Data from clinical trials

The most frequently reported adverse reactions after vaccination with AstraZeneca were injection site tenderness (63.7%); injection site pain (54.2%), headache (52.6%), fatigue (53.1%); myalgia (44.0%), malaise (44.2%); pyrexia (includes feverishness [33.6%] and fever ≥38°C [7.9%]), chills (31.9%), arthralgia (26.4%) and nausea (21.9%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. By day 7 the incidence of subjects with at least one local or systemic reaction was 4% and 13% respectively. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

9.3% of subjects experienced grade 3 systemic AEs, being malaise, chills and feverishness the most frequently grade 3 solicited systemic AE reported. A single Grade 4 event was reported after the first dose in the AZD1222 group for fever (i.e., > 40°C).

Reactogenicity events were generally milder and reported less frequently in older adults (≥65 years old).

Based on the percentages provided in the SmPC of the three vaccines (see Table 1 below), there does not seem to be an overall difference in systemic reactogenicity profile, except the higher frequency of events after 2nd dose of the mRNA vaccines.

However, it is difficult to compare directly severity or grading of systemic reactogenicity between the COVID-19 vaccines. The EPAR/Overview data are all presented differently (not all with %, different age-groups etc.) and uncertainties remain whether the reactogenicity was measured in a comparable way for all vaccines.

Table 1 – Systemic reactogenicity for COMIRNATY, COVID-19 Vaccine Moderna, and COVID-19 Vaccine AstraZeneca (SmPC data)

	Pfizer/BioNtech	MODERNA	AstraZeneca
population	43.448 (21,744 vaccinated)	30,351 (15,185 vaccinated)	23,745 (12,021 vaccinated)
fatigue	>60	70	53,1
malaise			44,2
pyrexia	>10*	15.5	7,9
feverishness			33,6
chills	>30	45.4	31,9
myalgia	>30	61.5	44
arthralgia	>20	46.4	26,4
nausea	common	23	21,9
headache	>50	64.7	52,6
	*A higher frequency of pyrexia was observed after the 2nd dose	Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.	

Data from the post-marketing experience

From EudraVigilance data provided by EMA, pyrexia, chills, nausea and myalgia are also among the most frequently reported adverse events in post-marketing. Cases were mainly from UK and reported as serious non-fatal.

More particularly, post-marketing data are published for the UK by the MHRA in the Coronavirus vaccine - weekly summary of Yellow Card reporting. The summary, dated of 11.02.2021, provided exposure and reporting data for the Pfizer/BioNTech vaccine and the Oxford University/AstraZeneca vaccine. From those data (see Table 2 below), fever, chills, myalgia and nausea are reported at a higher rate for the Oxford University/AstraZeneca vaccine. However, those data should be put in the perspective of the vaccinated population (i.e. age, dose). Indeed, clinical trials for both vaccines showed that reactogenicity decreases with age. Whereas reactogenicity was described to increase at the second dose for the Pfizer/BioNTech vaccine and decrease at the second dose for the Oxford University/AstraZeneca vaccine.

Post-marketing data stratified by age (and dose) would be of interest for an appropriate interpretation. The Pfizer/BioNTech vaccine, which was available earlier, may have been mainly given to elderly compared to the Oxford University/AstraZeneca vaccine. This may explain in part the reactogenicity difference.

Table 2 – Post-marketing data in UK (last update: 11.02.2021)

	Pfizer/BioNTech vaccine [6.6 million first doses administered + ~ 0.5 million second doses administered]*		Oxford University/AstraZeneca vaccine [3 million doses administered]	
	N	**Rate (events/100,000 doses)**	**N**	**Rate (events/100,000 doses)**
Pyrexia and hyperpyrexia	3668	52	4570	152
Chills	2310	33	2971	99
Myalgia	2678	38	1983	66
Nausea	2889	41	2320	77
Rash	796	11	271	9
Headache	5506	78	5112	170
Anaphylactic reaction	116	2	28	1
Anaphylactic shock	4	<0,1	0	0,0
N Yellow cards	**20319**	**286**	**11748**	**392**

* around 0.5 million second doses, mostly the Pfizer/BioNTech vaccine, had been administered

Preliminary conclusion

Based on available data, it can be concluded that all three vaccine are reactogenic and could trigger grade 3 systemic events in a certain proportion of vaccinees (eg 9.3% after a dose of COVID-19 vaccine AstraZeneca, or 15.8% after the 2nd dose of COVID-19 vaccine Moderna).

