153155	8	837899	0,17	5,94				
Male 60-69	0	29318	18	682041	0,09	0,00				
Male 70-79	0	15800	21	384552	0,10	0,00				
Male 80+	1	5370	6	124569	0,03	33,60				
Male all age	**2**	**484353**	**78**	**5588658**	**0,70**	**2,86**	**2,86**	**0,34**	**10,32**	*
Female 0-19	0	12185	5	1304761	0,01	0,00				
Female 20-29	0	78661	4	715268	0,05	0,00				
Female 30-39	0	84513	4	770452	0,05	0,00				
Female 40-49	0	126547	9	882174	0,15	0,00				
Female 50-59	1	142131	16	850091	0,31	**3,25**				
Female 60-69	0	25970	17	708276	0,07	0,00				
Female 70-79	0	13500	10	457900	0,03	0,00				
Female 80+	0	14358	5	213046	0,04	0,00				
Female all age	**1**	**497865**	**70**	**5901968**	**0,71**	**1,41**	**1,41**	**0,04**	**7,88**	*
Male/ female al	**3**	**982218**	**148**	**11490626**	**1,46**	**2,06**	**2,06**	**0,43**	**6,02**	*
MODERNA - dose 2										
Male 0-19	0	10097	2	1327124	0,00	0,00				
Male 20-29	0	61686	6	662716	0,06	0,00				
Male 30-39	0	69987	10	713006	0,11	0,00				
Male 40-49	1	114841	7	856751	0,11	**9,26**				
Male 50-59	1	143985	8	837899	0,16	**6,32**				
Male 60-69	0	27717	18	682041	0,08	0,00				
Male 70-79	0	15066	21	384552	0,09	0,00				
Male 80+	0	4827	6	124569	0,03	0,00				
Male all age	**2**	**448206**	**78**	**5588658**	**0,65**	**3,07**	**3,07**	**0,37**	**11,10**	*
Female 0-19	0	10545	5	1304761	0,00	0,00				
Female 20-29	0	70777	4	715268	0,05	0,00				
Female 30-39	0	77806	4	770452	0,05	0,00				
Female 40-49	1	117723	9	882174	0,14	7,24				
Female 50-59	0	133463	16	850091	0,29	0,00				
Female 60-69	0	24451	17	708276	0,07	0,00				
Female 70-79	0	12739	10	457900	0,03	0,00				
Female 80+	0	12901	5	213046	0,03	0,00				
Female all age	**1**	**460405**	**70**	**5901968**	**0,66**	**1,52**	**1,52**	**0,04**	**8,46**	*
Male/ female al	**3**	**908611**	**148**	**11490626**	**1,35**	**2,23**	**2,23**	**0,46**	**6,51**	*
MODERNA - dose 3										
Male 0-19	0	151	2	1327124	0,00	0				
Male 20-29	0	805	6	662716	0,00	0				
Male 30-39	0	1208	10	713006	0,00	0				
Male 40-49	0	210162	7	856751	0,20	0				
Male 50-59	0	601915	8	837899	0,66	0				
Male 60-69	0	649045	18	682041	1,97	0				
Male 70-79	0	535009	21	384552	3,36	0				
Male 80+	0	179998	6	124569	1,00	0				
Male all age	**0**	**2178142**	**78**	**5588658**	**3,50**	**0**	**0**			
Female 0-19	0	185	5	1304761	0,00	0				
Female 20-29	0	789	4	715268	0,00	0				
Female 30-39	0	1103	4	770452	0,00	0				
Female 40-49	0	193495	9	882174	0,23	0				
Female 50-59	0	529095	16	850091	1,15	0				
Female 60-69	0	618205	17	708276	1,71	0				
Female 70-79	0	558610	10	457900	1,40	0				
Female 80+	0	239265	5	213046	0,65	0				
Female all age	**0**	**2140747**	**70**	**5901968**	**2,92**	**0**	**0**			
Male/ female al	**0**	**4318889**	**148**	**11490626**	**6,40**	**0**	**0**			
MODERNA - dose 1-2-3										
MALE	4	3110701	78	5588658	5,00	0,80	**0,80**	**0,22**	**2,05**	*
FEMALE	2	3099017	70	5901968	4,23	0,47	**0,47**	**0,06**	**1,71**	*
ALL	6	6209718	148	11490626	9,20	0,65	**0,65**	**0,24**	**1,42**	*

Risk period / TTO 14 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
