Handling adverse effects reported in proximity to the vaccine against the coronavirus

12/2021-06/2022

Data updated for 31/01/2022

Manner of Collection, Processing and Evaluation of reports of adverse effects in proximity to the vaccine against the coronavirus

- The data was collected, assembled and evaluated regularly by a dedicated team from the Clinical Pharmacology and Toxicology Unit, Shamir Medical Center (Assaf Harofeh)
- The team analyzed data that was received via an online reporting form that was assimilated and entered into force in December 2021

Collection, Processing and Evaluation of the reports – work methods

Collection

- Receiving daily and cumulative reports (daily) from the "Nahlieli" system

Concentrating & Cataloguing

- Concentrating and summarizing the reports, daily, weekly and cumulatively
- Cataloguing the reports according to age groups, hospitalization/ER, free text
- Cataloguing the reports that include free text for MedDRA labeling and systemic categorization, time characteristics – Rechallenge, Onset/Duration

Presenting the data to the Epidemiology Unit

- Producing the daily report that sums the number of daily and cumulative reports. The report includes a total of Hospitalization/ER cases, adverse effects described in free text including MedDRA and systematic categories. Total reports presented as summary and by age group distribution.

2 reports were received each day:

1. Daily report – including reports from the previous day
2. Cumulative report from beginning of data collection until the reporting date.

- In order to preserve a reliable reporting database (regarding both the total number of reports and the number of reported adverse events), the reports were reviewed and empty reports (without any adverse effect) / double reports were removed.

Concentrating and cataloguing

Predetermined fields

1. Daily frequency – summary of all valid reports + number of cases of hospitalization/Emergency Room visit + reports that include free text (could include more than one adverse event per report). All the data was segmented by age group
2. Cumulative reports

Cumulative report 9.12.21-12.1.22			
	5-11 yrs	12-17 yrs	18 yrs +
Total reports	448	152	2184
Reports of severe adverse effects (Hospital/ ER)	11	2	75
Reported adverse effects (text)	35	11	377

Total reports	4568
Valid reports	2784

Daily report 12.1.22			
	5-11 yrs	12-17 yrs	18 yrs +
Total reports	10	7	268
Reports of severe adverse effects (Hospital/ ER)	0	0	0
Reported adverse effects (text)	0	0	2
Reports with reported adverse effects	1	2	16

Concentrating and cataloguing

Predetermined fields

1. Weekly frequency – summary of the 32 predetermined fields carrying cumulative data regarding reported adverse events, with segmentation by age groups

9.12.21-25.5.22 adverse events (predetermined fields) with distribution by age groups

9.12.21-25.5.22 של תופעות (שדות סגורים) עם התפלגות ע"פ קבוצות גיל

	אודם	נפיחות	פריחה מקומית	כאב באזור ההזרקה	נפיחות ביד המוזרקת	הגבלה בתנועת היד	חום מעל 38.0	כאב ראש	כאב שרירים / מפרקים	דופק מואץ	שינויים בזוסת	לחץ דם גבוה	לחץ דם נמוך	הלשה או עייפות	הקאות או בחילה	צהבת	שיעול	כאבי בטן
Sum.	801	146	167	4653	1197	2268	1110	2070	1979	485	303	111	117	3192	664	1598	465	574
5-11 yrs	61	19	14	405	61	203	183	219	104	11	4	3	1	235	112	103	79	117
12-17 yrs	42	15	6	241	55	151	111	163	96	15	11	2	7	180	68	96	26	48
> 18 yrs	698	112	147	4007	1081	1914	816	1688	1779	459	288	106	109	2777	484	1399	360	409

Total num. of reports 6231

Concentrating and cataloguing

Reports of Hospitalization / Emergency Room visits:

1. Daily incidence – Hospitalization / Emergency room visits reported in the group aged 5-17 years, were then located from the “Ofek” system. The data produced by the Ofek system were concentrated in a dedicated form. Additionally, the relevant medical documents were (securely) distributed to the members of a dedicated committee.
2. At the completion of the committee, its conclusions were concentrated and distributed

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
שחרור	10	44571	[illegible]	Muscle weakness	Dermatomyositis	21	FL8094	pfizer	20.12.21	2	נקבה	7					NA
שחרור	4 days	44570	[illegible]	[illegible]	[illegible] DIABETIC KETOACIDOSIS [illegible] (BIC 7, PH 7.1) [illegible]	26 days	FL8094	pfizer	44544	2	זכר	8					NA
שחרור	4 days	44596	[illegible]		Acute peicarditis	15 days	FL8094	pfizer	44581	2	נקבה	9					NA
שחרור	1 days	44559	[illegible]		LOSS OF CONSCIOUSNESS	0 days	FL8094	pfizer	44559	1	זכר	10					NA
שחרור	5 days	44593	[illegible]		ACUTE PERICARDITIS UNSPECIFIED	2 days	FL7309	pfizer	44581	1	זכר	14					NA

Concentrating and cataloguing

- In the online report form, there was an option to add details in free text
- It is extremely important to collect and analyze these data in order to widen the knowledge about unknown adverse events and to recognize new and unexpected signals following the vaccination.
- **Important to note** – the adverse events that were collected and analyzed were in one of the following categories:

1. An adverse effect that does not appear in the physician's leaflet
2. An adverse effect that appears in the leaflet but its characteristics are different from the data included in the physician's leaflet. For example – Duration different from that reported in the leaflet.

- Reports of adverse events submitted as free text were reported in sentences in natural language that occasionally included a number of adverse events interweaved in the same sentence.

  For example: "I am suffering from **fatigue**, the **menstrual cycle was two weeks late** and was **sparse**, **restrictive muscle pain** for over six months and the end is still not in sight".
- For collection, characterization and categorization, the data were "broken" into separate phrases to include one adverse event per phrase.

Concentrating and cataloguing

Reports in Free Text

- In the next stage the phrase was translated into English in order **to convert it into medical terminology in a valid and systematic manner** using MedDRA (Medical Dictionary for Regulatory activities)

The phrase was classified into 3 categories of different levels:

1. MedDRA LLT (lower term level)
2. MedDRA PT (preferred term)
3. MOH category

- Reporting characteristics that could assist in establishing causal relationship, such as Onset, Duration, Rechallenge were identified, characterized and concentrated.

Concentrating and cataloguing

Some background about MedDRA:

- This is a dictionary used by the regulatory authorities and the pharmaceutical industry in classification, appraisal and presentation of adverse events, and safety data collected during the pre/post marketing activities.
- The dictionary is kept and updated by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- The dictionary is translated into various languages but not Hebrew. Therefore the current activity required translation of the text to Hebrew and then use of a dictionary.
- The MedDRA categorizes the data into 5 levels of hierarchy:

  System Organ Classes (SOCs), High-Level Group Terms (HLGTs), High-Level Terms (HLTs), Preferred Terms (PT), Lowest Level Term (LLT)

  This cataloguing enables production and presentation of data according to desired specificity (resolution) level.

Concentrating and cataloguing

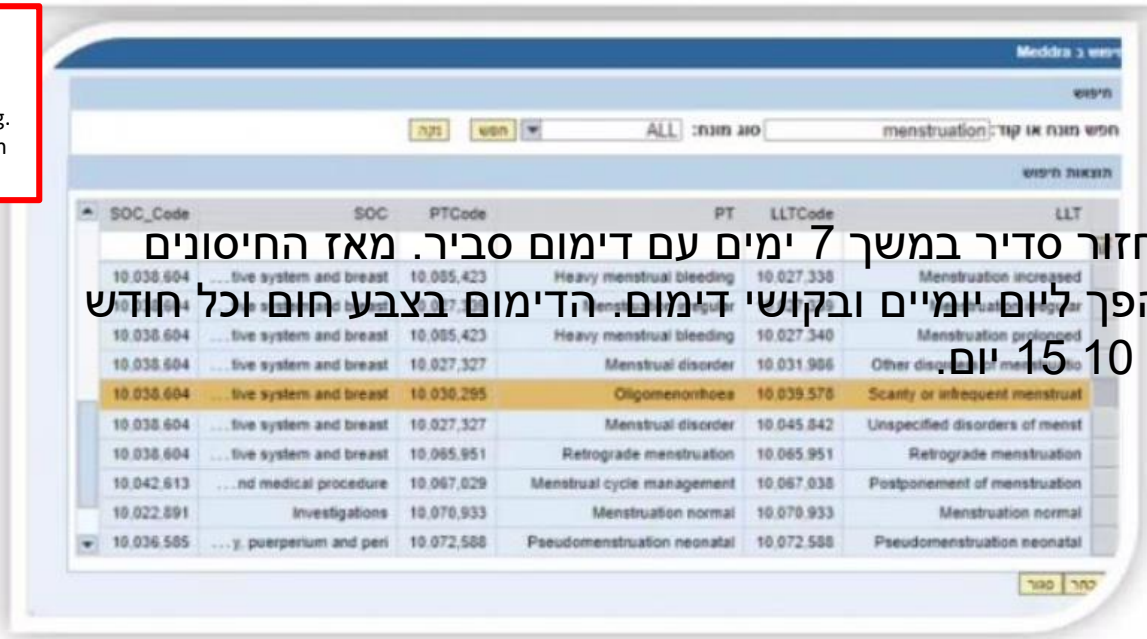
Example of handling one phrase:

פירוט נוסף	נטילת תרופה	פנה לטיפול רפואי	סוג מרכז רפואי	בית חולים	אישפוז	Unexpected	היגד	MEDdra LLT	MEDdra PT	קטגוריה
היה לי מחזור סדיר במשך 7 ימים עם דימום סביר . מאז החיסונים המחזור הפך ליום יומיים ובקושי דימום הדימום בצבע חום וכל חודש איחור של 10 15 יום	לא	לא			לא	1	מחזור הפך ליום יומיים ובקושי דימום הדימום בצבע חום	scanty or infrequent menstruation	Oligomenorrhea	הפרעה במחזור הוסת

No No No

Menstrual cycle disorder

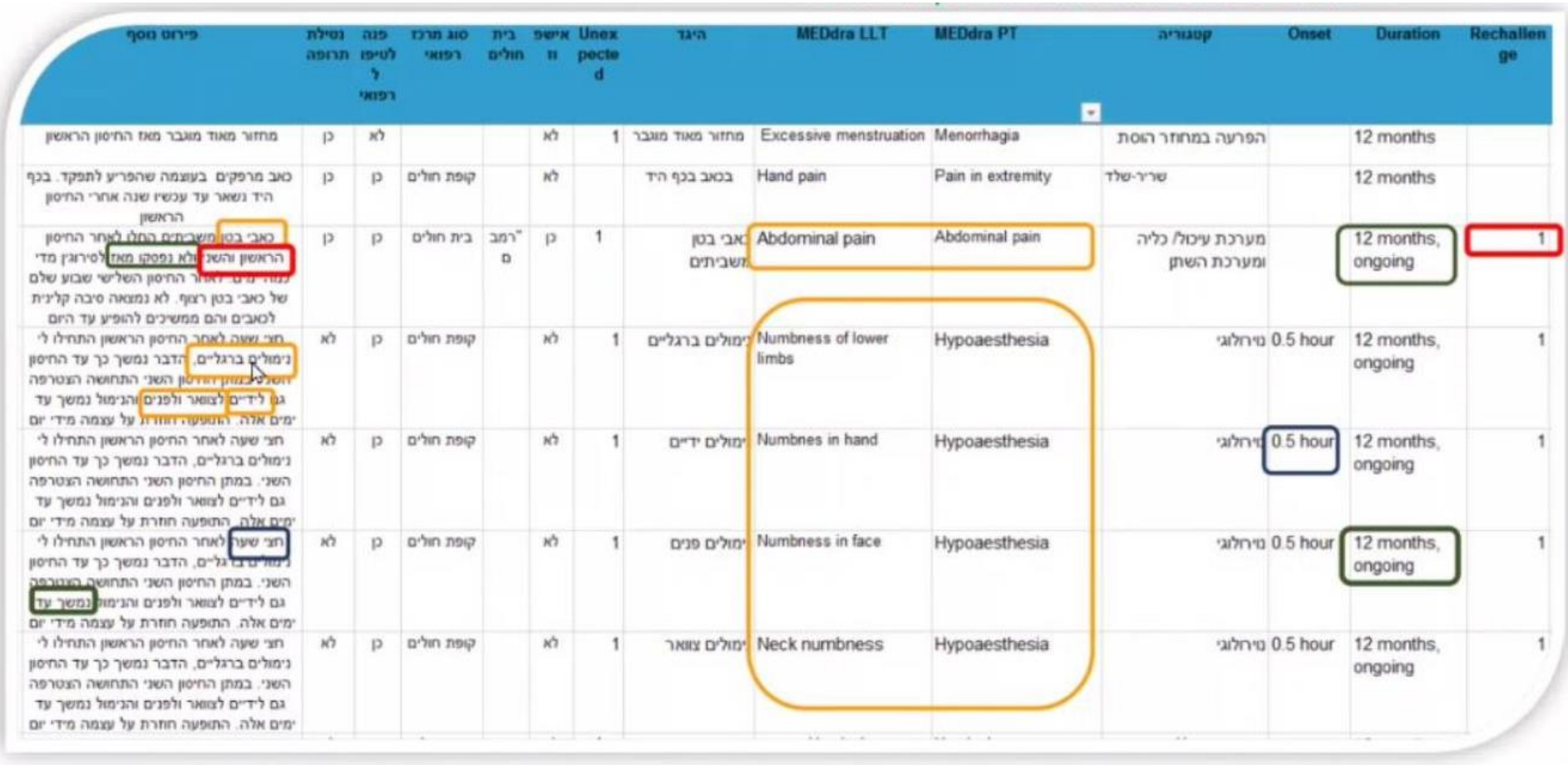
I had a regular period for 7 days with reasonable bleeding. Since the vaccinations the period has become every two days and hardly any bleeding. The bleeding is brown and every month there is a delay of 10-15 days.



היה לי מחזור סדיר במשך 7 ימים עם דימום סביר. מאז החיסונים המחזור הפך ליום יומיים ובקושי דימום. הדימום בצבע חום וכל חודש איחור של 10 15 יום.

Concentrating and cataloguing

Example of handling one report of free text:



פירוט נוסף	נטילת תרופה	פנה לטיפול רפואי	סוג מרכז רפואי	בית חולים	אישפוז	Unexpected	היגד	MEDdra LLT	MEDdra PT	קטגוריה	Onset	Duration	Rechallenge
מחזור מאוד מוגבר מאז החיסון הראשון	כן	לא			לא	1	מחזור מאוד מוגבר	Excessive menstruation	Menorrhagia	הפרעה במחזור הוסת		12 months	
כאב מרפקים בעצמה שהפריע לתפקד. בכף היד נשאר עד עכשיו שנה אחרי החיסון הראשון	כן	כן	קופת חולים		לא		בכאב בכף היד	Hand pain	Pain in extremity	שריר-שלד		12 months	
כאבי בטן משביתים החלו לאחר החיסון הראשון והשני ולא נפסקו מאז. לסירוגין מדי כמה ימים. לאחר החיסון השלישי שבוע שלם של כאבי בטן רצוף. לא נמצאה סיבה קלינית לכאבים והם ממשיכים להופיע עד היום	כן	כן	בית חולים	"רמב"ם	כן	1	כאבי בטן משביתים	Abdominal pain	Abdominal pain	מערכת עיכול/ כליה ומערכת השתן		12 months, ongoing	1
חצי שעה לאחר החיסון הראשון התחילו לי נימולים ברגליים, הדבר נמשך כך עד החיסון השני. במתן החיסון השני התחושה הצטרפה גם לידיים לצוואר ולפנים והנימול נמשך עד ימים אלה. התופעה חוזרת על עצמה מידי יום	לא	כן	קופת חולים		לא	1	נימולים ברגליים	Numbness of lower limbs	Hypoaesthesia	נוירולוגי	0.5 hour	12 months, ongoing	1
חצי שעה לאחר החיסון הראשון התחילו לי נימולים ברגליים, הדבר נמשך כך עד החיסון השני. במתן החיסון השני התחושה הצטרפה גם לידיים לצוואר ולפנים והנימול נמשך עד ימים אלה. התופעה חוזרת על עצמה מידי יום	לא	כן	קופת חולים		לא	1	נימולים ידיים	Numbnes in hand	Hypoaesthesia	נוירולוגי	0.5 hour	12 months, ongoing	1
חצי שעה לאחר החיסון הראשון התחילו לי נימולים ברגליים, הדבר נמשך כך עד החיסון השני. במתן החיסון השני התחושה הצטרפה גם לידיים לצוואר ולפנים והנימול נמשך עד ימים אלה. התופעה חוזרת על עצמה מידי יום	לא	כן	קופת חולים		לא	1	נימולים פנים	Numbness in face	Hypoaesthesia	נוירולוגי	0.5 hour	12 months, ongoing	1
חצי שעה לאחר החיסון הראשון התחילו לי נימולים ברגליים, הדבר נמשך כך עד החיסון השני. במתן החיסון השני התחושה הצטרפה גם לידיים לצוואר ולפנים והנימול נמשך עד ימים אלה. התופעה חוזרת על עצמה מידי יום	לא	כן	קופת חולים		לא	1	נימולים צוואר	Neck numbness	Hypoaesthesia	נוירולוגי	0.5 hour	12 months, ongoing	1

Concentrating and cataloguing – cooperation with Military Unit 8200

For the joint work, a team of 2 researchers from the field of NLP and one professional commander from the field of research were assigned.

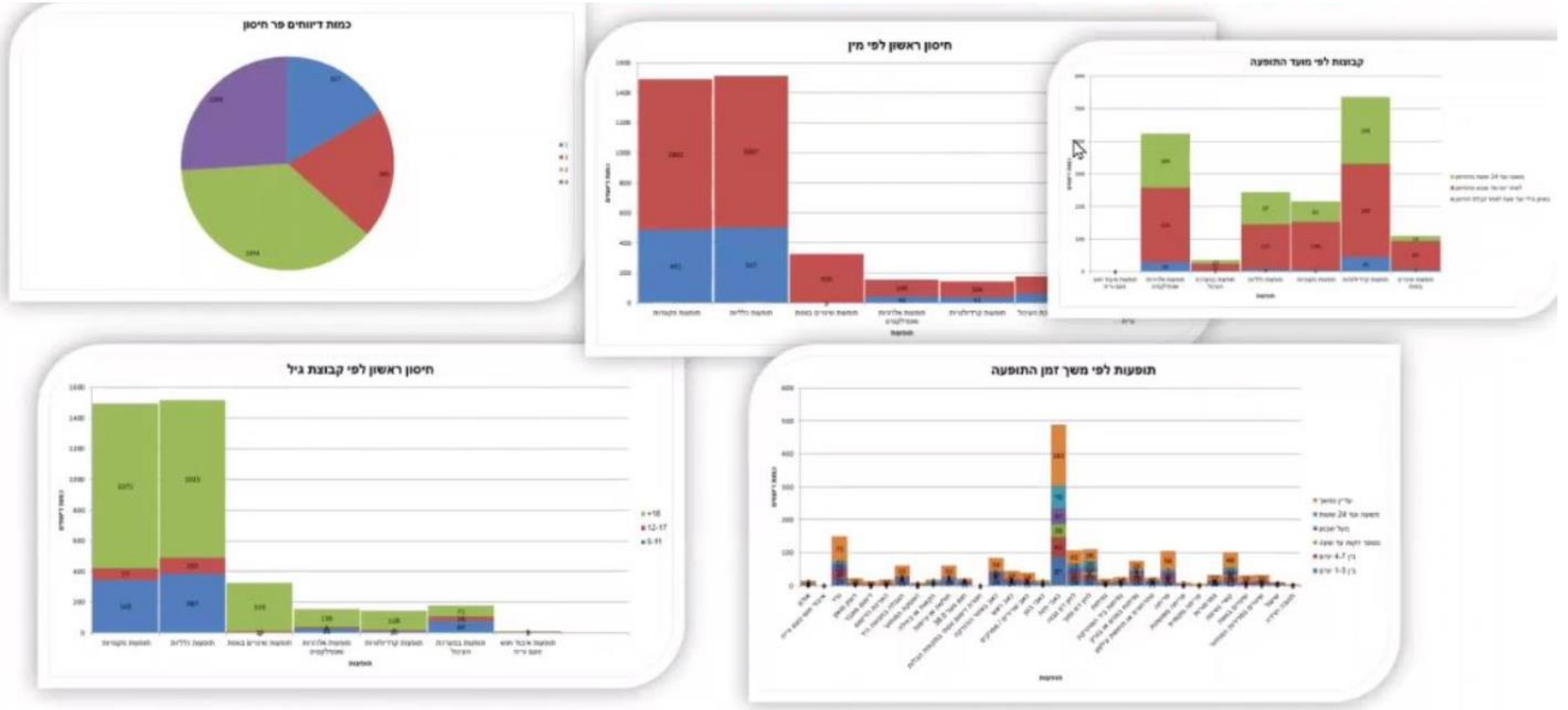
We focused on two projects:

1. Development of a tool for automatic analysis of **Predetermined fields** in a systematic and effective manner (saves time of manual analysis and prevents mistakes)

- Summary of the reported adverse events and graphic presentation – by requested segmentation (Age groups /Gender /Dose number)
- Concentrating the adverse events into categories (according to a key by the Shamir team), summary and graphic presentation – by requested segmentation (Age groups /Gender /Dose number)
- Summary and graphic presentation of time characteristics (event time and duration) of the reported adverse events in the predetermined fields

Concentrating and cataloguing – cooperation with Military Unit 8200

Example of the results of an automatic analysis tool of the **Predetermined fields**



Concentrating and cataloguing

2. Development and improvement of an artificial intelligence tool with analysis abilities of data reported as **Free text**

- In the course of the cooperation, our goal was to “teach” the Artificial Intelligence system to decipher free text, so that it would be able to retrieve phrases that carry information regarding a medical effect from the text and convert it to a valid MedDRA label.
- The work process was based on surveying medical forums, collecting information that was submitted as free text by the forum participants (layperson) in natural language, and converting it to MedDRA terminology.
- The aim of the process – creating a Hebrew “Pool” with “Translation” to a valid and monovalent MedDRA term. This phase would ensure precise conversion of future free text reports into valid terminology that will enable analysis, discovery of new signals and a valid and systematic production of conclusions.