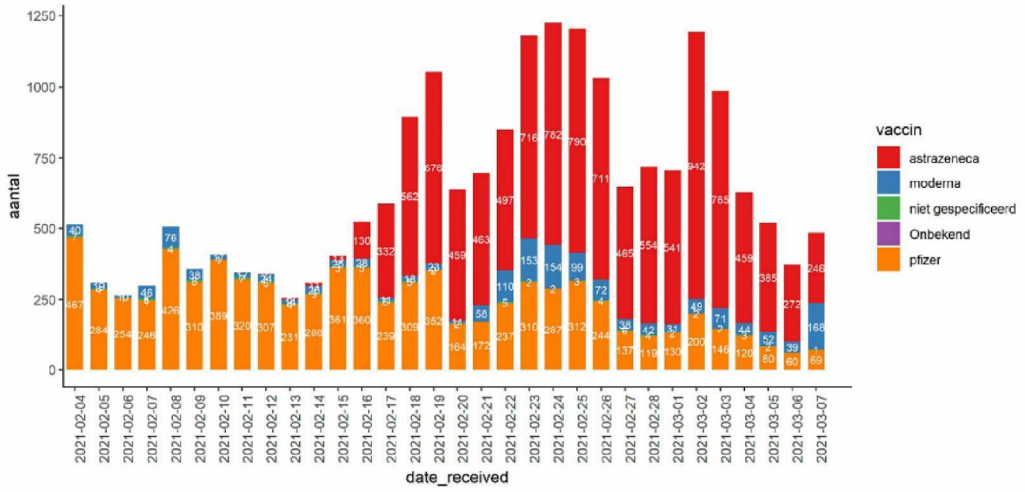
Higher reporting of flu-like syndrome after vaccination with COVID-19 vaccine AstraZeneca should be objectified in countries other than UK. For example, FR described a much higher reporting rate of flu-like syndrome (~1490 cases per 100,000 vaccinees).

Moreover, current data should be interpreted cautiously as they may also reflect different age groups of the vaccinated population, known effect of dose on the reactogenicity and a possible reporting bias (due to e.g. differences in vaccine confidence between the brands, age or profession of those who experienced the events)

Further analysis is needed to draw stronger conclusions and to evaluate if the current reporting data on flu-like syndrome constitute or not a validated signal.

Gegevens van Lareb

Figuur 1: Aantal ontvangen meldingen per dag



In Tabel 3 staat de stand van zaken tot 8/3/2021 weergegeven van de inclusie van deelnemers aan LIM (Lareb Intensive Monitoring, een cohortstudie opgezet door Lareb). Doel is om uiteindelijk voor ieder vaccin 5000 mensen te includeren. Deze mensen zullen een half jaar gevolgd worden. Duidelijk is dat veel mensen na AstraZeneca klachten hebben tov bv Comirnaty. Hierbij moet natuurlijk wel in ogenschouw worden genomen dat de leeftijdsverdeling op dit moment tussen de verschillende vaccins heel anders is.

Tabel 3: Registraties/deelnemers per vaccin

	Comirnaty	**Moderna**	**AstraZeneca**	**Onbekend**
Deelnemers				
Totaal (aantal)	2031	112	1733	26
Mannen (aantal, %)	1050 (52%)	9 (8%)	165 (10%)	13(50%)
Vrouwen (aantal, %)	981 (48%)	103 (92%)	1568 (90%)	13(50%)
12-20 jaar (aantal)	18 (1%)	0	30 (2%)	0
20-65 jaar (aantal)	583 (29%)	109 (97%)	1700 (98%)	9 (35%)
65-80 jaar (aantal)	104 (5%)	3 (3%)	1	2 (8%)
>80 jaar (aantal)	1326 (65%)	0	2	15 (58%)
Deelnemers met reactie na 1e prik (aantal)	856 (45%)	103 (92%)	1636 (97%)	11(42%)
Deelnemers met minimaal een	589 (29%)	84 (75%)	1491 (86%)	n.v.t.

reactogene bijwerking na 1e prik **(aantal)**				