ASTRAZENECA - dose 1										
Male 0-19	0	1286	2	1327124	0,00	0,00				
Male 20-29	0	12484	6	662716	0,01	0,00				
Male 30-39	0	14369	10	713006	0,01	0,00				
Male 40-49	0	18654	7	856751	0,01	0,00				
Male 50-59	0	30601	8	837899	0,02	0,00				
Male 60-69	5	513854	18	682041	0,72	**6,98**				
Male 70-79	0	11678	21	384552	0,03	0,00				
Male 80+	0	7695	6	124569	0,02	0,00				
Male all age	**5**	**610621**	**78**	**5588658**	**0,81**	**6,17**	**6,17**	**2,00**	**14,41**	*
Female 0-19	0	3263	5	1304761	0,00	0,00				
Female 20-29	0	33835	4	715268	0,01	0,00				
Female 30-39	0	34458	4	770452	0,01	0,00				
Female 40-49	1	47604	9	882174	0,02	**53,68**				
Female 50-59	1	78647	16	850091	0,06	**17,61**				
Female 60-69	5	466156	17	708276	0,43	**11,65**				
Female 70-79	0	10721	10	457900	0,01	0,00				
Female 80+	0	14652	5	213046	0,01	0,00				
Female all age	**7**	**689336**	**70**	**5901968**	**0,54**	**12,93**	**12,93**	**5,19**	**26,64**	*
Male/ female al	**12**	**1299957**	**148**	**11490626**	**0,64**	**18,69**	**18,69**	**9,45**	**31,03**	
ASTRAZENECA - dose 2										
Male 0-19	0	1154	2	1327124	0,00	0,00				
Male 20-29	0	11348	6	662716	0,01	0,00				
Male 30-39	0	13221	10	713006	0,01	0,00				
Male 40-49	0	17294	7	856751	0,01	0,00				
Male 50-59	0	28520	8	837899	0,01	0,00				
Male 60-69	1	479719	18	682041	0,67	**1,50**				
Male 70-79	0	10733	21	384552	0,03	0,00				
Male 80+	0	6570	6	124569	0,02	0,00				
Male all age	**1**	**568559**	**78**	**5588658**	**0,75**	**1,33**	**1,33**	**0,03**	**7,39**	*
Female 0-19	0	3022	5	1304761	0,00	0,00				
Female 20-29	0	31103	4	715268	0,01	0,00				
Female 30-39	0	31412	4	770452	0,01	0,00				
Female 40-49	0	43711	9	882174	0,02	0,00				
Female 50-59	0	72869	16	850091	0,05	0,00				
Female 60-69	0	434585	17	708276	0,40	0,00				
Female 70-79	0	9825	10	457900	0,01	0,00				
Female 80+	0	12638	5	213046	0,01	0,00				
Female all age	**0**	**639165**	**70**	**5901968**	**0,50**	**0,00**	**0**			
Male/ female al	1	1207724	148	11490626	0,60	1,68	**1,68**	**0,04**	**9,34**	*
ASTRAZENECA - dose 1-2										
MALE	6	1179180	78	5588658	0,63	9,50	**9,50**	**3,49**	**20,69**	*
FEMALE	7	1328501	70	5901968	0,60	11,58	**11,58**	**4,65**	**23,86**	*
ALL	13	2507681	148	11490626	1,24	10,49	**10,49**	**5,48**	**17,12**	

Risk period / TTO 42 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp (# O > E=0)	SMR	95% CI SMR (* O<10 with poisson table)		
ASTRAZENECA - dose 1										
Male 0-19	0	1286	2	1327124	0,00	0,00				
Male 20-29	0	12484	6	662716	0,01	0,00				
Male 30-39	0	14369	10	713006	0,02	0,00				
Male 40-49	0	18654	7	856751	0,02	0,00				
Male 50-59	0	30601	8	837899	0,03	0,00				
Male 60-69	6	513854	18	682041	1,56	3,84				
Male 70-79	0	11678	21	384552	0,07	0,00				
Male 80+	0	7695	6	124569	0,04	0,00				
Male all age	**6**	**610621**	**78**	**5588658**	**1,76**	**3,40**	**3,40**	**1,25**	**7,40**	*
Female 0-19	0	3263	5	1304761	0,00	0,00				
Female 20-29	0	33835	4	715268	0,02	0,00				
Female 30-39	0	34458	4	770452	0,02	0,00				