Concentrating and cataloguing

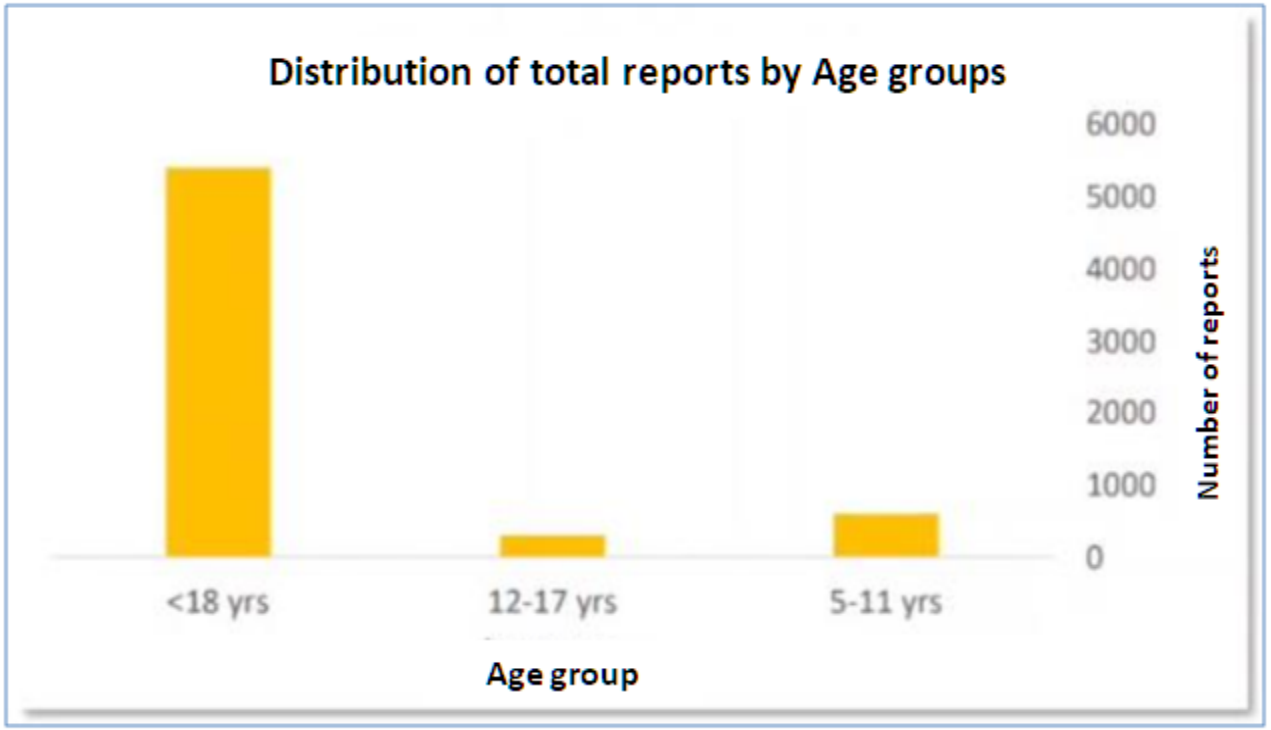
Example of the work process:

MedDRAPT	No. of phrases	Alternative MedDRAPT	Phrases
Abnormal behavior	1		Unusual behavior
Abnormal behavior			Strange behavior
Abnormal behavior			Behaves not in the normal way
Abnormal behavior			Does strange things
Abnormal behavior			Behavior that does not match age
Abnormal behavior			Her behavior at home changed, she cried a lot and is uncomfortable all the time. She wants to sleep much more than before
Abnormal behavior			The child demands more attention using provocative and abnormal behavior
Abnormal behavior			Bangs her head against the bed and moves her body forwards and backwards. This could continue for over an hour until she falls asleep
Abnormal dreams	3		Wake up remembering strange dreams, sometimes nightmares. I wake up tired
Abnormal dreams			Multiple dreams at night. I wake up after every sleep with many long dreams
Abnormal dreams			Strange dreams have appeared that feel real, long and confused with many details that give an uneasy feeling
Abnormal dreams			Every night I dream bad dreams. Actually I remember them in detail when I wake up. They are always strange, about animals, places and people I have never met
Abnormal dreams			26 years old, lately I have been suffering from long and realistic dreams that cause me to wake up exhausted in the morning
Abortion induced	1		Abortion was performed
Abortion induced			Planned abortion
Abortion induced			A year ago my pregnancy was unfortunately aborted using drugs
Abortion induced			6 weeks ago I underwent an abortion
Abortion induced			My pregnancy was stopped at 17 weeks due to fetal malformation
Abortion induced			Week 7 pulseless fetus. I underwent abortion with cytotec

Results of data analysis of predetermined fields

Between 09.12.2021-31.5.2022, a total of 8,054 reports of adverse events* in close proximity to receiving the vaccine were reported. Of these, 6,259 Valid reports (without double reporting/empty fields)

- It is noteworthy that some of the reports relate to adverse events that occurred **before** this date range



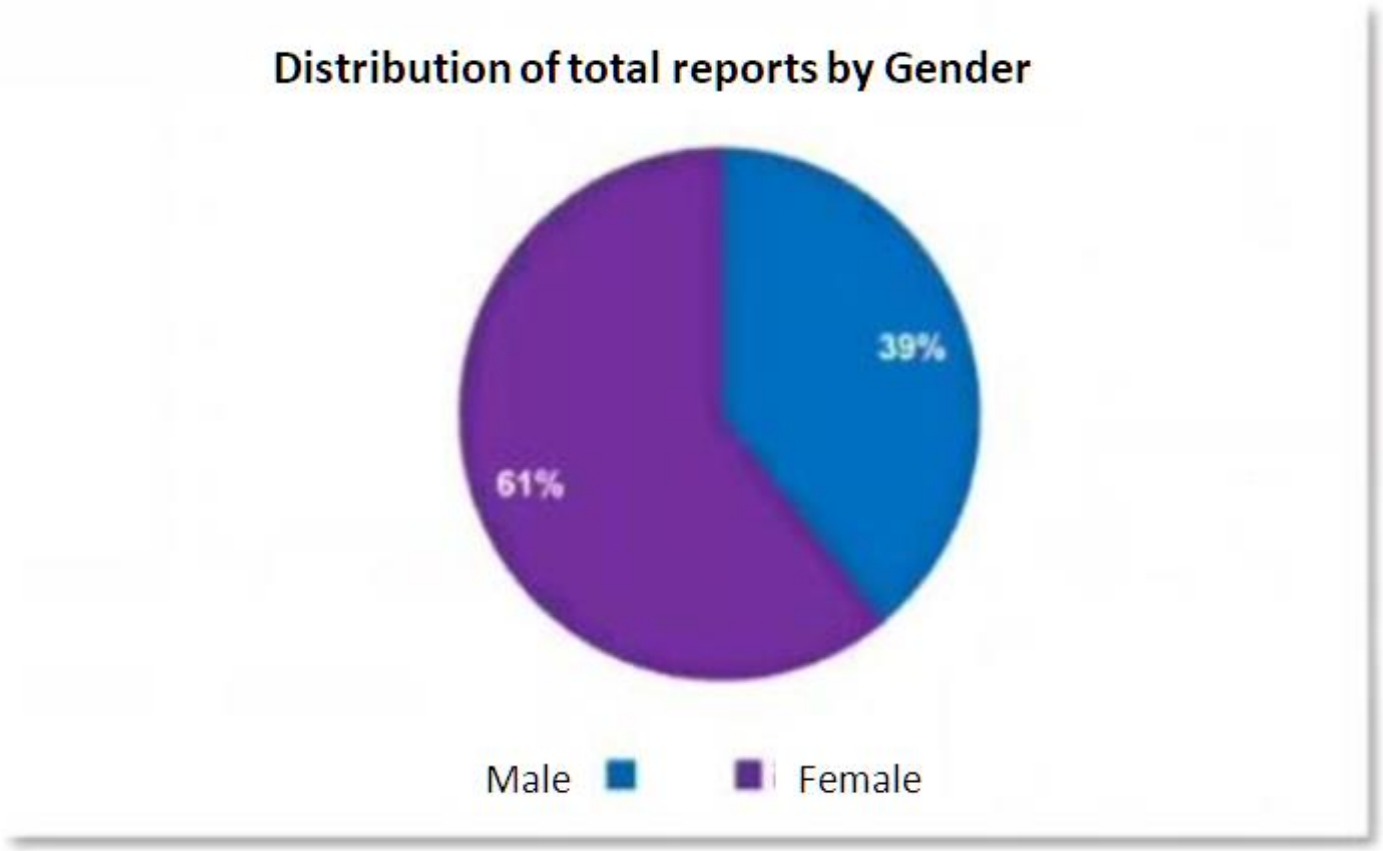
Distribution of reports by Age groups:

5-11 years: 599 reports
12-17 years: 299 reports
18 years and up: 5,411 reports

* **Comment:** some reports include more than one adverse event per report

Results of data analysis of predetermined fields

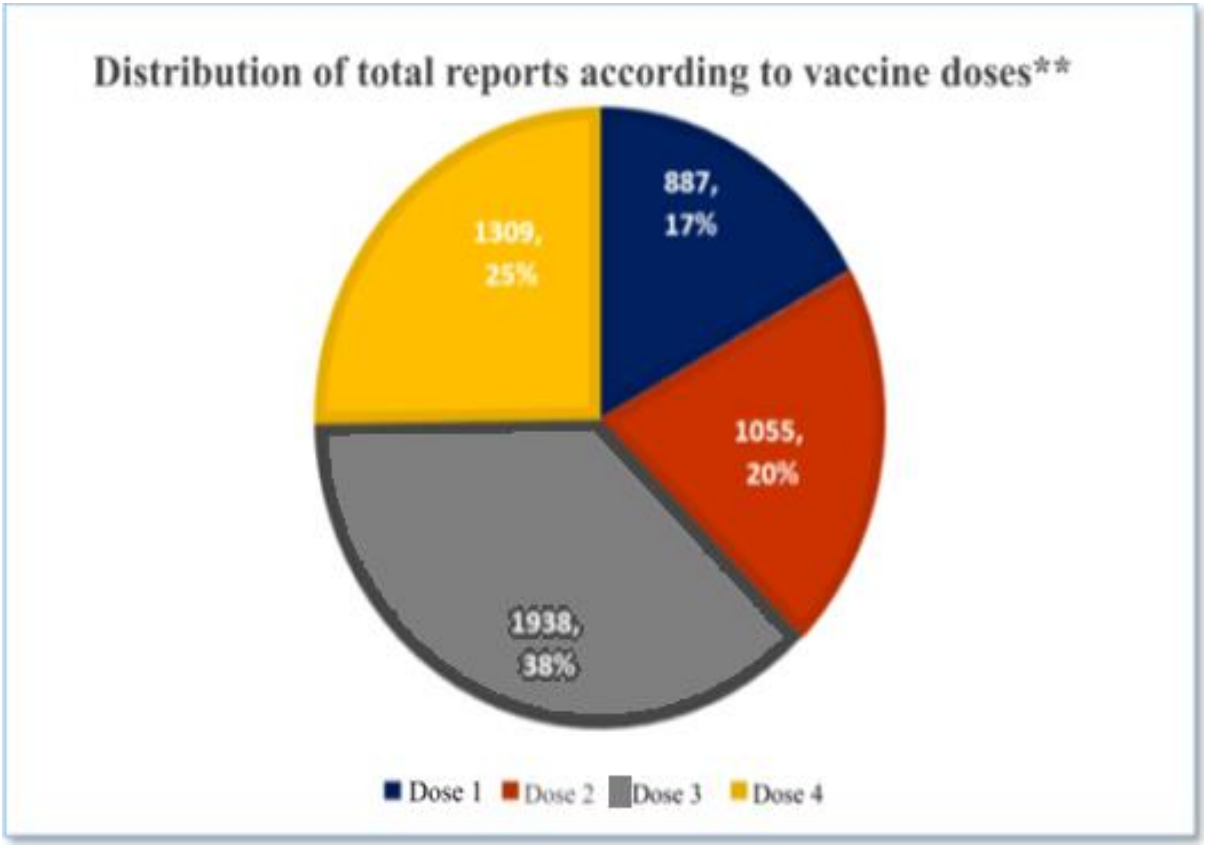
Between 09.12.2021-31.5.2022, a total of 8,054 reports of adverse events* in close proximity to receiving the vaccine were reported. Of these, 6,259 Valid reports (without double reporting/empty fields)



* **Comment:** some reports include more than one adverse effect per report

Results of data analysis of predetermined fields

Between 09.12.2021-31.5.2022, a total of **5,189** reports of adverse events in close proximity to receiving the vaccine were reported, that include mention of Dose number



- Distribution of reports by Dose number:

  1st dose: 887 reports

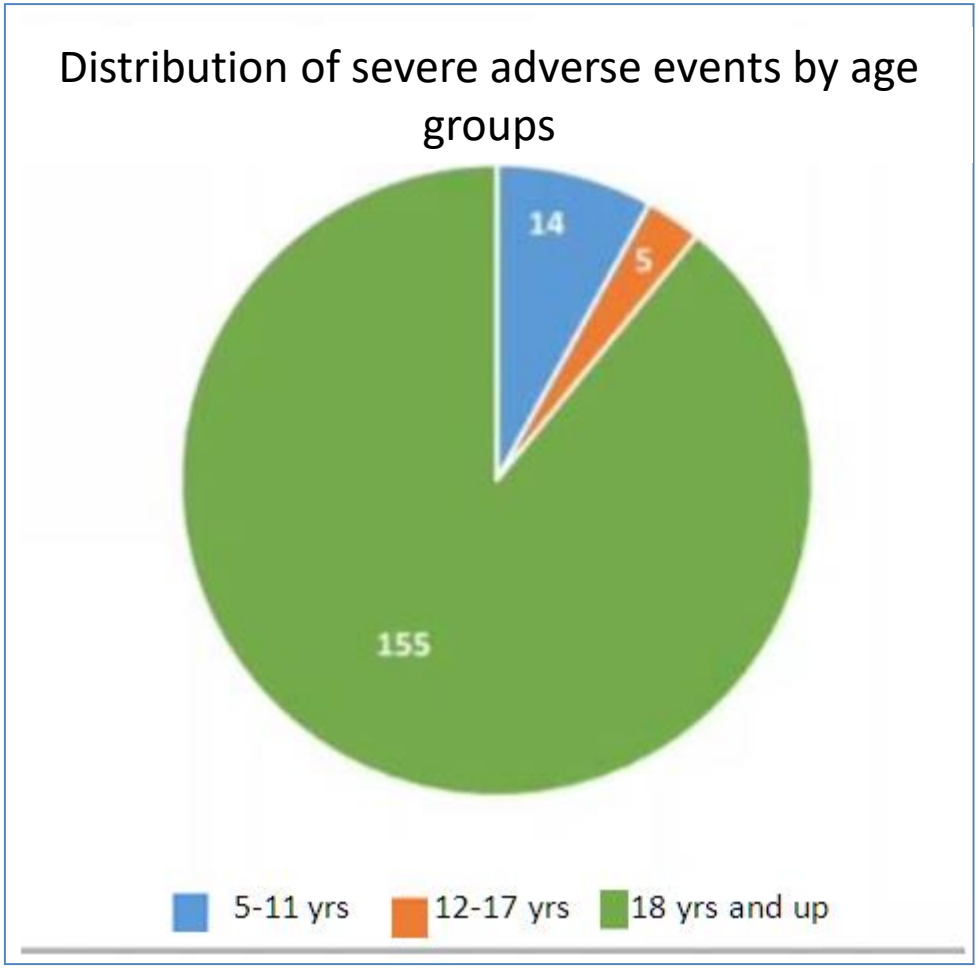
  2nd dose: 1,055 reports

  3rd dose: 1,938 reports

  4th dose: 1,309 reports

** For reports in which Dose number was included

Analysis results of predetermined fields



- Total reports of severe adverse events (Emergency room / Hospitalization): **173**
- Distribution of severe adverse events by age groups:

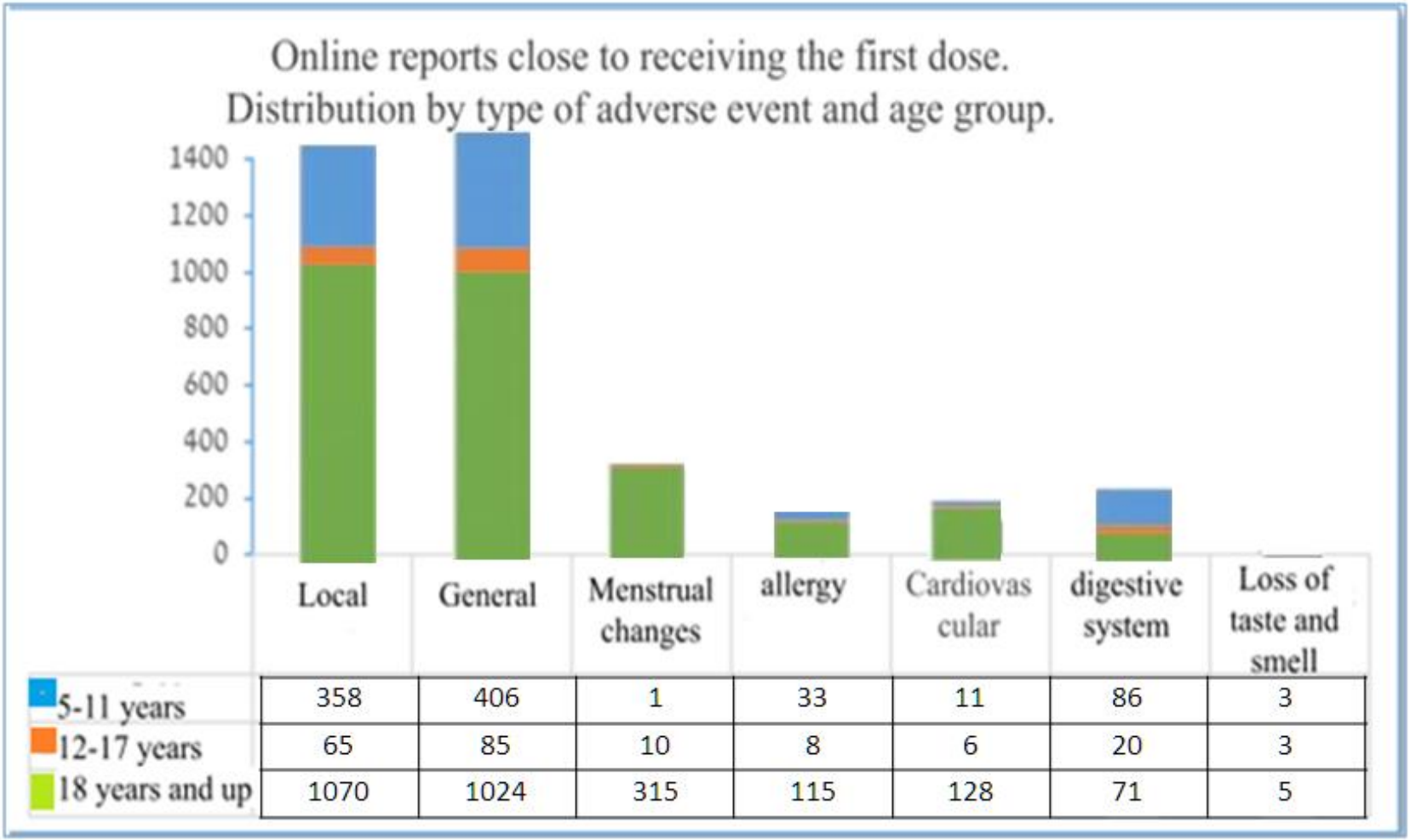
5-11 years: 14 reports

12-17 years: 5 reports

18 years and up: 155 reports

Adverse events reported in predetermined fields in close proximity to receiving the 1st dose, by Age groups (years)

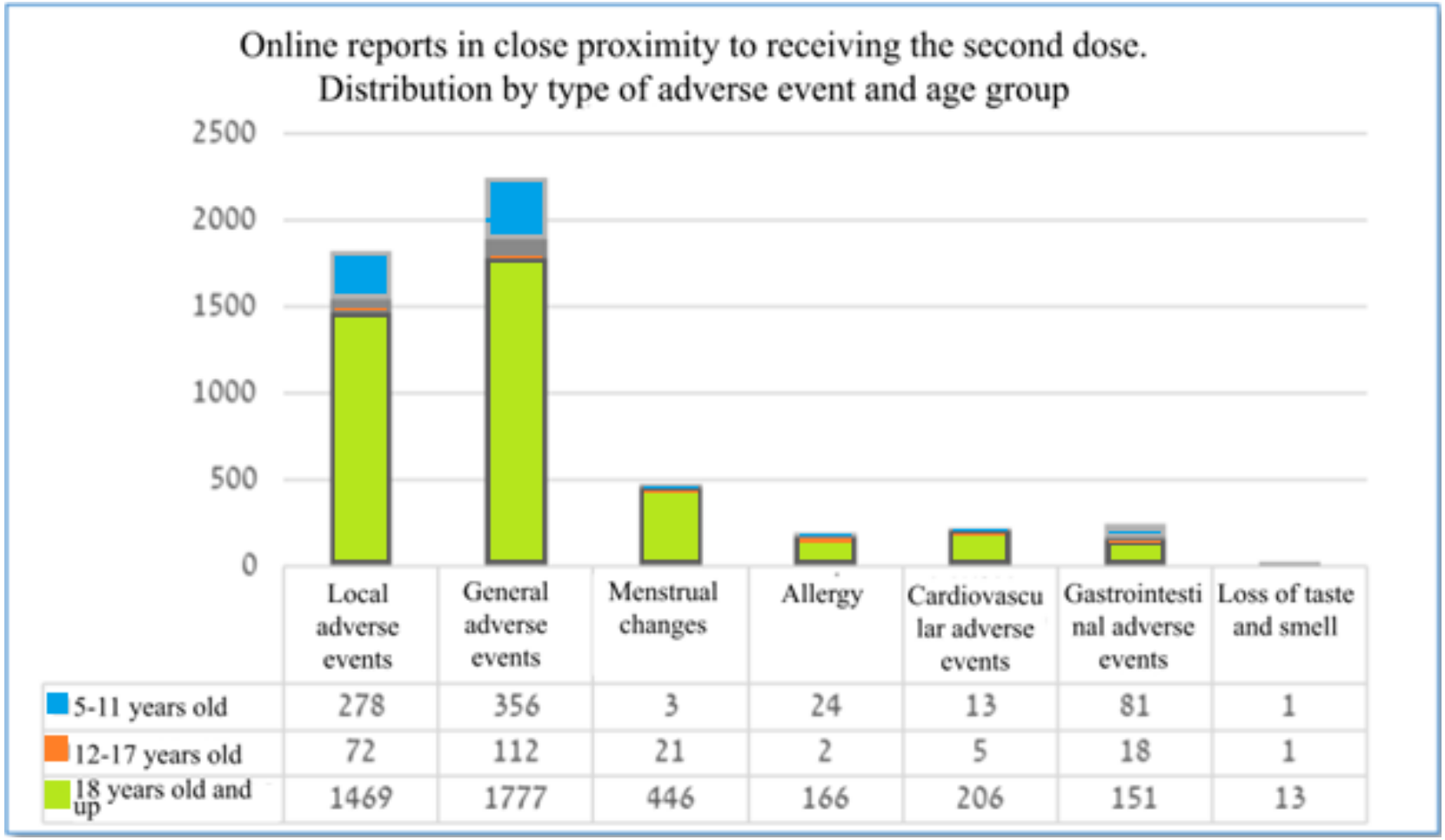
Up to 31.5.2022, **3,823** adverse events were reported in close proximity to the 1st dose, in all age groups



	Local	General	Menstrual changes	allergy	Cardiovascular	digestive system	Loss of taste and smell
5-11 years	358	406	1	33	11	86	3
12-17 years	65	85	10	8	6	20	3
18 years and up	1070	1024	315	115	128	71	5

Adverse events reported in predetermined fields in close proximity to receiving the 2nd dose, by Age groups (years)

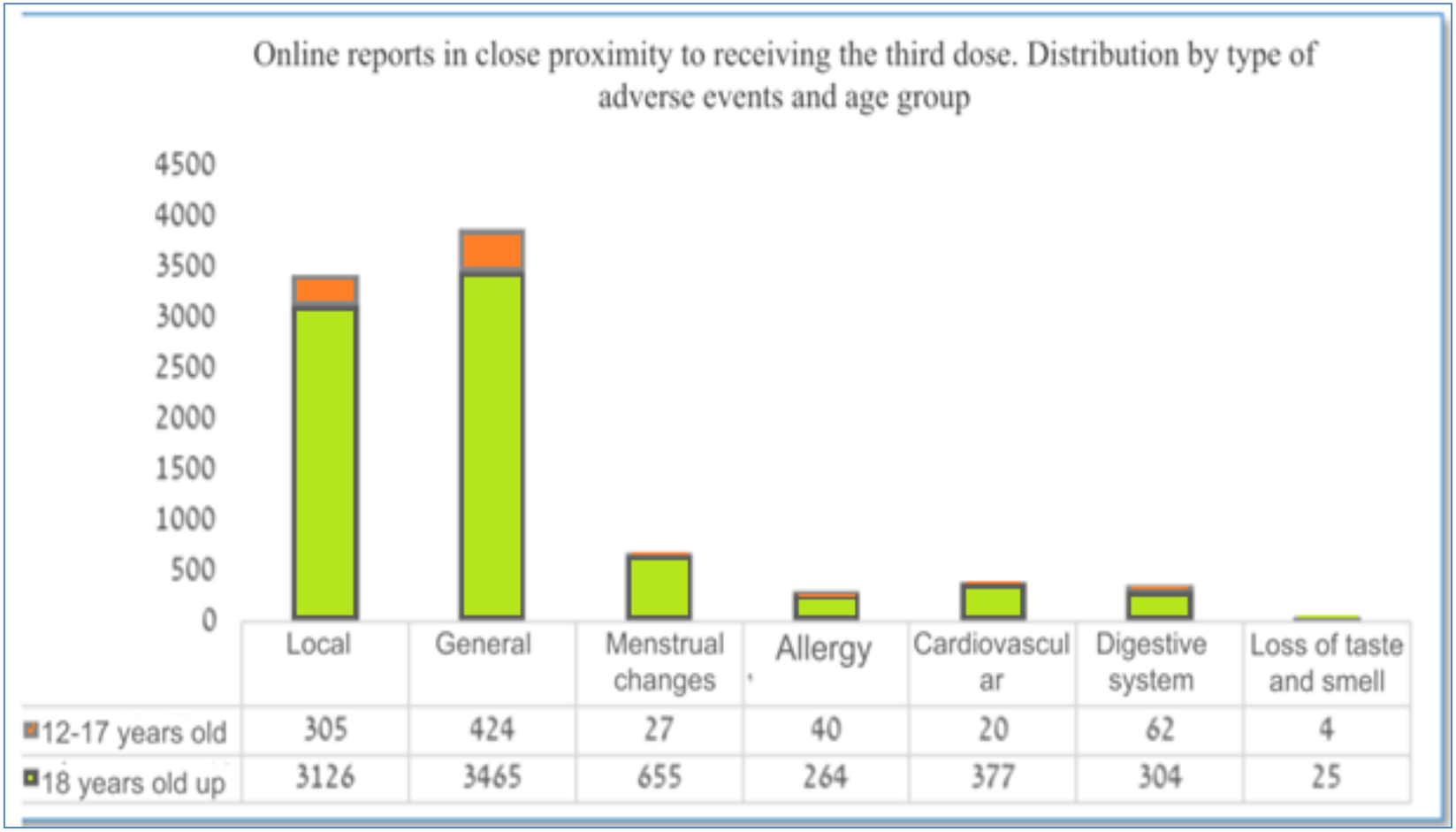
Up to 31.5.2022, **5,215** adverse events were reported in close proximity to the 2nd dose, in all age groups



	Local adverse events	General adverse events	Menstrual changes	Allergy	Cardiovascular adverse events	Gastrointestinal adverse events	Loss of taste and smell
5-11 years old	278	356	3	24	13	81	1
12-17 years old	72	112	21	2	5	18	1
18 years old and up	1469	1777	446	166	206	151	13

Adverse events reported in predetermined fields in close proximity to receiving the 3rd dose, by Age groups (years)

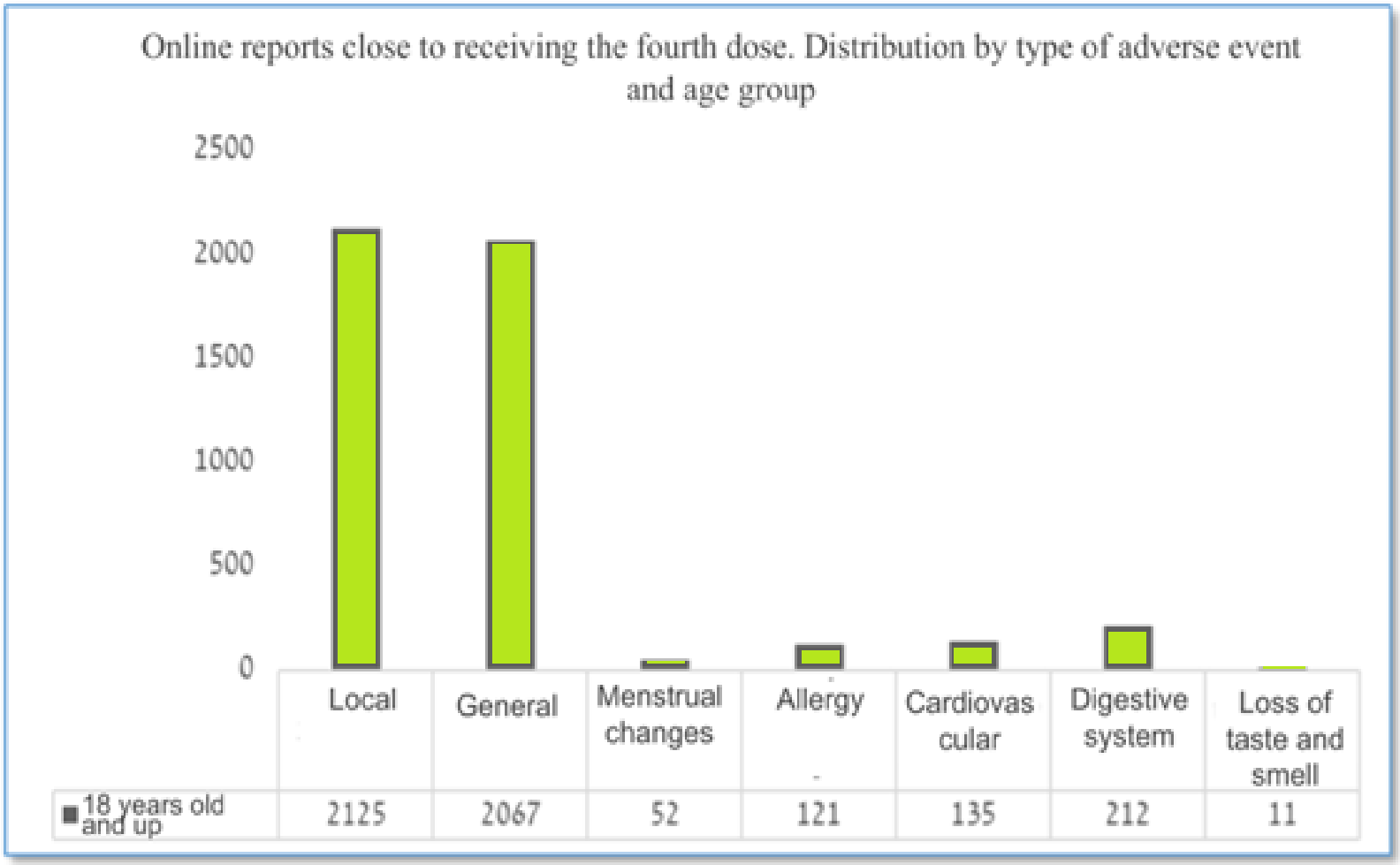
Up to 31.5.2022, **9,098** adverse events were reported in close proximity to the 3rd dose, in all age groups



	Local	General	Menstrual changes	Allergy	Cardiovascular	Digestive system	Loss of taste and smell
12-17 years old	305	424	27	40	20	62	4
18 years old up	3126	3465	655	264	377	304	25

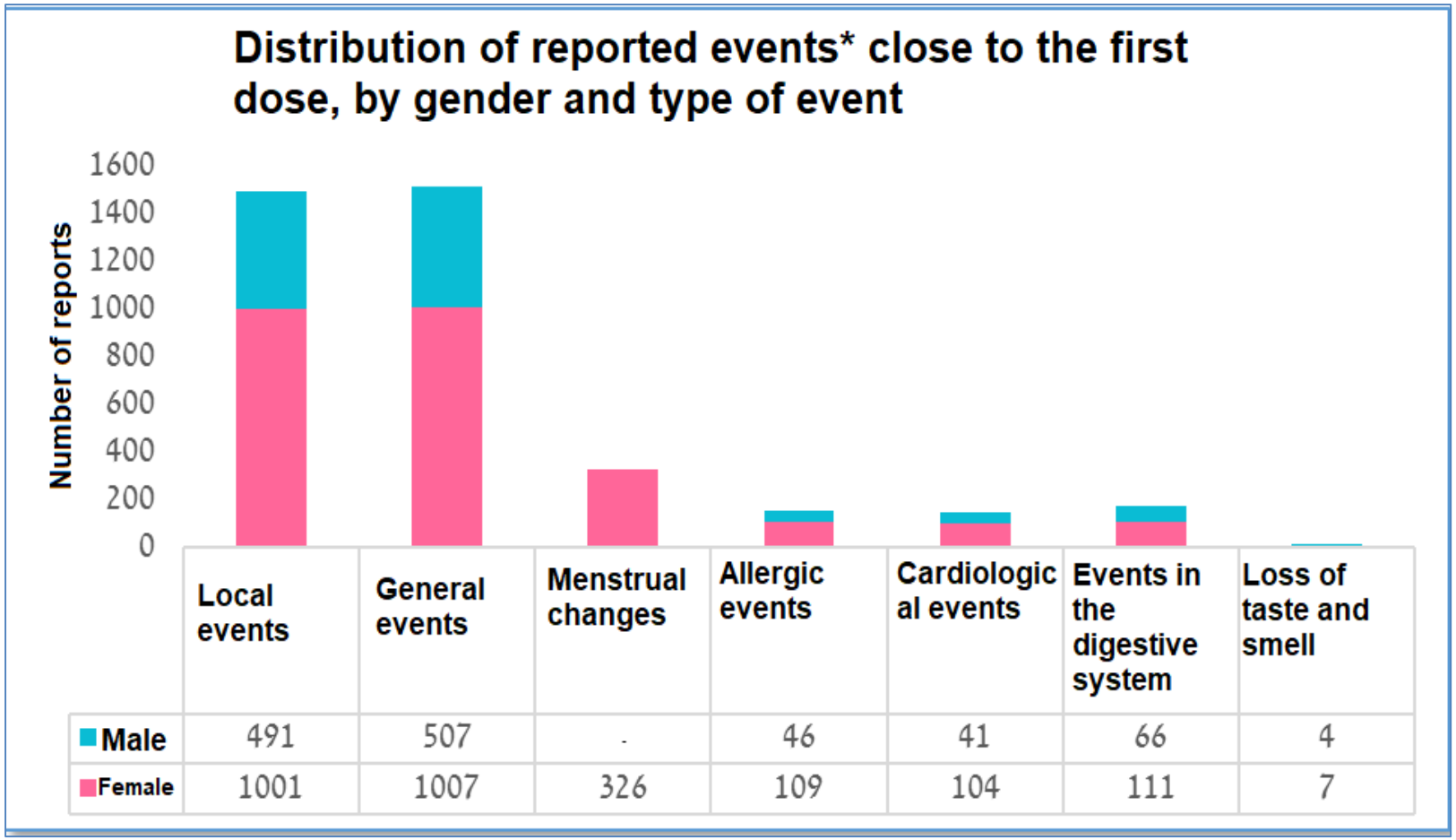
Adverse events reported in predetermined fields in close proximity to receiving the 4th dose, by Age groups (years)

Up to 31.5.2022, **4,723** adverse events were reported in close proximity to the 4th dose, in all age groups



Distribution of adverse events reported* in predetermined fields in close proximity to receiving the 1st dose, by Gender

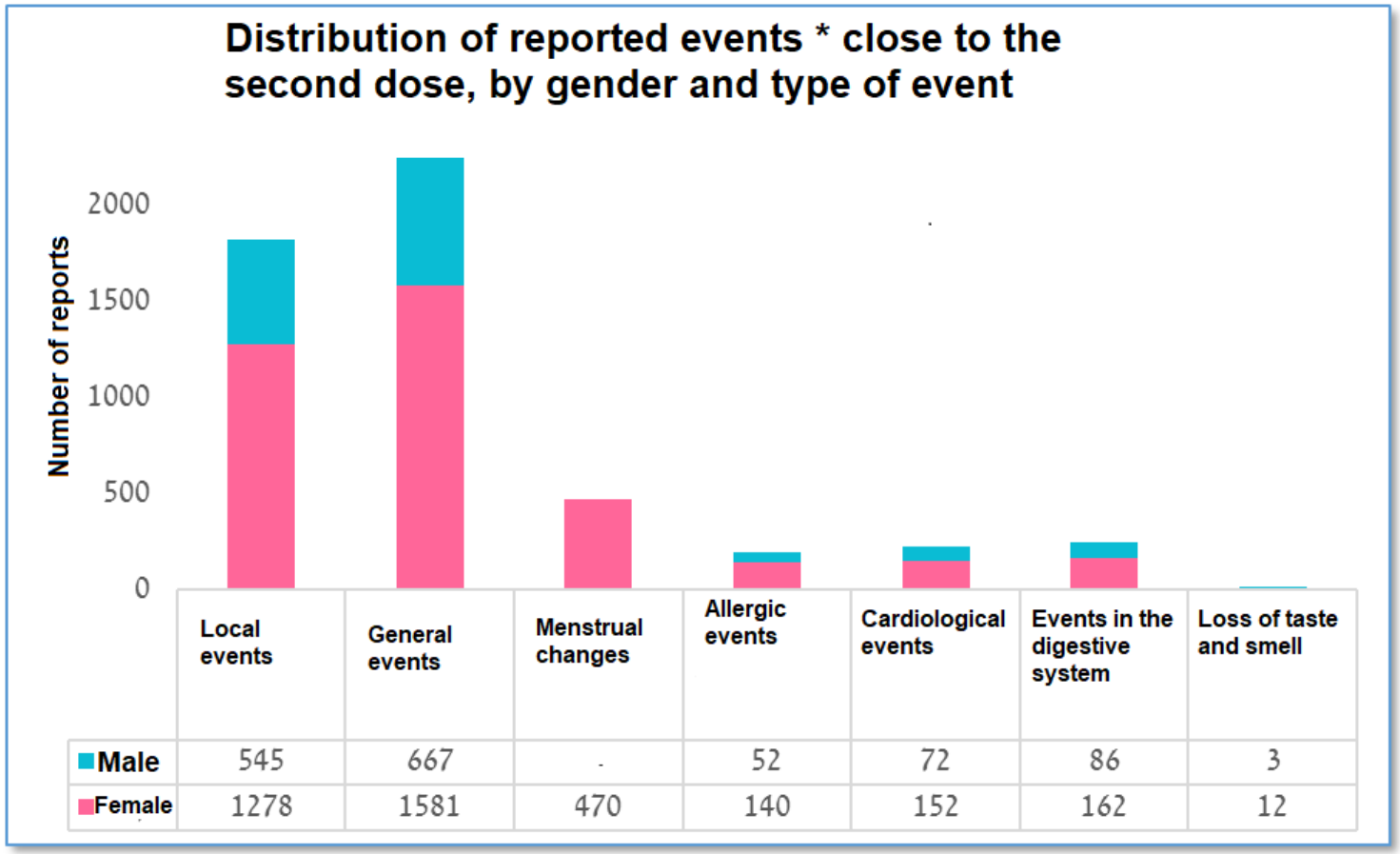
Up to 31.5.2022, 828 reports were received (317 male, 511 female) in close proximity to the 1st dose, that included 3,820 adverse events



	Local events	General events	Menstrual changes	Allergic events	Cardiological events	Events in the digestive system	Loss of taste and smell
Male	491	507	-	46	41	66	4
Female	1001	1007	326	109	104	111	7

Distribution of adverse events reported* in predetermined fields in close proximity to receiving the 2nd dose, by Gender

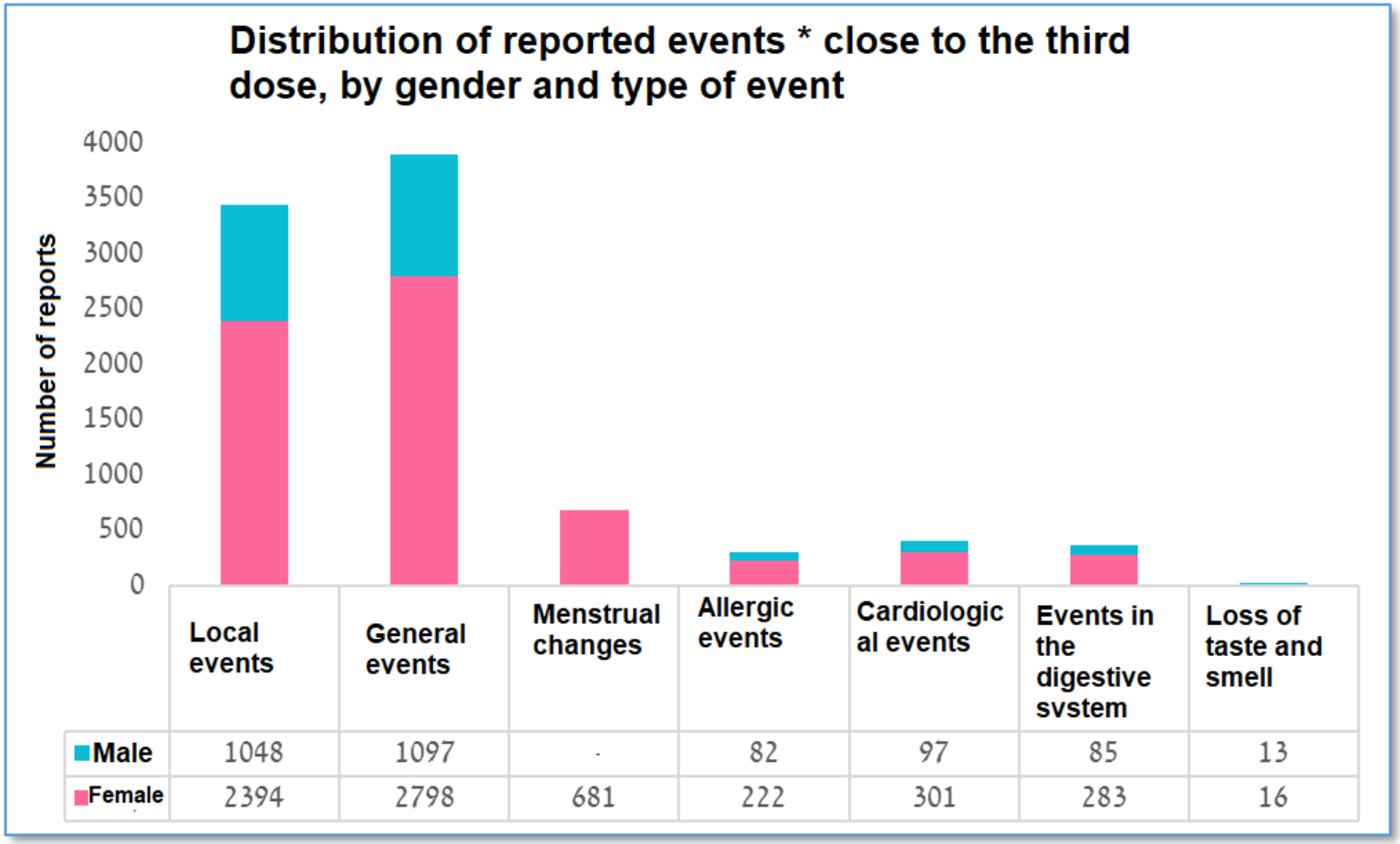
Up to 31.5.2022, 981 reports were received (336 male, 645 female) in close proximity to the 2nd dose, that included 5,220 adverse events



	Local events	General events	Menstrual changes	Allergic events	Cardiological events	Events in the digestive system	Loss of taste and smell
Male	545	667	.	52	72	86	3
Female	1278	1581	470	140	152	162	12

Distribution of adverse events reported* in predetermined fields in close proximity to receiving the 3rd dose, by Gender