Female 40-49	1	47604	9	882174	0,06	**17,89**				
Female 50-59	1	78647	16	850091	0,17	**5,87**				
Female 60-69	6	466156	17	708276	1,29	**4,66**				
Female 70-79	0	10721	10	457900	0,03	0,00				
Female 80+	0	14652	5	213046	0,04	0,00				
Female all age	**8**	**689336**	**70**	**5901968**	**1,62**	**4,93**	**4,93**	**2,12**	**9,70**	*
Male/ female al	**14**	**723171**	**148**	**11490626**	**1,07**	**13,06**	**13,06**	**7,01**	**20,98**	
ASTRAZENECA - dose 2										
Male 0-19	0	1154	2	1327124	0,00	0,00				
Male 20-29	0	11348	6	662716	0,01	0,00				
Male 30-39	0	13221	10	713006	0,02	0,00				
Male 40-49	0	17294	7	856751	0,02	0,00				
Male 50-59	0	28520	8	837899	0,03	0,00				
Male 60-69	1	479719	18	682041	1,46	0,69				
Male 70-79	0	10733	21	384552	0,07	0,00				
Male 80+	0	6570	6	124569	0,04	0,00				
Male all age	**1**	**568559**	**78**	**5588658**	**1,64**	**0,61**	**0,61**	**0,02**	**3,39**	*
Female 0-19	0	3022	5	1304761	0,00	0,00				
Female 20-29	0	31103	4	715268	0,02	0,00				
Female 30-39	0	31412	4	770452	0,02	0,00				
Female 40-49	0	43711	9	882174	0,05	0,00				
Female 50-59	0	72869	16	850091	0,16	0,00				
Female 60-69	0	434585	17	708276	1,20	0,00				
Female 70-79	0	9825	10	457900	0,02	0,00				
Female 80+	0	12638	5	213046	0,03	0,00				
Female all age	**0**	**639165**	**70**	**5901968**	**1,51**	**0,00**	**0**			
Male/ female al	**1**	**1207724**	**148**	**11490626**	**1,79**	**0,56**	**0,56**	0,01	3,11	*
ASTRAZENECA - dose 1-2										
MALE	7	1179180	78	5588658	1,89	3,70	**3,70**	**1,48**	**7,61**	*
FEMALE	8	1328501	70	5901968	1,81	4,41	**4,41**	**1,90**	**8,69**	*
ALL	15	2507681	148	11490626	3,72	4,04	**4,04**	**2,22**	**6,39**	

Risk period / TTO 14 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
JANSSEN - dose 1										
Male 0-19	0	25024	2	1327124	0,00	0,00				
Male 20-29	0	138147	6	662716	0,07	0,00				
Male 30-39	0	55588	10	713006	0,04	0,00				
Male 40-49	1	61032	7	856751	0,03	**37,96**				
Male 50-59	4	139064	8	837899	0,07	**57,02**				
Male 60-69	0	5669	18	682041	0,01	0,00				
Male 70-79	0	1574	21	384552	0,00	0,00				
Male 80+	0	425	6	124569	0,00	0,00				
Man all age	**5**	**426523**	**78**	**5588658**	**0,22**	**22,80**	**22,80**	**7,39**	**53,22**	*
Female 0-19	0	16241	5	1304761	0,00	0,00				
Female 20-29	0	83246	4	715268	0,02	0,00				
Female 30-39	0	40719	4	770452	0,01	0,00				
Female 40-49	0	52584	9	882174	0,02	0,00				
Female 50-59	2	114874	16	850091	0,08	**24,12**				
Female 60-69	0	5251	17	708276	0,00	0,00				
Female 70-79	0	1157	10	457900	0,00	0,00				
Female 80+	0	412	5	213046	0,00	0,00				
Female all age	**2**	**314484**	**70**	**5901968**	**0,14**	**14,49**	**14,49**	**1,74**	**52,31**	*
Male/ female al	**7**	**741007**	**148**	**11490626**	**0,37**	**19,12**	**19,12**	**7,68**	**39,39**	*
JANSSEN - dose 2										
Male 0-19	0	24	2	1327124	0,00	0,00				
Male 20-29	0	176	6	662716	0,00	0,00				
Male 30-39	0	137	10	713006	0,00	0,00				
Male 40-49	0	96	7	856751	0,00	0,00				
Male 50-59	0	142	8	837899	0,00	0,00				