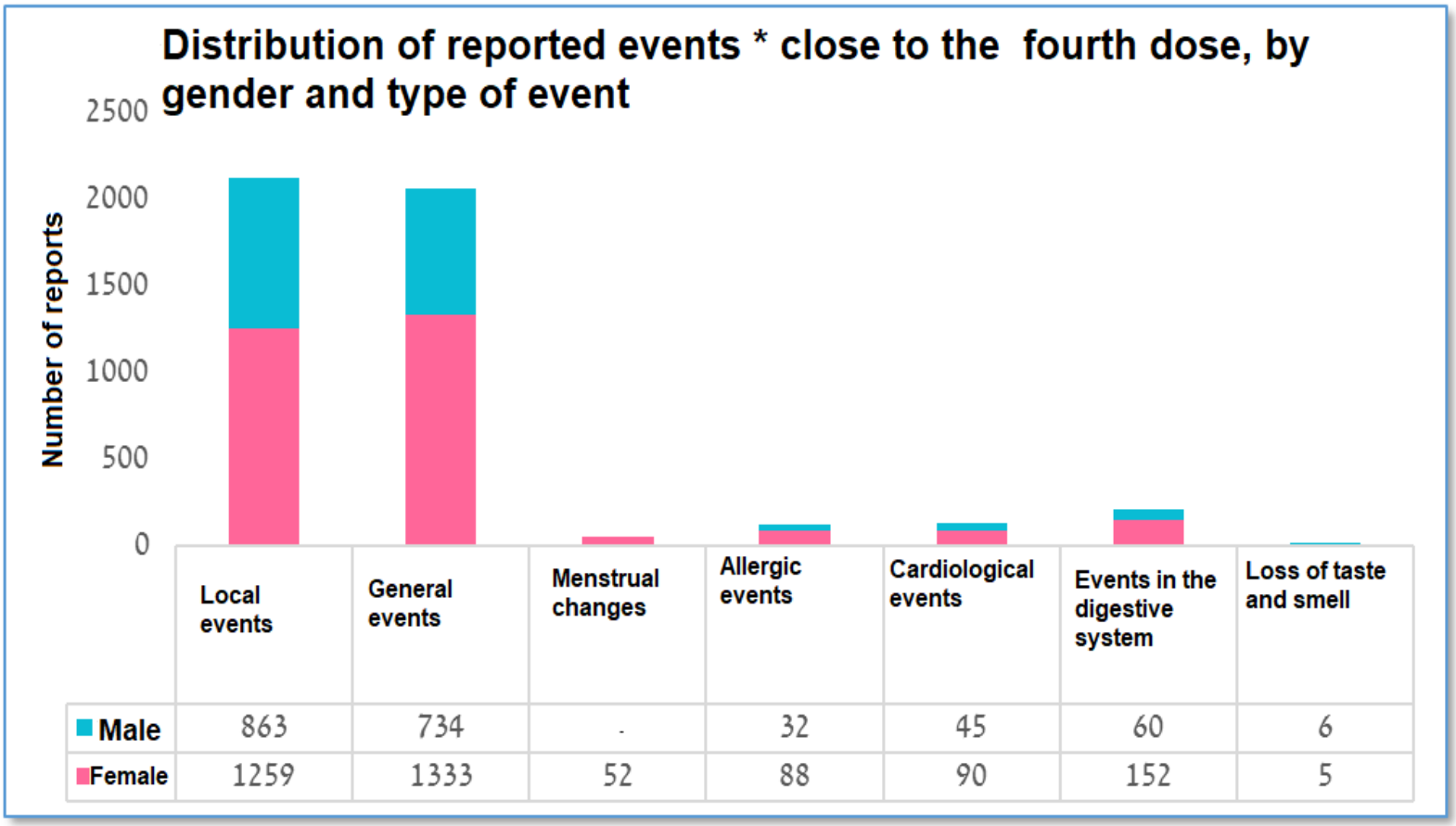
Up to 31.5.2022, 1,854 reports were received (685 male, 1,169 female) in close proximity to the 3rd dose, that included 9,117 adverse events



	Local events	General events	Menstrual changes	Allergic events	Cardiological events	Events in the digestive system	Loss of taste and smell
Male	1048	1097	-	82	97	85	13
Female	2394	2798	681	222	301	283	16

Distribution of adverse events reported* in predetermined fields in close proximity to receiving the 4th dose, by Gender

Up to 31.5.2022, 1,289 reports were received (619 male, 670 female) in close proximity to the 4th dose, that included 4,719 adverse events

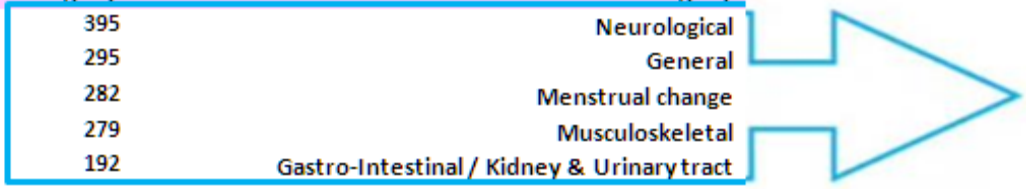


	Local events	General events	Menstrual changes	Allergic events	Cardiological events	Events in the digestive system	Loss of taste and smell
Male	863	734	-	32	45	60	6
Female	1259	1333	52	88	90	152	5

Total adverse events reported in the form as free text, distribution according to MOH Categories

Up to 31.5.2022, **2075 adverse events were reported as free text** distributed according to the Categories presented in the following table:

Category count	Category
395	Neurological
295	General
282	Menstrual change
279	Musculoskeletal
192	Gastro-Intestinal / Kidney & Urinary tract
148	Cardiovascular
94	Pulmonary
69	Dermatologic
50	Inflammatory-infectious
50	Ophthalmologic
45	Psychiatric
43	Gynecological
29	Hearing and Balance
18	Laboratory results
17	Obstetric
13	Allergic
12	Endocrine
12	Hematologic
9	Vascular
5	Autoimmune
4	Metabolic
3	Oncologic
2	Procedural
2	Lymphatic
1	Congenital / Hereditary / Genetic
1	Procedural
2076	Total count

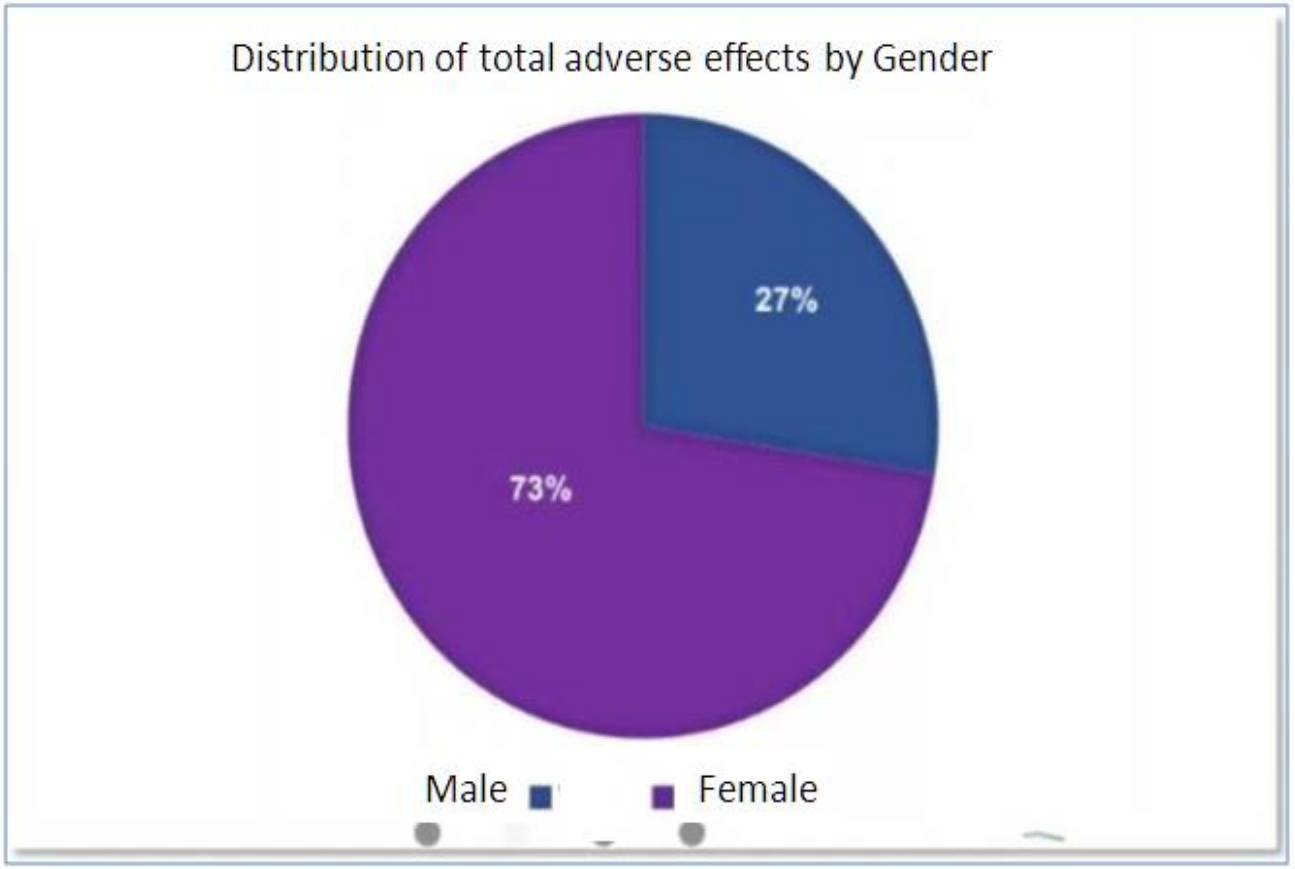


- 5 categories that amount to about 70% of total reported adverse events
- Each adverse effect amounts separately to about 10% of total reported adverse events

Total adverse events reported in the form as free text, distribution by Gender

Up to 31.5.2022, **2,075 adverse events were reported as free text**

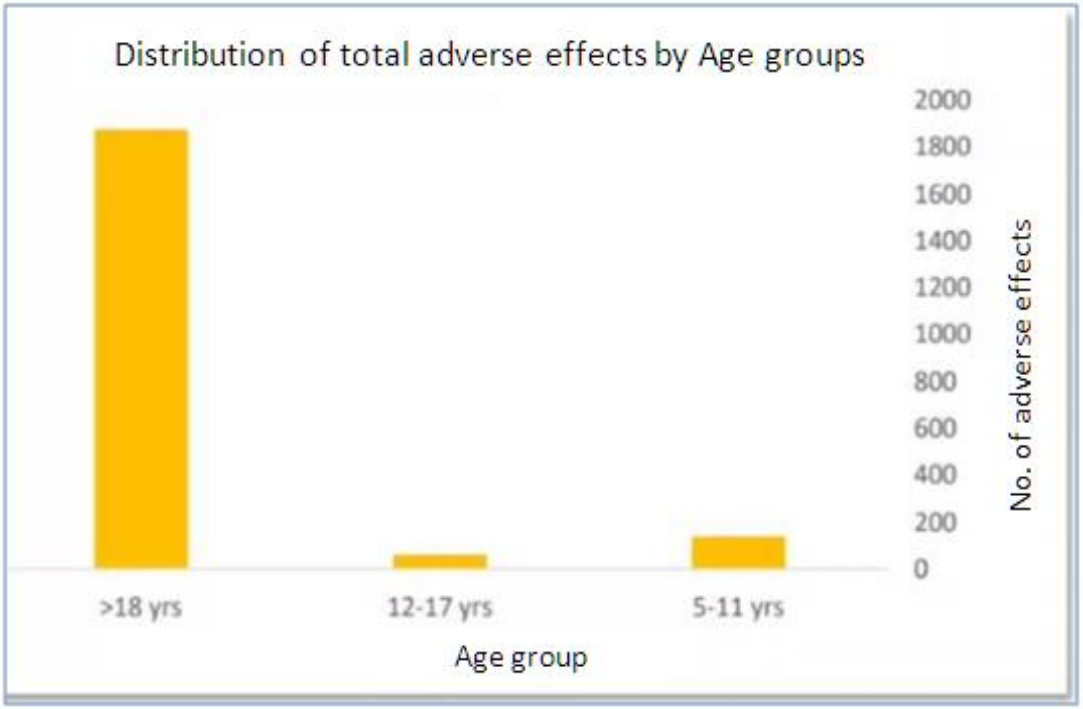
The distribution of the most common adverse events by Gender. 1,505 adverse events were reported in Females, compared with 570 in Males

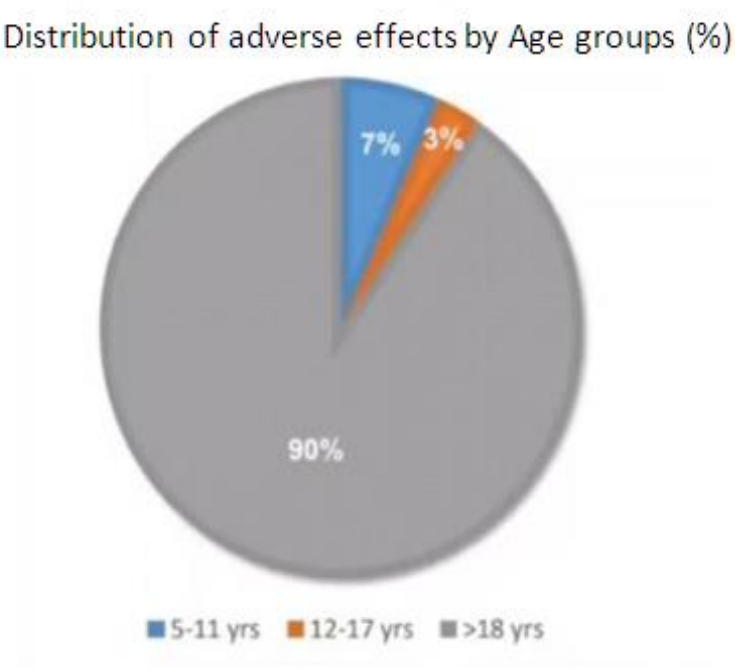


Total adverse events reported in the form as free text, distribution by Age group

Up to 31.5.2022, **2,075 adverse events were reported as free text**

The distribution of the most common adverse events by Age groups:

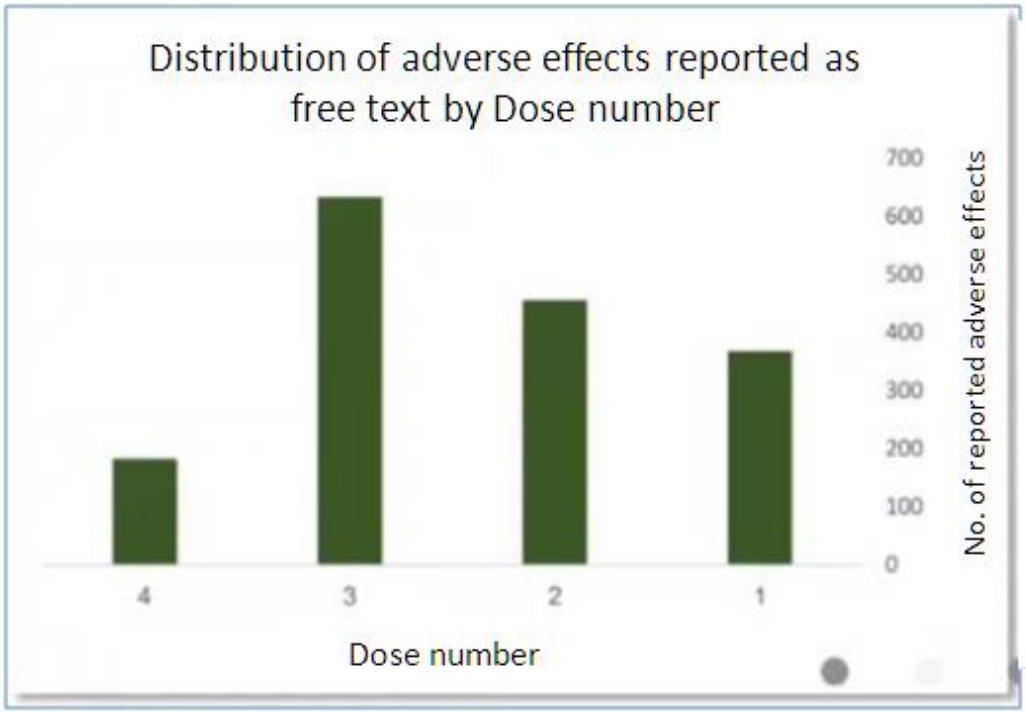


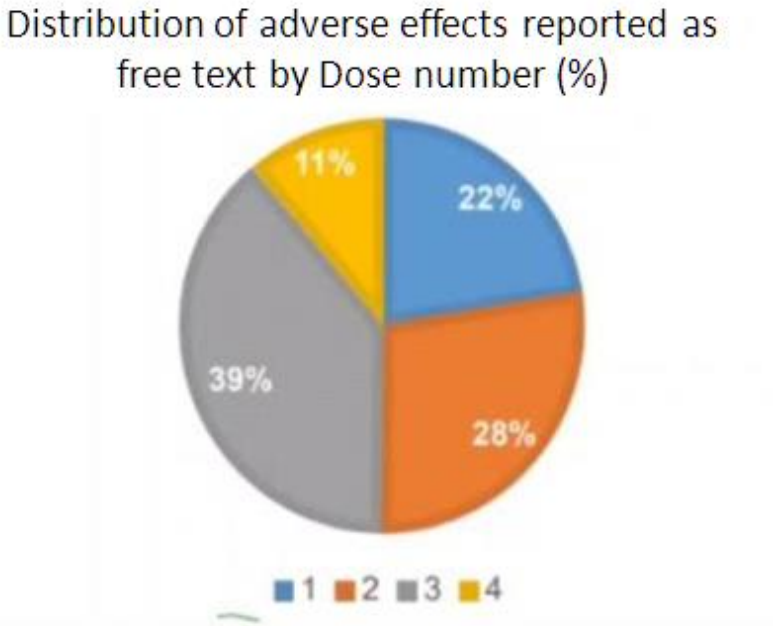


Total adverse events reported in the form as free text, distribution according to Dose number

Up to 31.5.2022, **2,075 adverse events were reported as free text**

The distribution of adverse events in all Categories by Dose number:

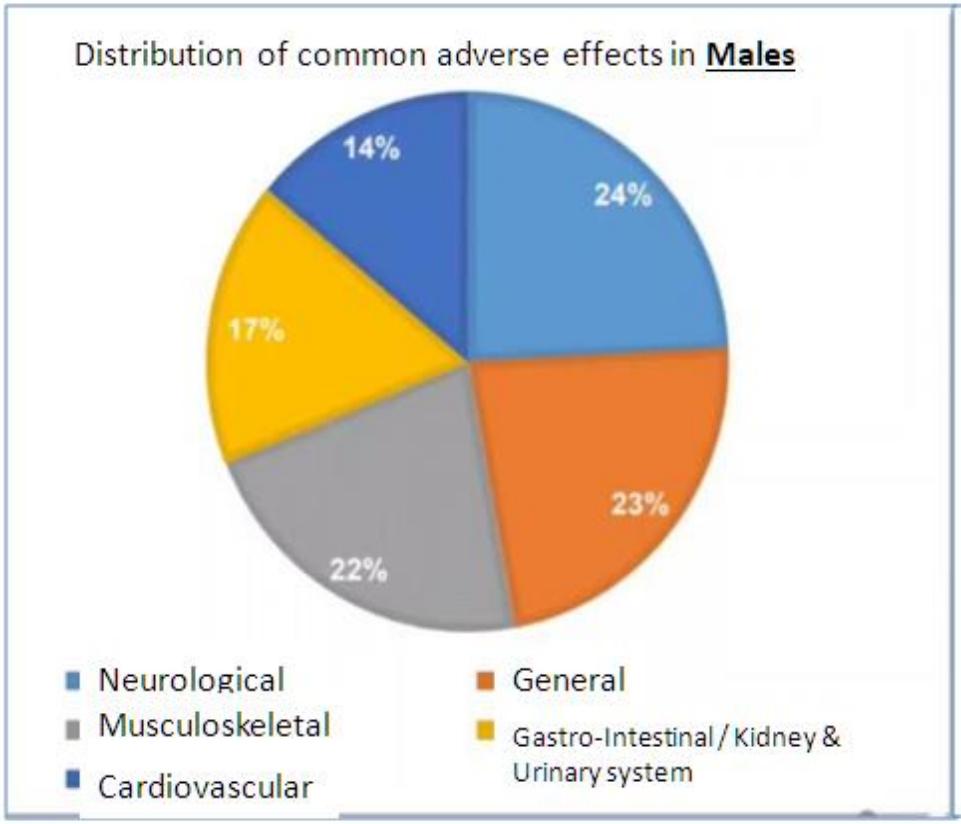


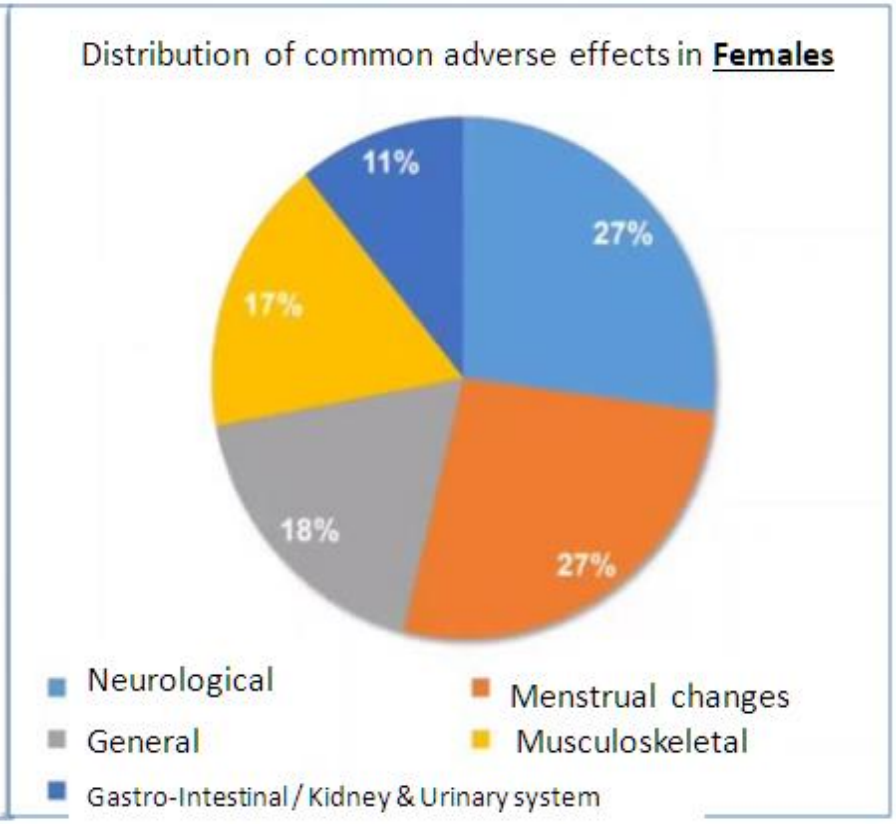


Total adverse events reported in the form as free text, distribution according to MOH Categories, and Gender

Up to 31.5.2022, **2,075 adverse events were reported as free text**

The distribution of the most common adverse events by Category and by Gender:

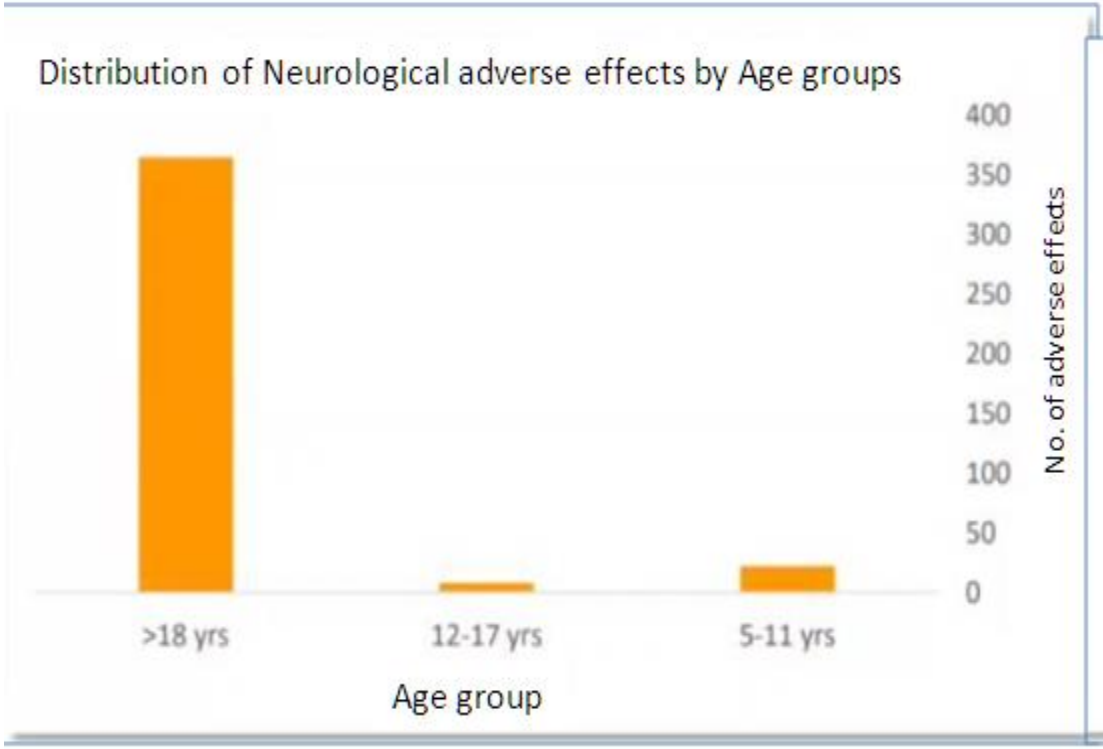


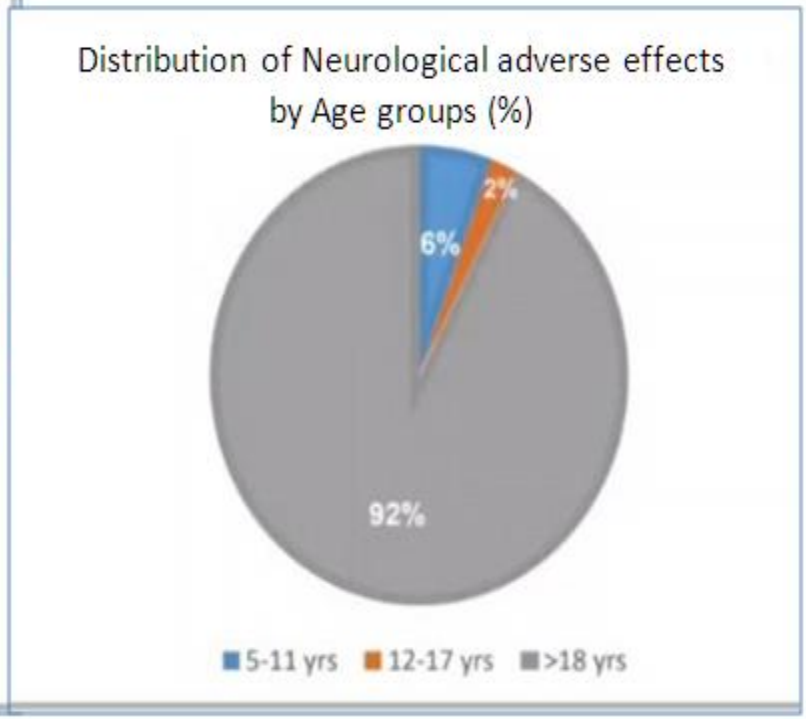


Neurological adverse events reported in the form as free text

Up to 31.5.2022, **395 adverse events classified as Neurological were reported as free text**

The following graphs present the distribution of the Neurological adverse events by Age groups

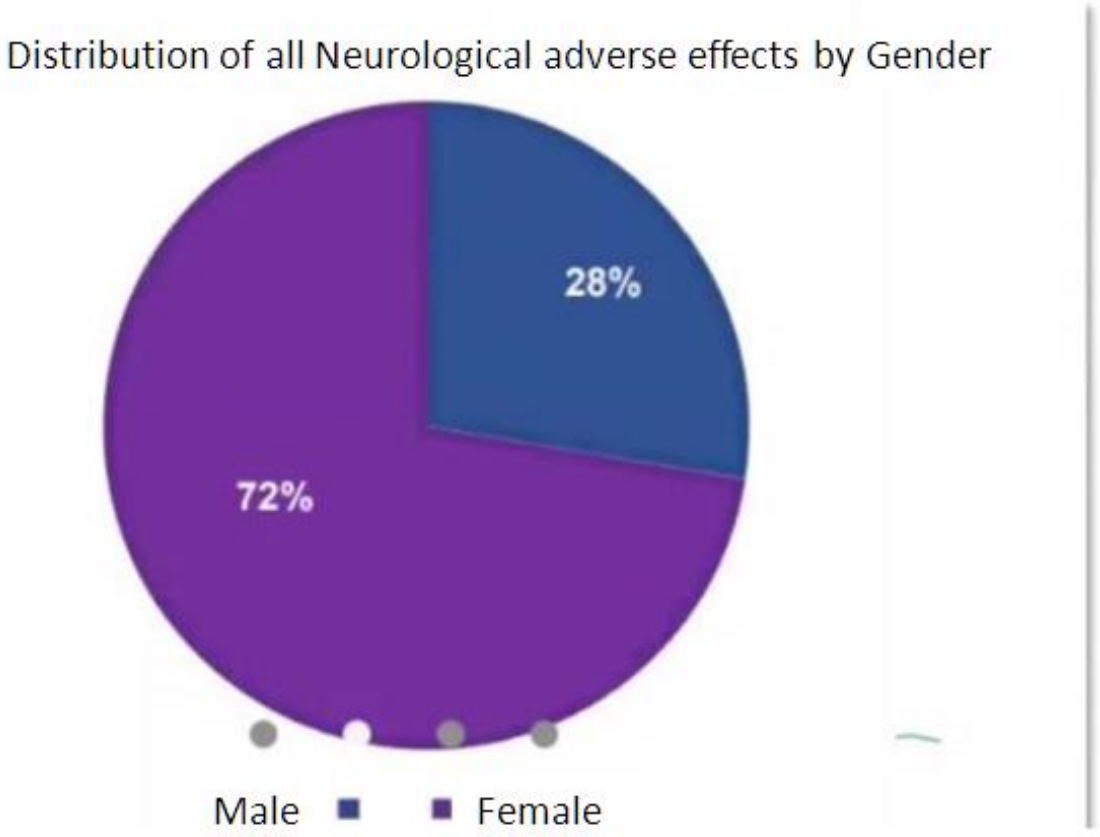




Neurological adverse events reported in the form as free text

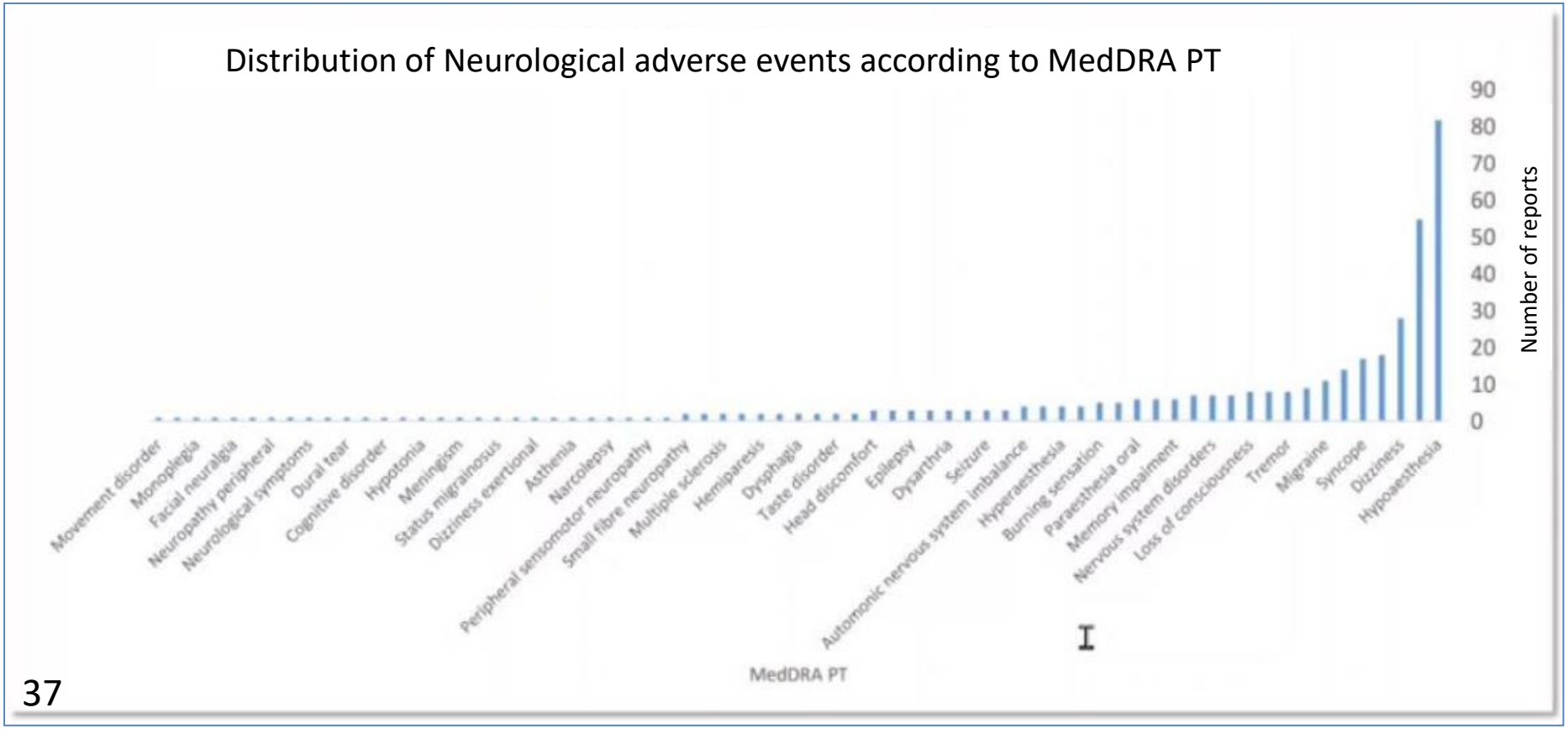
Up to 31.5.2022, **395 adverse events classified as Neurological were reported as free text**

The following graph presents their distribution by Gender



Neurological adverse events reported in the form as free text

Up to 31.5.2022, **395 adverse events classified as Neurological** were reported as free text (19% of all reported adverse events). The following graph presents their distribution according to MedDRA PT



Neurological adverse events reported in the form as free text

Up to 31.5.2022, **395 adverse events classified as Neurological** were reported as free text. The following table presents the common adverse events that amount to 70% of total adverse events categorized as Neurological.

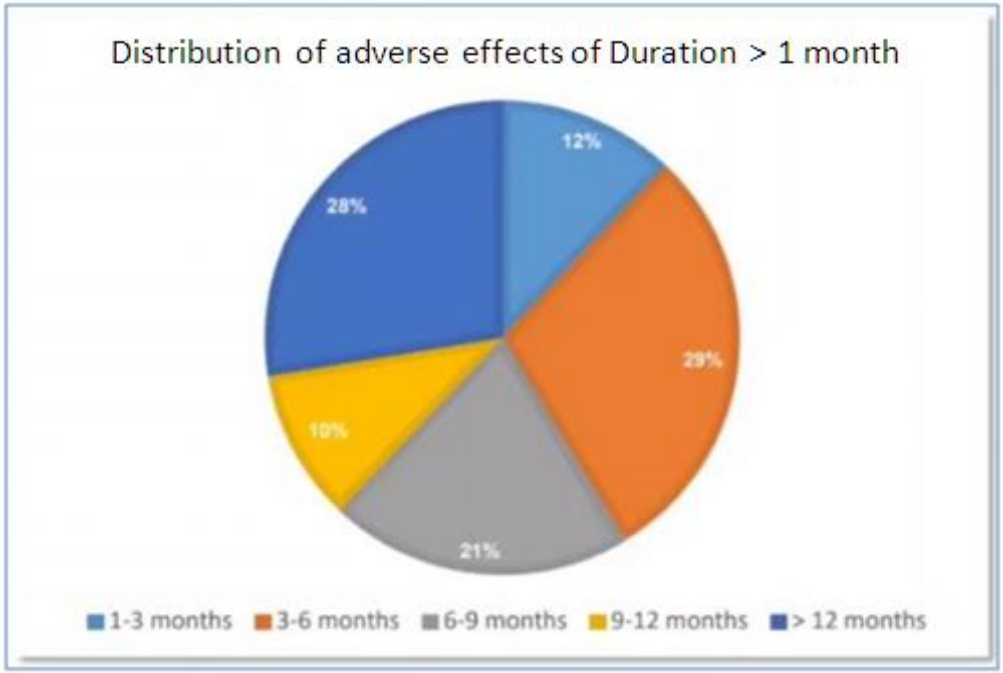
MedDRA PT that amount to about 70% of total reports categorized as Neurological

395	**Total Neurological**
82	Hypoaesthesia
55	Paraesthesia
28	Dizziness
18	Tinnitus
17	Syncope
14	Facial paralysis
11	Migraine
9	Vertigo
8	Tremor
8	Presyncope
8	Loss of consciousness
7	Hypoaesthesia oral
7	Nervous system disorders

Neurological adverse events reported in the form as free text

Up to 31.5.2022, **395 adverse events classified as Neurological** were reported as free text. Out of the 395 reports, in 85 cases (22%) **Duration** of the adverse event was reported.

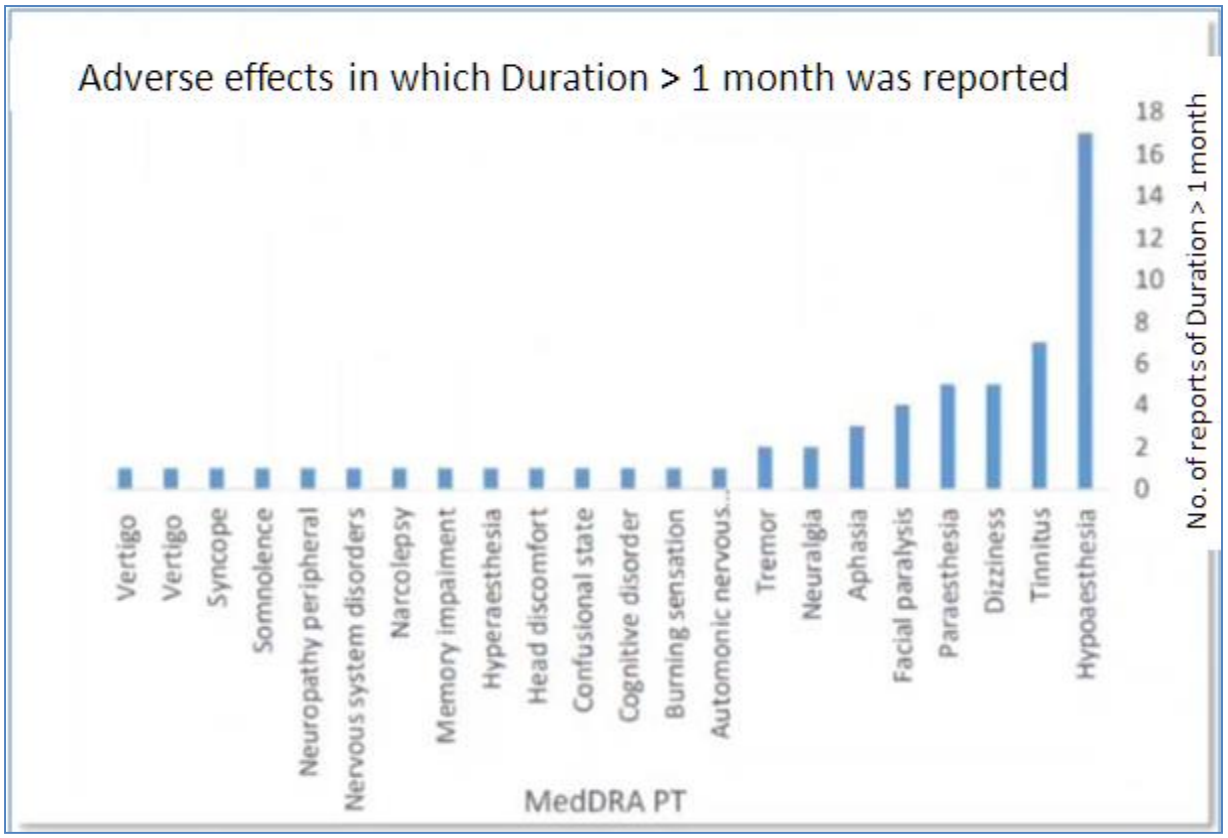
- In 58 cases (68%) out of the 85, Duration of adverse event above 1 month was reported
- In 38 cases (65%) in which Duration of more than 1 month was recorded, the adverse event was described as ongoing, i.e. its end could not be determined, but it was possible to determine its duration until the time the report was submitted
- The following graph presents the Neurological adverse events (according to MedDRA PT) of Duration > 1 month



Neurological adverse events reported in the form as free text

Up to 31.5.2022, **395 adverse events classified as Neurological** were reported as free text. Out of the 395 reports, in 85 cases (22%) **Duration** of the adverse event was reported.

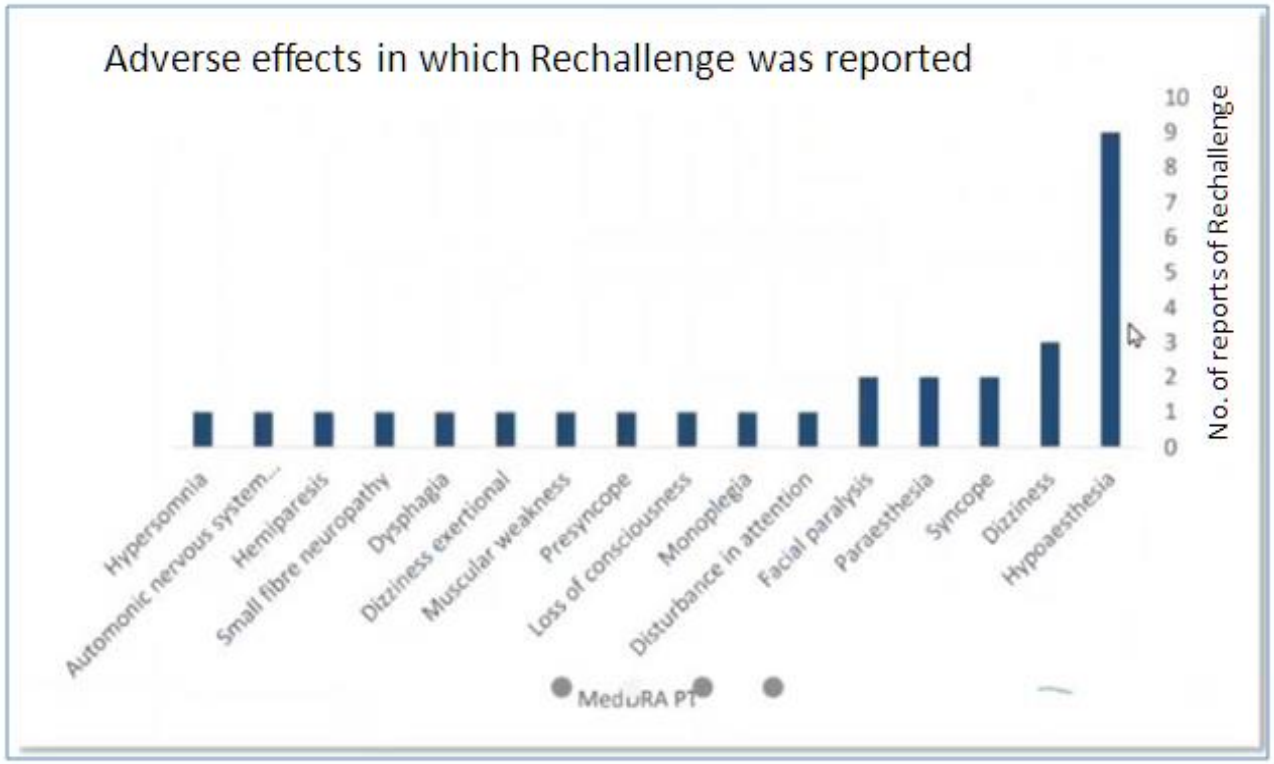
- In 58 cases (68%) out of the 85, Duration of adverse event above 1 month was reported
- The following graph presents the Neurological adverse events (according to MedDRA PT) in which Duration > 1 month was reported



Neurological adverse events reported in the form as free text

Up to 31.5.2022, **395 adverse events classified as Neurological** were reported as free text. Out of the 395 reports, in 29 cases (7%) **Rechallenge** was reported (return/ worsening following another dose)

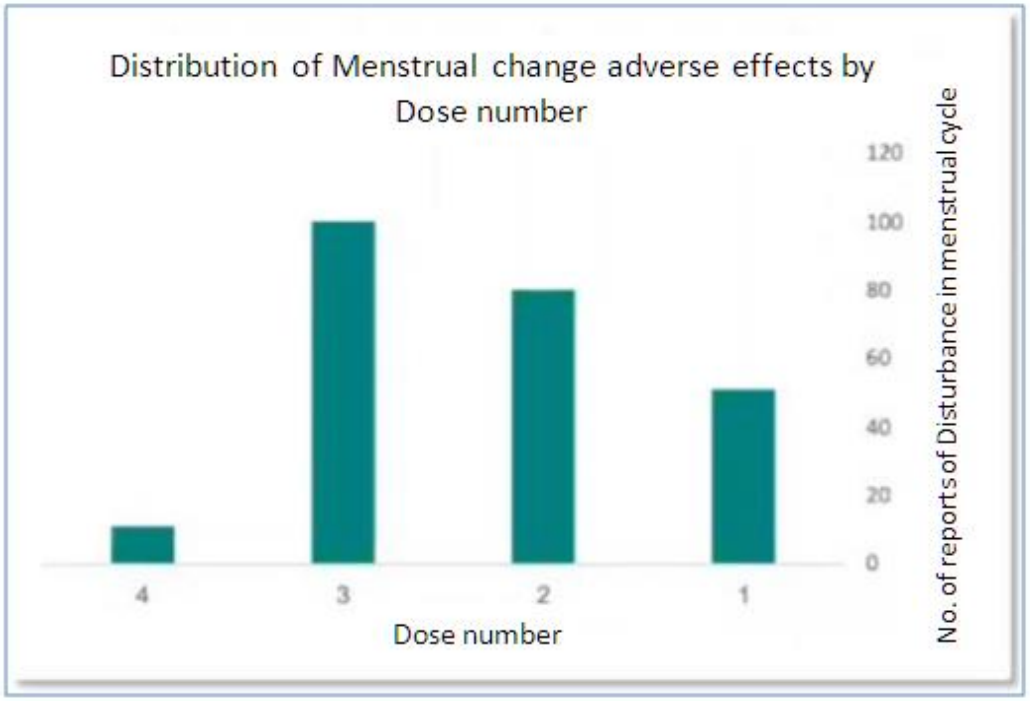
- The following graph presents the Neurological adverse events (according to MedDRA PT) in which Rechallenge was reported