Male 60-69	0	99	18	682041	0,00	0,00				
Male 70-79	0	20	21	384552	0,00	0,00				
Male 80+	0	1	6	124569	0,00	0,00				
Man all age	**0**	**695**	**78**	**5588658**	**0,00**	**0,00**				
Female 0-19	0	19	5	1304761	0,00	0,00				
Female 20-29	0	88	4	715268	0,00	0,00				
Female 30-39	0	75	4	770452	0,00	0,00				
Female 40-49	0	66	9	882174	0,00	0,00				
Female 50-59	0	105	16	850091	0,00	0,00				
Female 60-69	0	54	17	708276	0,00	0,00				
Female 70-79	0	23	10	457900	0,00	0,00				
Female 80+	0	2	5	213046	0,00	0,00				
Female all age	**0**	**432**	**70**	**5901968**	**0,00**	**0,00**				
Male/ female al	**0**	**1127**	**148**	**11490626**	**0,00**	**0,00**				
JANSSEN - dose 1-2										
MALE	5	427218	78	5588658	0,23	21,86	**21,86**	**7,08**	**51,03**	*
FEMALE	2	314916	70	5901968	0,14	13,96	**13,96**	**1,68**	**50,40**	*
ALL	7	742134	148	11490626	0,37	19,09	**19,09**	**7,66**	**39,33**	*

Risk period / TTO 42 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
JANSSEN - dose 1										
Male 0-19	0	25024	2	1327124	0,00	0,00				
Male 20-29	0	138147	6	662716	0,14	0,00				
Male 30-39	0	55588	10	713006	0,09	0,00				
Male 40-49	3	61032	7	856751	0,06	**52,28**				
Male 50-59	7	139064	8	837899	0,15	**45,82**				
Male 60-69	0	5669	18	682041	0,02	0,00				
Male 70-79	1	1574	21	384552	0,01	**101,11**				
Male 80+	0	425	6	124569	0,00	0,00				
Man all age	**11**	**426523**	**78**	**5588658**	**0,48**	**23,03**	**23,03**	**11,24**	**39,01**	
Female 0-19	0	16241	5	1304761	0,01	0,00				
Female 20-29	0	83246	4	715268	0,05	0,00				
Female 30-39	1	40719	4	770452	0,02	**41,11**				
Female 40-49	0	52584	9	882174	0,06	0,00				
Female 50-59	2	114874	16	850091	0,25	**8,04**				
Female 60-69	0	5251	17	708276	0,01	0,00				
Female 70-79	0	1157	10	457900	0,00	0,00				
Female 80+	0	412	5	213046	0,00	0,00				
Female all age	**3**	**314484**	**70**	**5901968**	**0,41**	**7,24**	**7,24**	**1,50**	**21,18**	*
Male/ female al	**14**	**741007**	**148**	**11490626**	**1,10**	**12,75**	**12,75**	**6,84**	**20,47**	
JANSSEN - dose 2										
Male 0-19	0	24	2	1327124	0,00	0				
Male 20-29	0	176	6	662716	0,00	0				
Male 30-39	0	137	10	713006	0,00	0				
Male 40-49	0	96	7	856751	0,00	0				
Male 50-59	0	142	8	837899	0,00	0				
Male 60-69	0	99	18	682041	0,00	0				
Male 70-79	0	20	21	384552	0,00	0				
Male 80+	0	1	6	124569	0,00	0				
Man all age	**0**	**695**	**78**	**5588658**	**0,00**	**0**				
Female 0-19	0	19	5	1304761	0,00	0				
Female 20-29	0	88	4	715268	0,00	0				
Female 30-39	0	75	4	770452	0,00	0				
Female 40-49	0	66	9	882174	0,00	0				
Female 50-59	0	105	16	850091	0,00	0				
Female 60-69	0	54	17	708276	0,00	0				
Female 70-79	0	23	10	457900	0,00	0				
Female 80+	0	2	5	213046	0,00	0				
Female all age	**0**	**432**	**70**	**5901968**	**0,00**	**0**				
Male/ female al	**0**	**1127**	**148**	**11490626**	**0,00**	**0**				
JANSSEN - dose 1-2										
MALE	11	427218	78	5588658	0,69	16,03	16,03	**7,82**	**27,16**	
FEMALE	3	314916	70	5901968	0,43	6,98	6,98	**1,44**	**20,41**	*
ALL	14	742134	148	11490626	1,10	12,73	12,73	**6,83**	**20,44**	