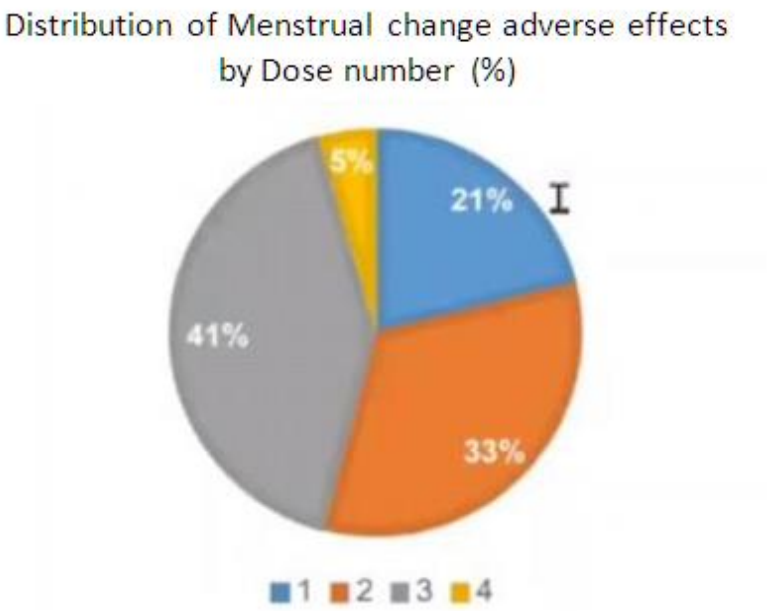


Menstrual change adverse events reported in the form as free text

Up to 31.5.2022, **282 adverse events classified as Menstrual change** were reported as free text (18% of adverse events reported in females)

- Out of the 282, in 242 reports data were given regarding **Dose number**
- The following graphs present the distribution of the number of adverse events by Dose number

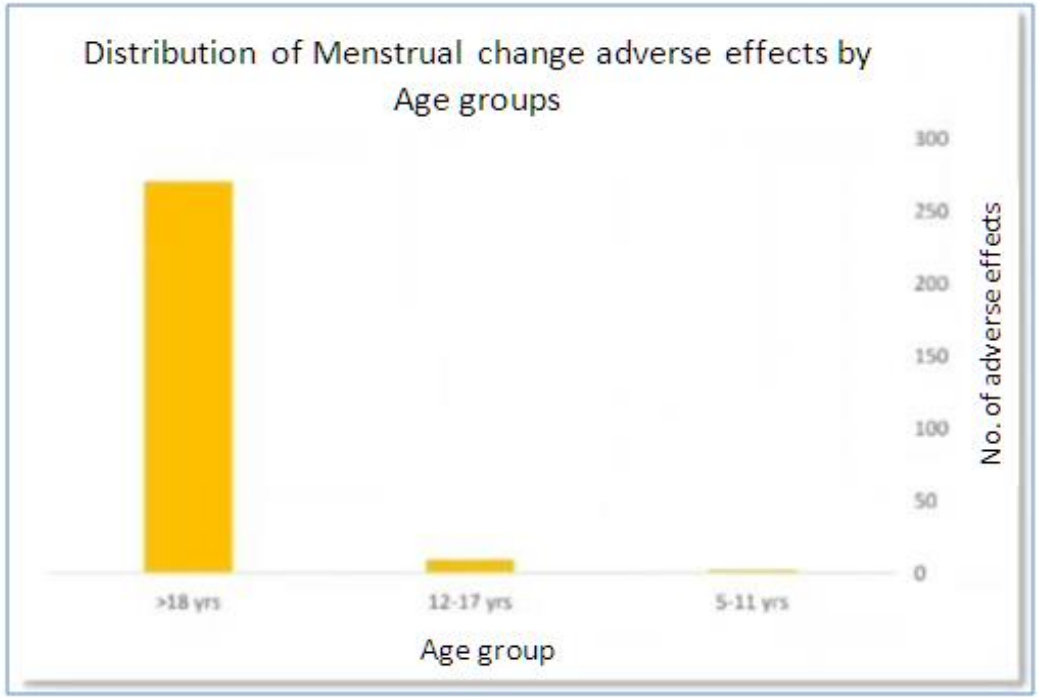


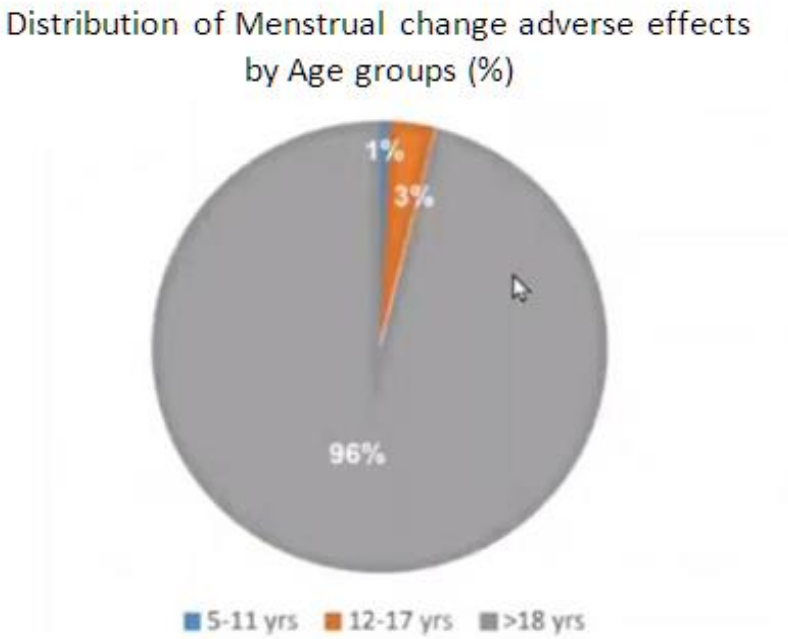


Menstrual change adverse events reported in the form as free text

Up to 31.5.2022, **282 adverse events classified as Menstrual change** were reported as free text.

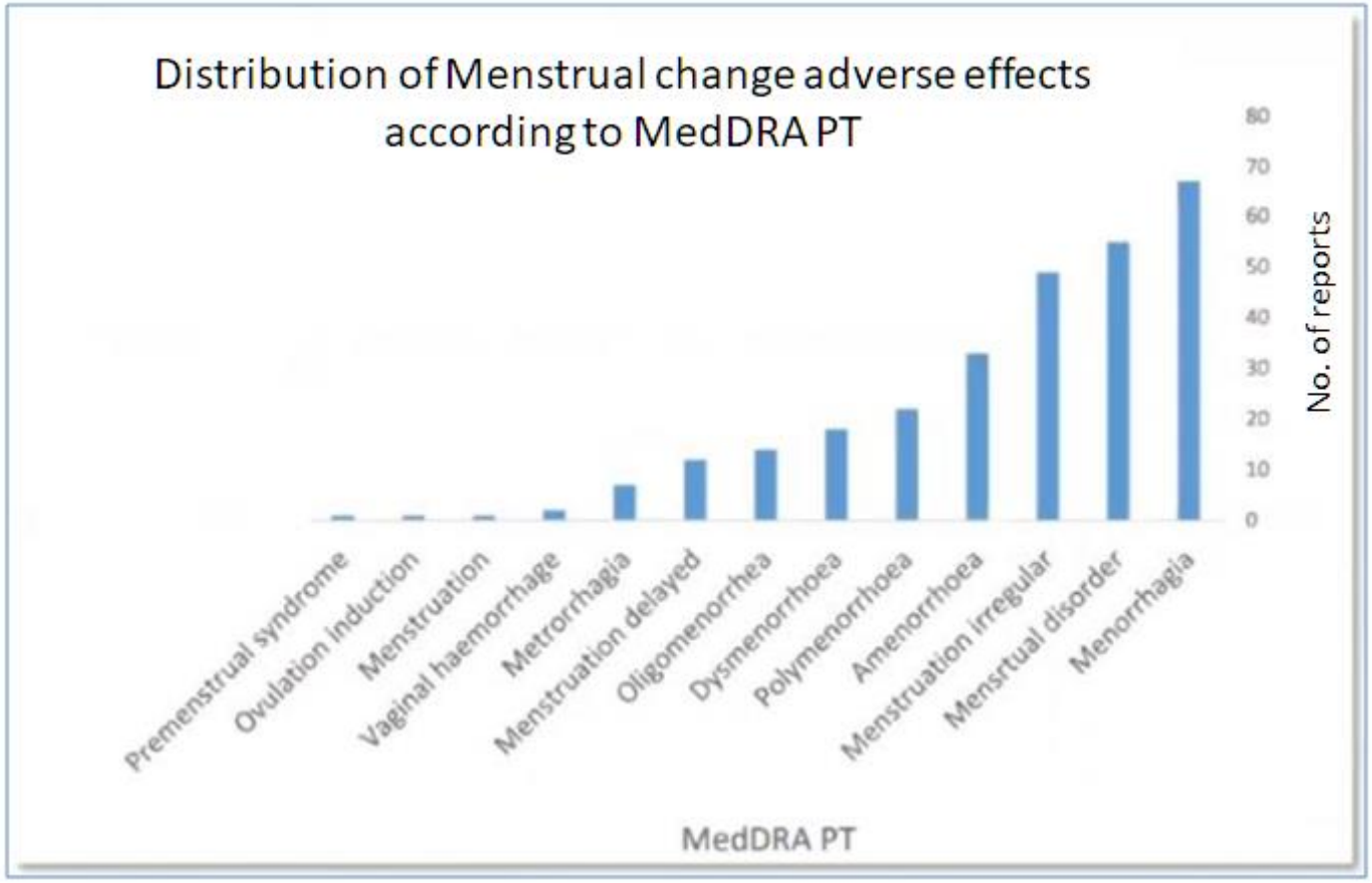
The following graphs present the distribution of adverse events by Age groups





Menstrual change adverse events reported in the form as free text

Up to 31.5.2022, **282 adverse events classified as Menstrual change** were reported as free text. The following graph presents their distribution according to MedDRA PT



Menstrual change adverse events reported in the form as free text

Up to 31.5.2022, **282 adverse events classified as Menstrual change** were reported as free text

The following table presents the common adverse events that amount to 80% of total adverse events categorized as Menstrual change

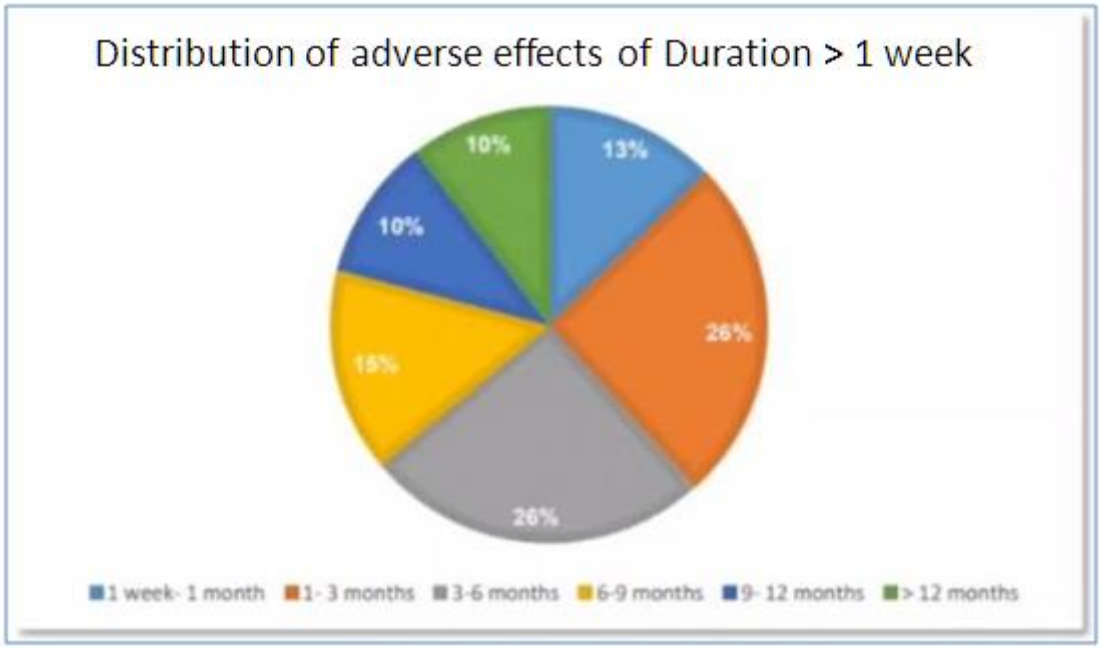
MedDRA PT that amount to about 80% of total reports categorized as Menstrual change adverse events

282	Total Menstrual change
67	Menorrhagia
55	Mensrtual disorder
49	Menstruation irregular
33	Amenorrhoea
22	Polymenorrhoea

Menstrual change adverse events reported in the form as free text

Up to the date 31.5.2022, **282 adverse events classified as Menstrual change** were reported as free text

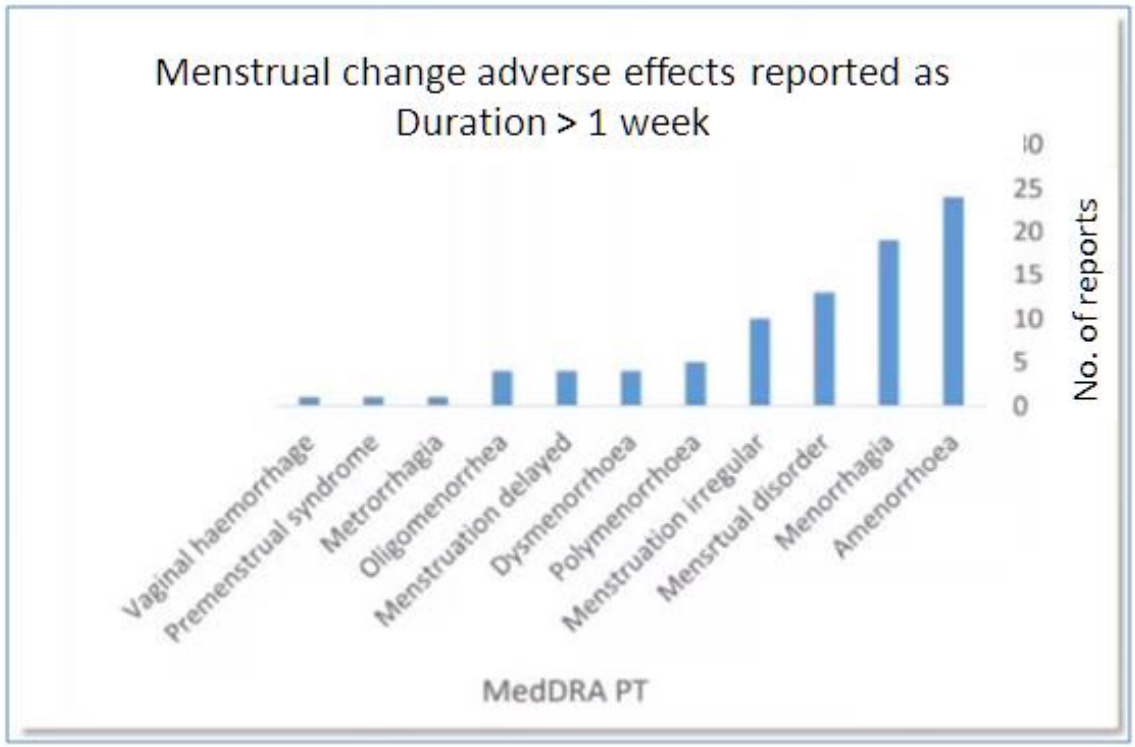
- Out of 282 reports, in 88 cases (31%) the **Duration** of the adverse effect was reported
- In 86 cases out of 88 (89%) Duration above 1 week was reported
- In 27 of the cases (30%) in which Duration of the adverse effect was reported > 1 week, the effects were described as ongoing, , i.e. its end could not be determined, but it was possible to determine its duration until the time the report was submitted
- The following graph presents the Menstrual change adverse events with Duration > 1 week



Menstrual change adverse events reported in the form as free text

Up to 31.5.2022, **282 adverse events classified as Menstrual change** were reported as free text

- Out of 282 reports, in 88 cases (31%) the **Duration** of the adverse event was reported
- In 86 cases out of 88 (89%) Duration above 1 week was reported
- The following graph presents the Menstrual change adverse events (according to MedDRA PT) that were reported as Duration > 1 week

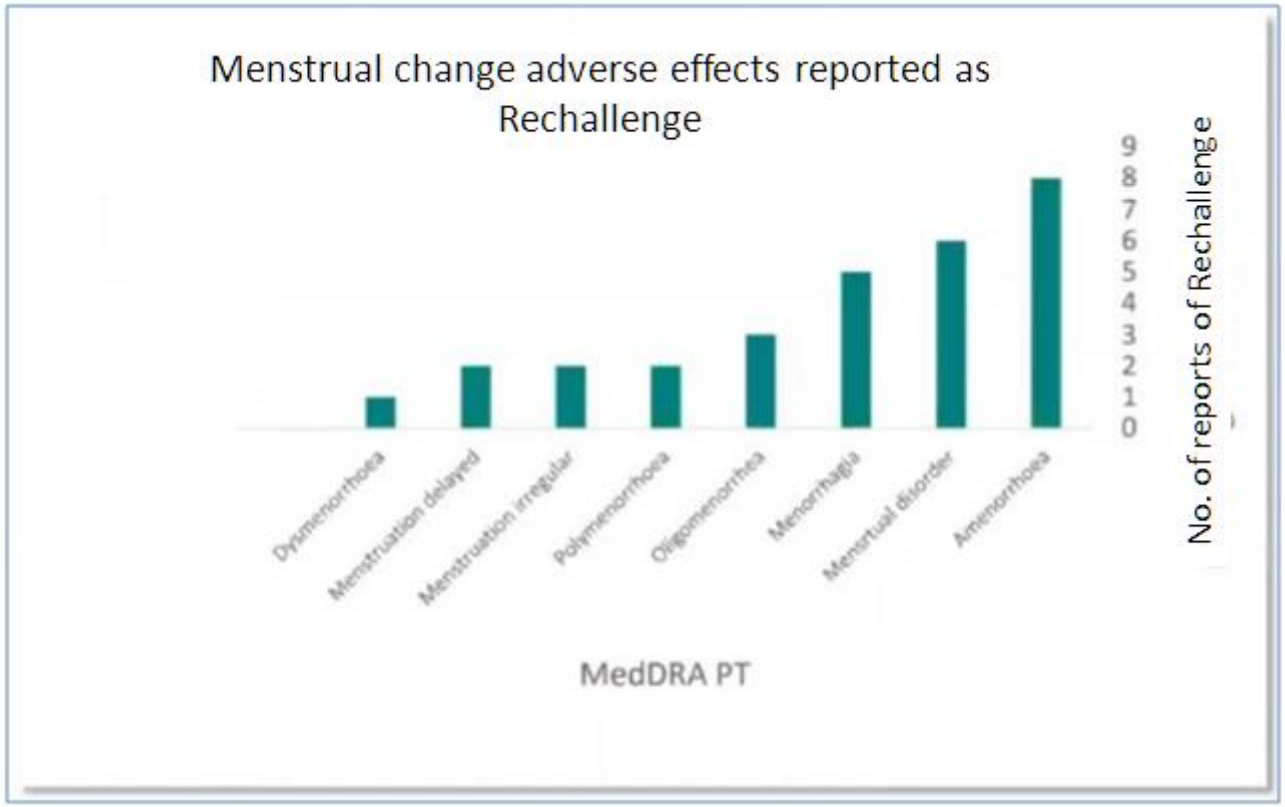


Menstrual change adverse events reported in the form as free text

Up to 31.5.2022, **282 adverse events classified as Menstrual change** were reported as free text

Out of 282 reports, in 29 cases (10%) **Rechallenge** was reported (return/ worsening after another dose)

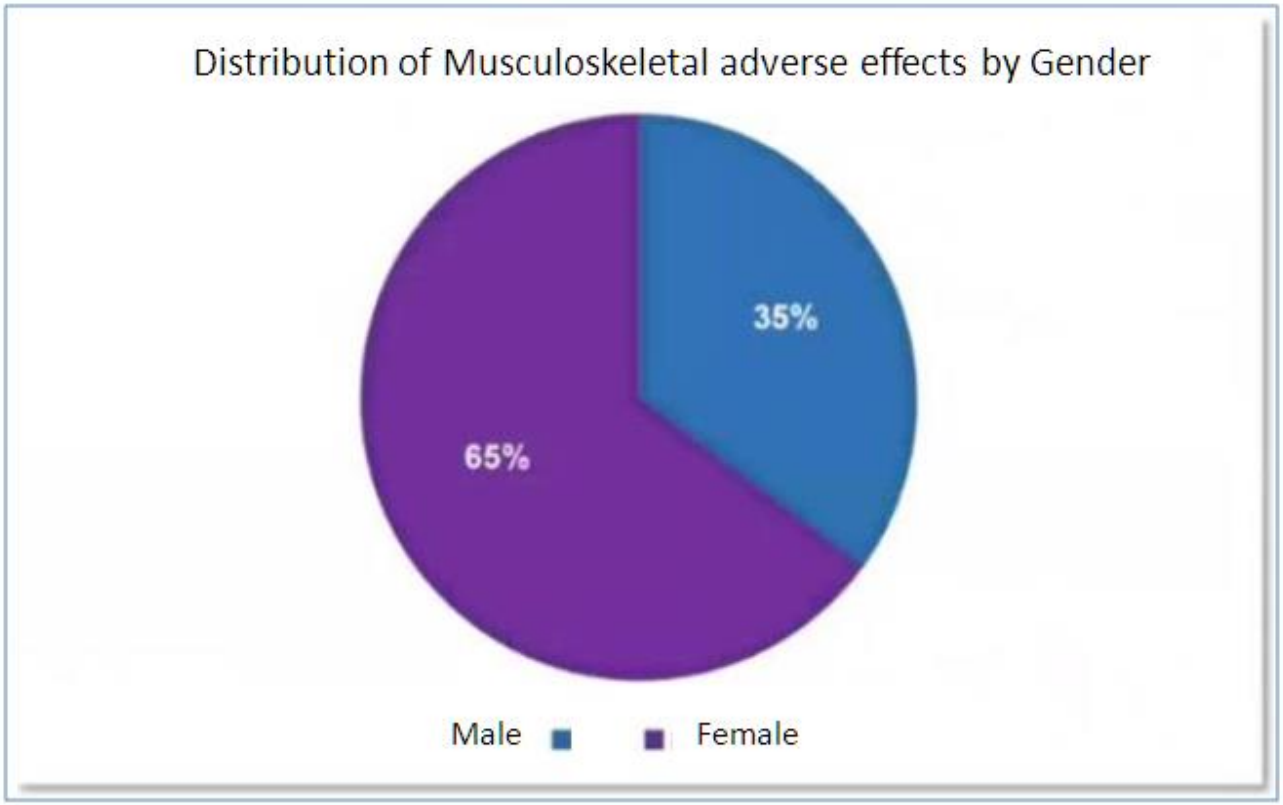
The following graph presents the Menstrual change adverse events (according to MedDRA PT) that were reported as Rechallenge



Musculoskeletal adverse events reported in the form as free text , distribution by Gender

Up to 31.5.2022, **279 adverse events classified as Musculoskeletal** were reported as free text (13% of the adverse events reported as free text)

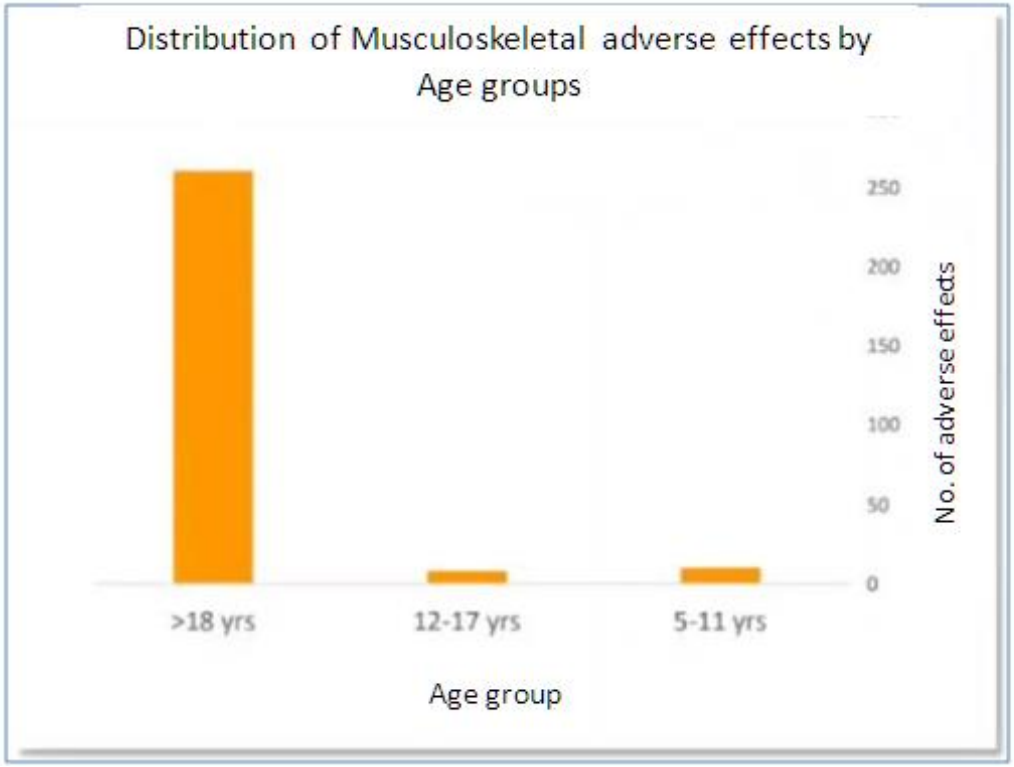
The following graph presents the distribution of adverse events by Gender

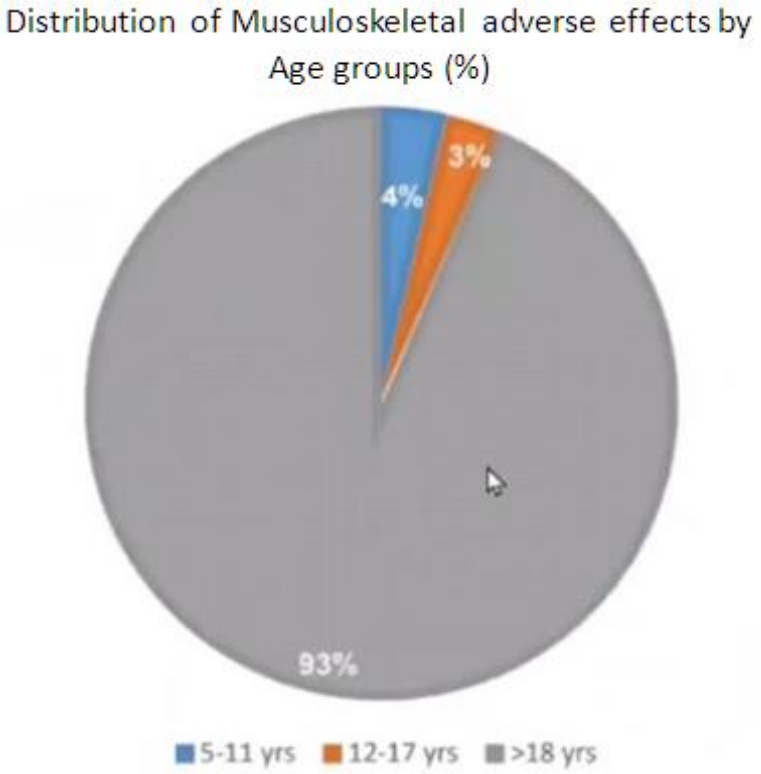


Musculoskeletal adverse events reported in the form as free text

Up to 31.5.2022, **279 adverse events classified as Musculoskeletal** were reported as free text

The following graphs present the distribution of adverse events by Age groups

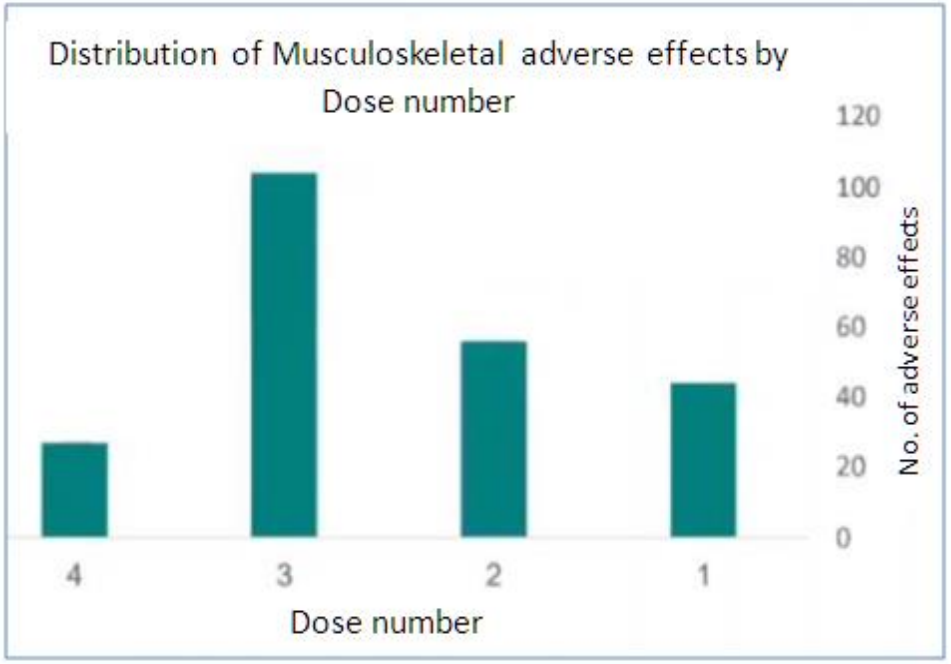


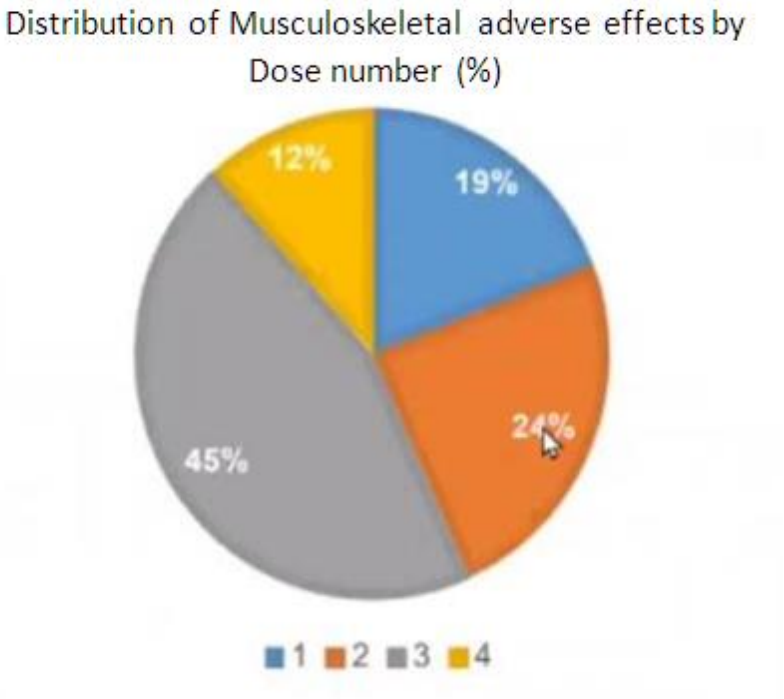


Musculoskeletal adverse events reported in the form as free text

Up to 31.5.2022, **279 adverse events classified as Musculoskeletal** were reported as free text

- Out of 279 reports, 231 reports included data regarding **Dose number**
- The following graphs present the distribution of the number of adverse events by Dose number

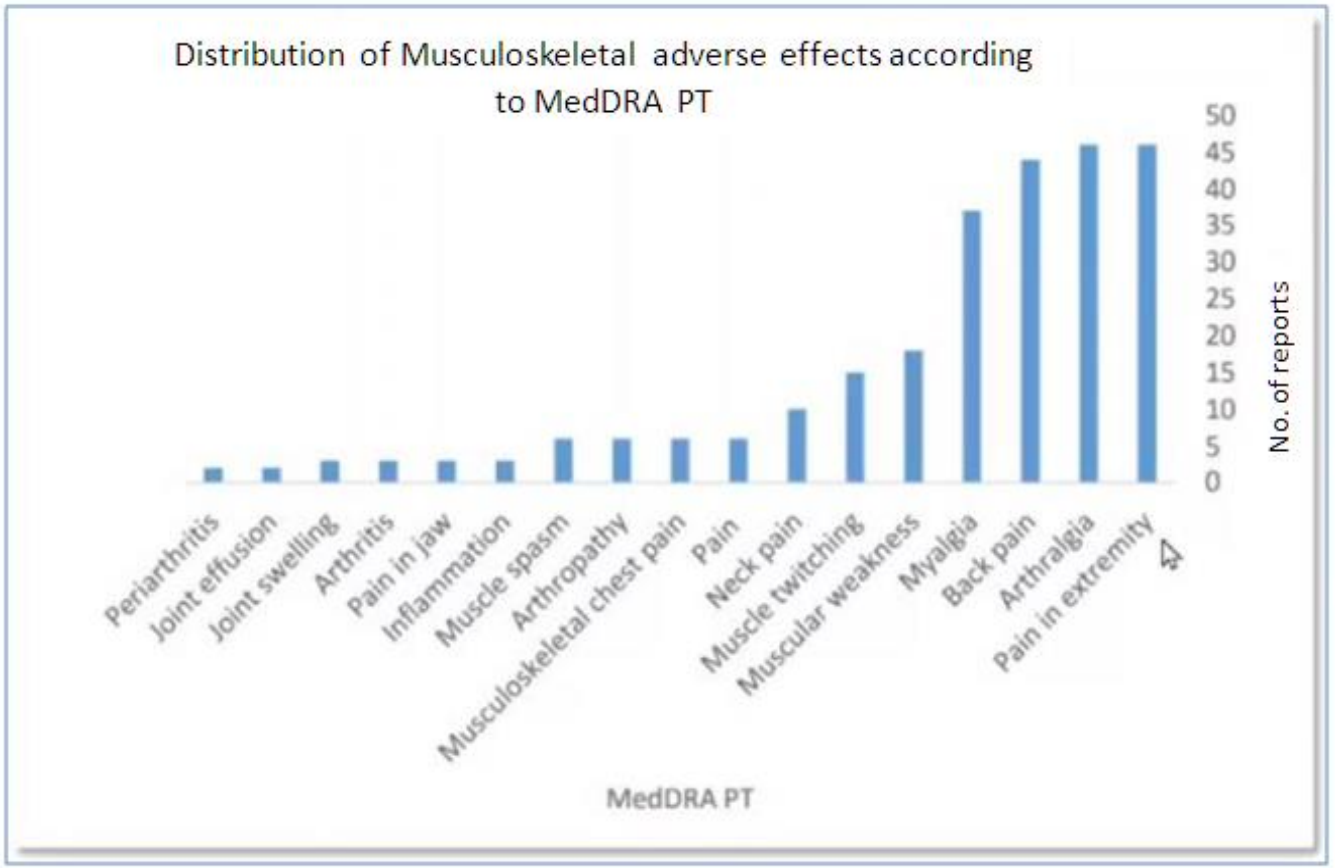




Musculoskeletal adverse events reported in the form as free text

Up to 31.5.2022, **279 adverse events classified as Musculoskeletal** were reported as free text

The following graph presents the distribution of common Musculoskeletal adverse events (92%) according to MedDRA PT

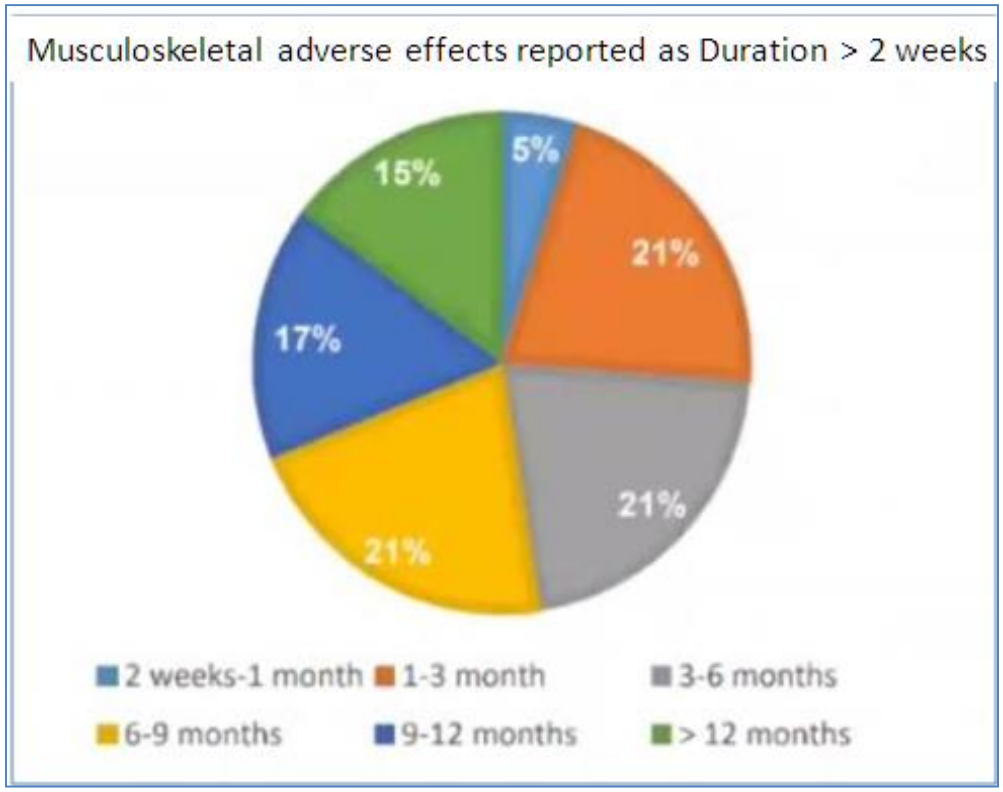


Musculoskeletal adverse events reported in the form as free text

Up to the date 31.5.2022, **279 adverse events classified as Musculoskeletal** were reported as free text

Out of 279 reports, in 79 cases (28%) **Duration** of the adverse event was reported.

- In 61 cases out of the 79 (77%), Duration of the adverse event was reported above 2 weeks
- In 33 of the cases (42%) in which Duration was reported > 2 weeks, the adverse events were described as ongoing, i.e. its end could not be determined, but it was possible to determine its duration until the time the report was submitted
- The following graph presents the distribution of adverse events (according to MedDRA PT) for which Duration was reported > 2 weeks

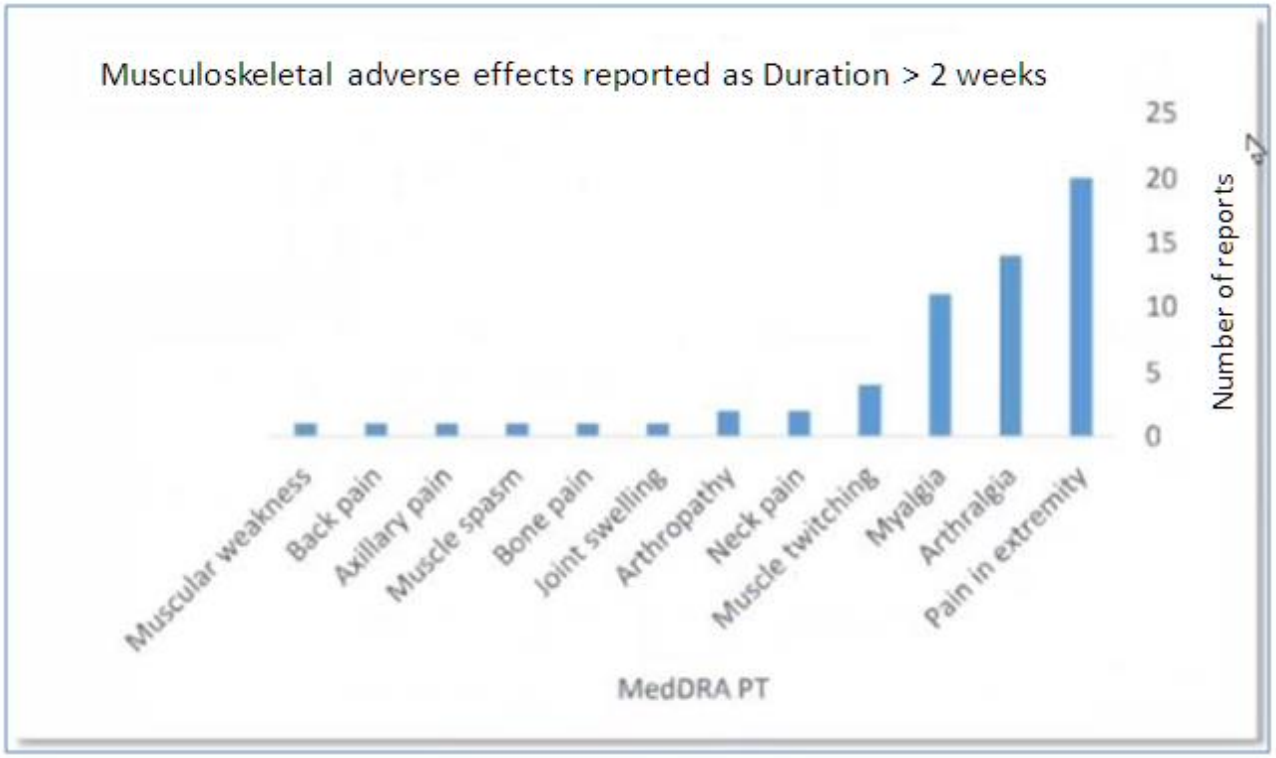


Musculoskeletal adverse events reported in the form as free text

Up to 31.5.2022, **279 adverse events classified as Musculoskeletal** were reported as free text

Out of 279 reports, in 79 cases (28%) **Duration** of the adverse event was reported

- In 61 cases out of 79 (77%), Duration of the adverse event was reported above 2 weeks
- The following graph presents the Musculoskeletal adverse events (according to MedDRA PT) for which Duration was reported > 2 weeks

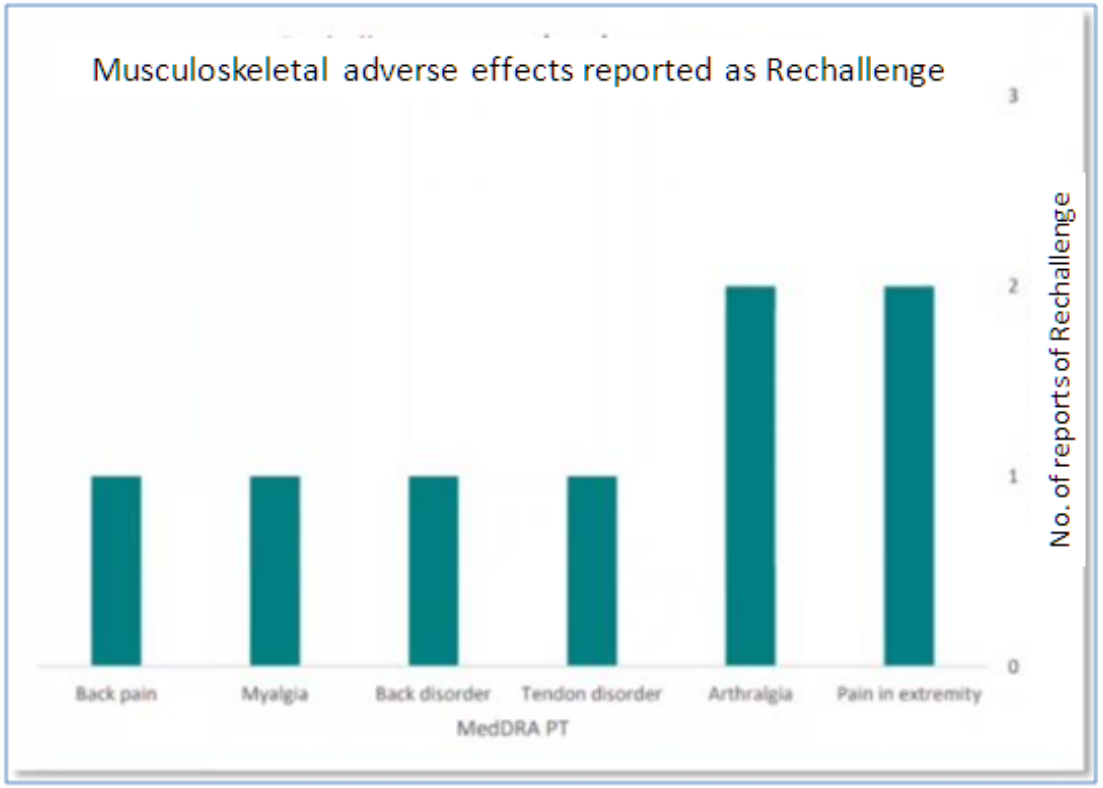


Musculoskeletal adverse events reported in the form as free text

Up to 31.5.2022, **279 adverse events classified as Musculoskeletal** were reported as free text