Risk period / TTO 14 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
mRNA - dose 1										
MALE	2	5139640	78	5588658	2,75	0,73	0,73	0,09	2,62	*
FEMALE	5	5153152	70	5901968	2,34	2,13	2,13	0,69	4,98	*
ALL	7	10292792	148	11490626	5,08	1,38	1,38	0,55	2,84	*
mRNA - dose 2										
MALE	6	4769017	78	5588658	2,55	2,35	2,35	0,86	5,12	*
FEMALE	5	5005334	70	5901968	2,28	2,20	2,20	0,71	5,13	*
ALL	11	9774351	148	11490626	4,83	2,28	2,28	1,11	3,86	
mRNA - dose 3										
MALE	0	4229883	78	5588658	2,26	0,00	0,00	0,00	1,63	*
FEMALE	1	4488892	70	5901968	2,04	0,49	0,49	0,01	2,73	*
ALL	1	8718775	148	11490626	4,31	0,23	0,23	0,01	1,29	*
mRNA vaccines - dose 1-2-3										
MALE	8	14138540	78	5588658	7,57	1,06	1,06	0,46	2,08	*
FEMALE	11	14647378	70	5901968	6,66	1,65	1,65	0,81	2,80	
ALL	19	28785918	148	11490626	14,22	1,34	1,34	0,79	2,02	
VECTOR - dose 1										
MALE	10	1037144	78	5588658	0,56	18,01	18,01	8,65	33,12	*
FEMALE	9	1003820	70	5901968	0,46	19,71	19,71	9,02	37,40	*
ALL	19	2040964	148	11490626	1,01	18,84	18,84	11,19	28,48	
VECTOR - dose 2										
MALE	1	569254	78	5588658	0,30	3,28	3,28	0,08	18,28	*
FEMALE	0	639597	70	5901968	0,29	0,00	0,00	0,00	12,68	*
ALL	1	1208851	148	11490626	0,60	1,67	1,67	0,04	9,33	*
Vector vaccines - dose 1-2										
MALE	11	1606398	78	5588658	0,86	12,79	12,79	6,24	21,67	
FEMALE	9	1643417	70	5901968	0,75	12,04	12,04	5,51	22,85	*
ALL	20	3249815	148	11490626	1,61	12,46	12,46	7,51	18,65	

Risk period / TTO 42 days	N reports Observed	N persons vaccine exposed	N Events - 1 yr PHARMO	N pyrs PHARMO	Expected	Obs/Exp *(# O > E=0)*	SMR	95% CI SMR *(* O<10 with poisson table)*		
mRNA - dose 1										
MALE	7	5139640	78	5588658	8,25	0,85	0,85	0,34	1,75	*
FEMALE	7	5153152	70	5901968	7,03	1,00	1,00	0,40	2,05	*
ALL	14	10292792	148	11490626	15,25	0,92	0,92	0,49	1,47	
mRNA - dose 2										
MALE	11	4769017	78	5588658	7,66	1,44	1,44	0,70	2,43	
FEMALE	6	5005334	70	5901968	6,83	0,88	0,88	0,32	1,91	*
ALL	17	9774351	148	11490626	14,49	1,17	1,17	0,67	1,81	
mRNA - dose 3										
MALE	0	4229883	78	5588658	6,79	0,00	0,00	0,00	0,54	*
FEMALE	3	4488892	70	5901968	6,13	0,49	0,49	0,10	1,43	*
ALL	3	8718775	148	11490626	12,92	0,23	0,23	0,05	0,68	*
mRNA vaccines - dose 1-2-3										
MALE	18	14138540	78	5588658	22,71	0,79	0,79	0,46	1,21	
FEMALE	16	14647378	70	5901968	19,99	0,80	0,80	0,45	1,25	
ALL mRNA	34	28785918	148	11490626	42,66	0,80	0,80	0,55	1,09	
VECTOR - dose 1										
MALE	17	1037144	78	5588658	1,67	10,21	10,21	5,86	15,76	
FEMALE	11	1003820	70	5901968	1,37	8,03	8,03	3,92	13,60	
ALL	28	2040964	148	11490626	3,02	9,26	9,26	6,09	13,09	
VECTOR - dose 2										
MALE	1	569254	78	5588658	0,91	0,91	0,91	0,03	6,09	*
FEMALE	0	639597	70	5901968	0,87	0,87	0,87	0,00	4,23	*
ALL	1	1208851	148	11490626	1,79	1,79	1,79	0,01	3,11	*
Vector vaccines - dose 1-2										
MALE	18	1606398	78	5588658	2,58	6,98	6,98	4,08	10,65	
FEMALE	11	1643417	70	5901968	2,24	4,90	4,90	2,39	8,31	
ALL vector	29	3249815	148	11490626	4,82	6,02	6,02	3,99	8,46	