- Out of 279 reports, in 8 cases (3%) **Rechallenge** was reported (return/ worsening of the adverse effect following another dose)

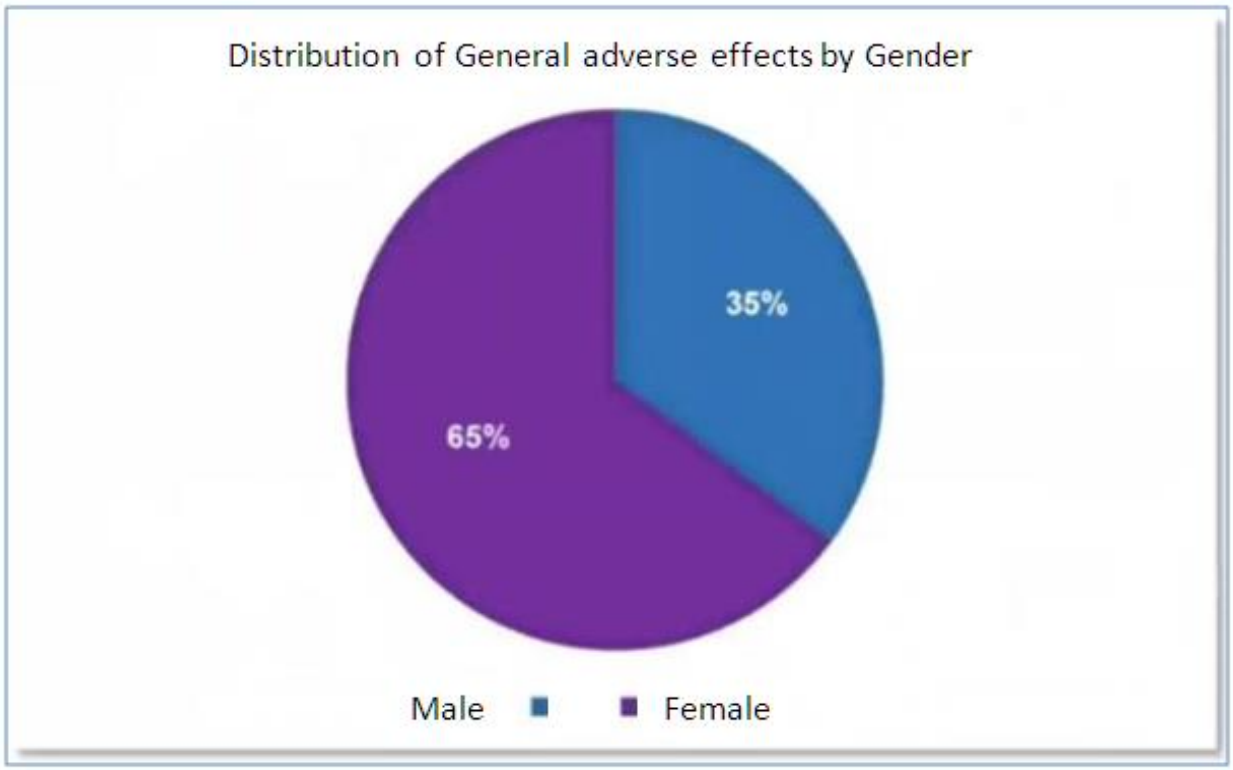
The following graph presents the Musculoskeletal adverse events (according to MedDRA PT) reported as Rechallenge



General adverse events reported in the form as free text, distribution by Gender

Up to 31.5.2022, **295 adverse events classified as General adverse events were reported as free text (14% of all adverse events reported as free text).**

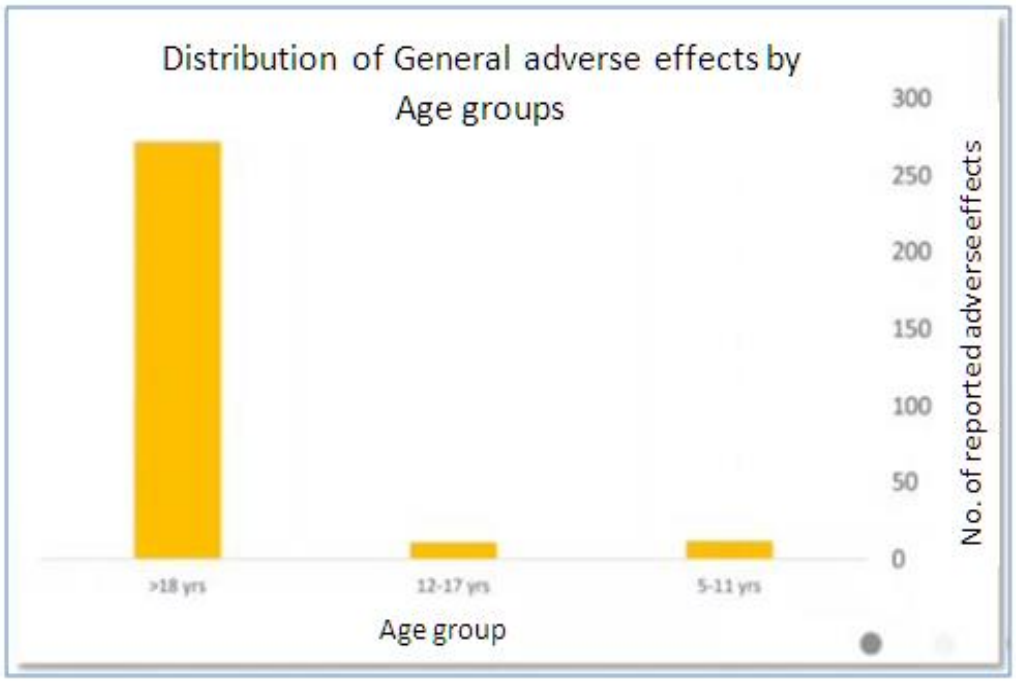
The following graph presents the distribution of the adverse events by Gender

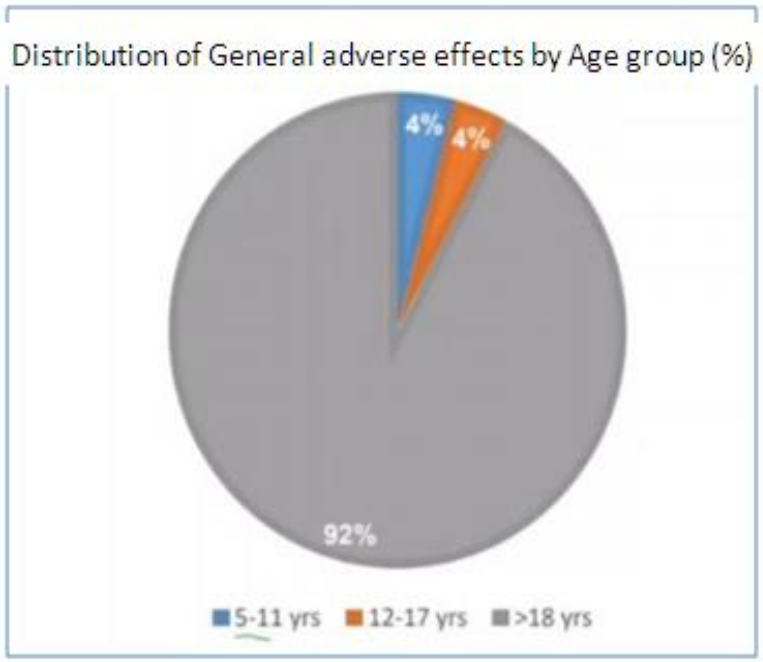


General adverse events reported in the form as free text, distribution by Age groups

Up to 31.5.2022, **295 adverse events classified as General** adverse events were reported as free text.

The following graphs present the distribution of adverse events by age groups

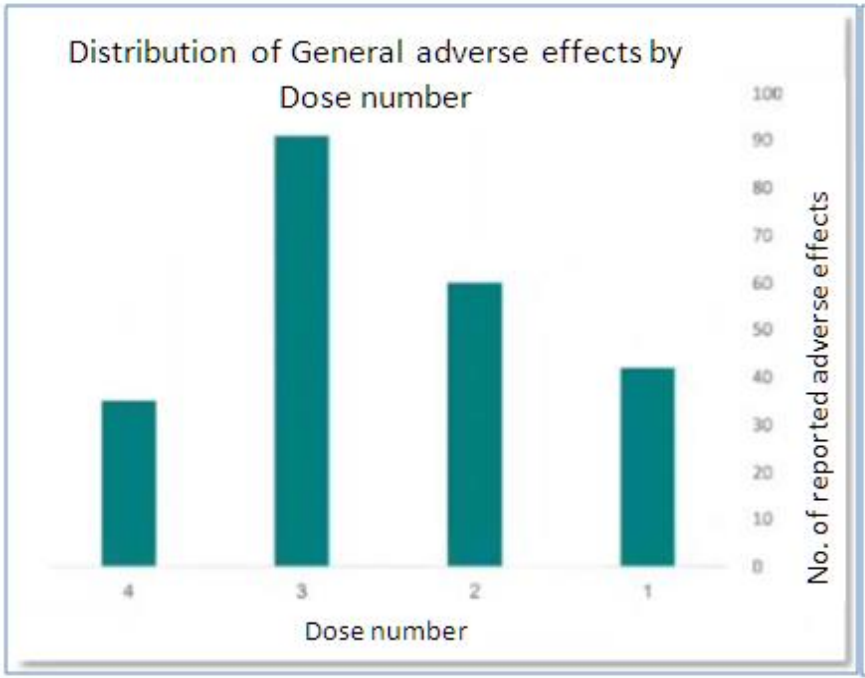


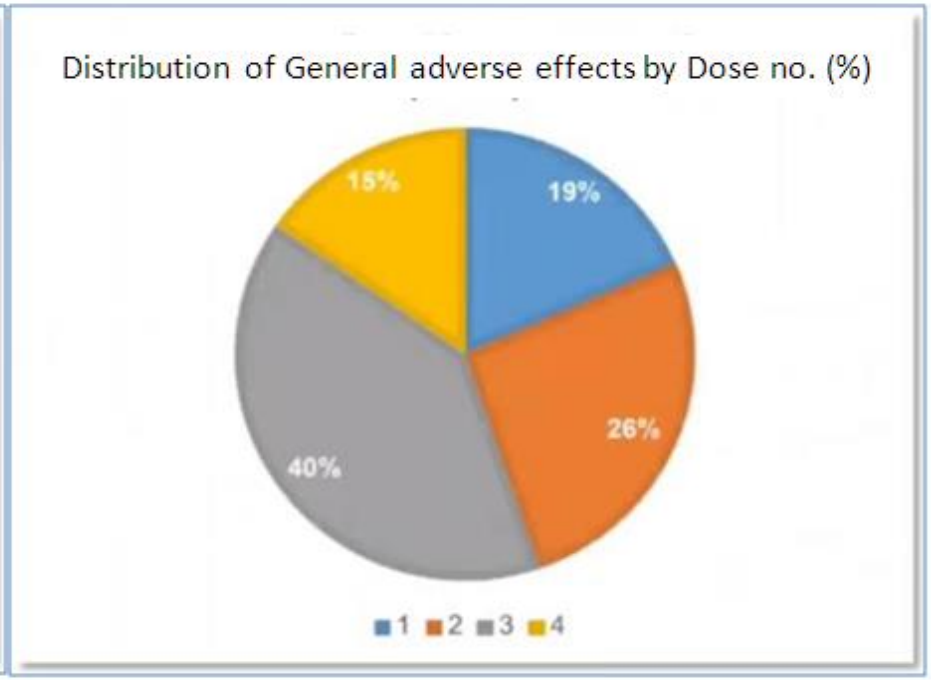


General adverse events reported in the form as free text, distribution by Dose number

Up to 31.5.2022, **295 adverse events classified as General** adverse events were reported as free text.

- Out of 295 reports, in 228 reports data were given regarding dose number.
- The following graphs present the distribution of adverse events by Dose number

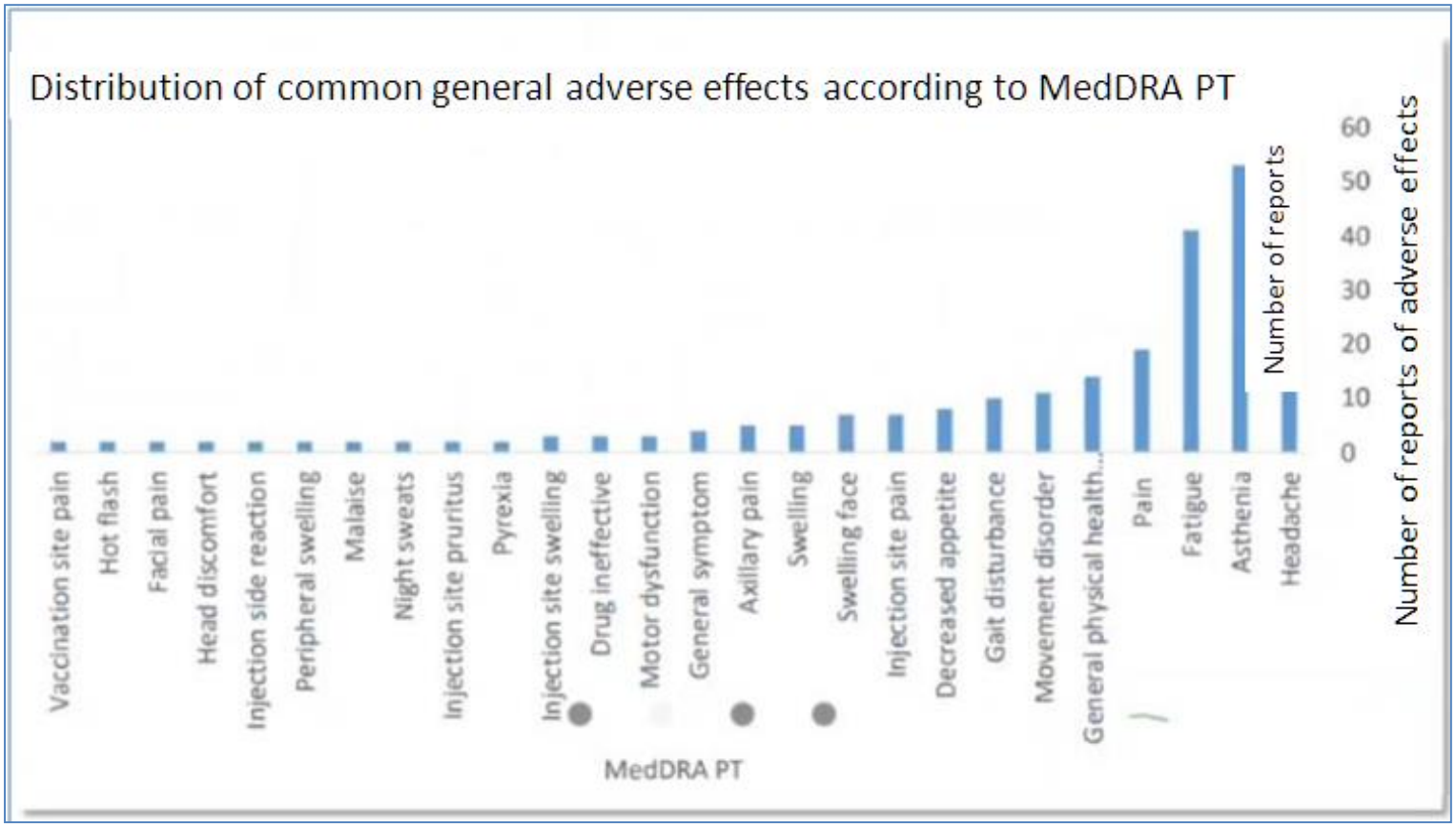




General adverse events reported in the form as free text, distribution by MedDRA PT and Rechallenge

Up to 31.5.2022, **295 adverse events classified as General** adverse events were reported as free text.

The following graph presents the distribution of common general adverse events (91%) according to MedDRA PT

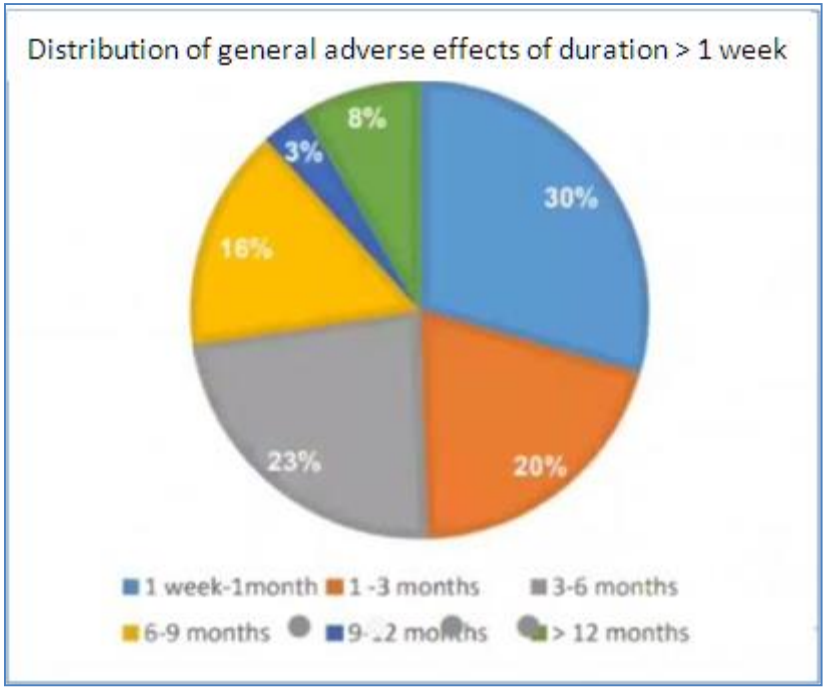


General adverse events reported in the form as free text, distribution by Duration of the adverse event

Up to 31.5.2022, **295 adverse events classified as General** adverse events were reported as free text.

Out of 295 reports, in 103 cases (35%), **Duration** of the adverse event was reported

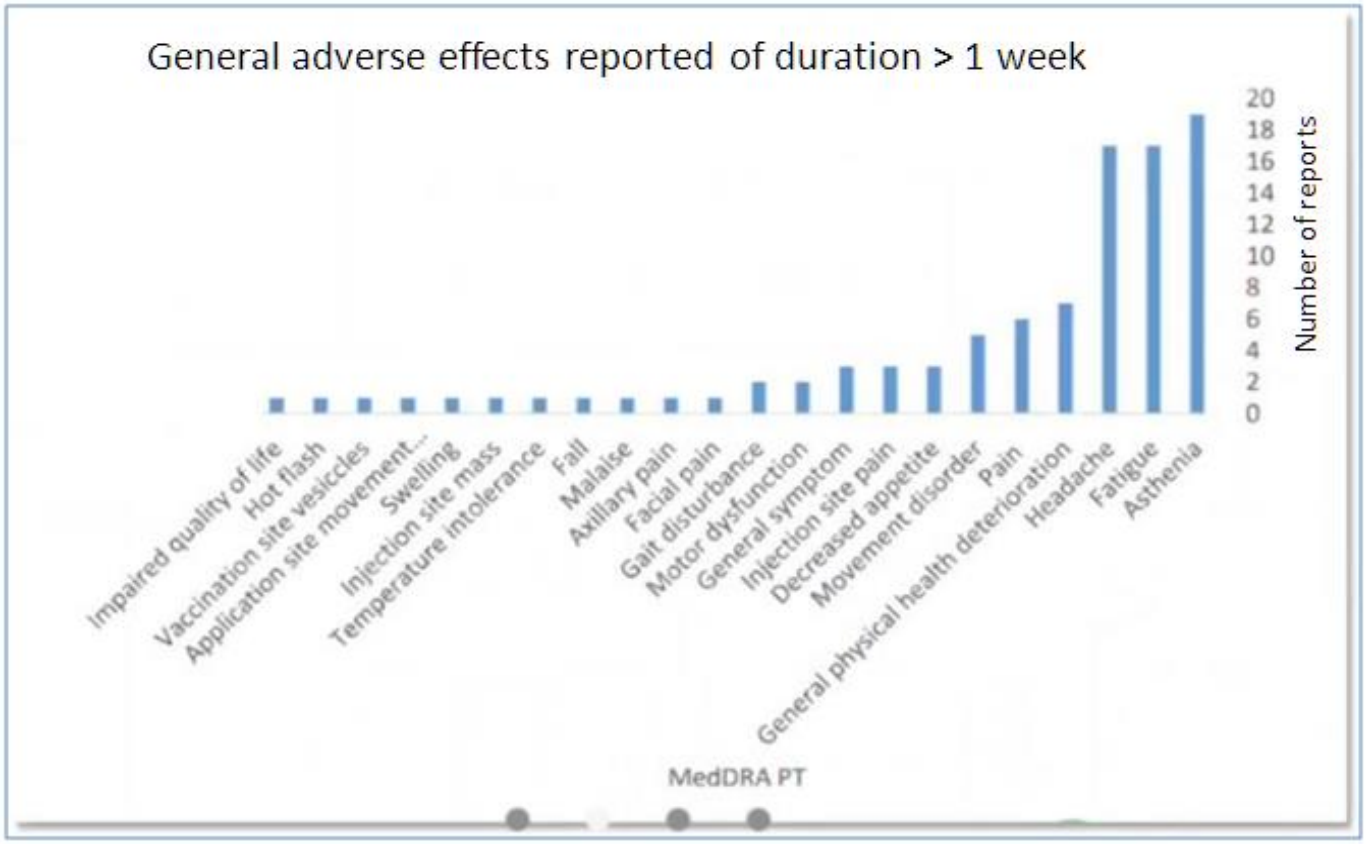
- In 95 cases out of the 103 (92%) an adverse event was reported of duration above 1 week
- In 44 cases (46%) in which duration longer than 1 week was reported, the adverse event was described as ongoing, i.e. its end could not be determined, but it was possible to determine its duration until the time the report was submitted
- The following graph presents the distribution of adverse events reported of duration > 1 week



General adverse events reported in the form as free text, distribution by MedDRA PT and Rechallenge

Up to 31.5.2022, **295 adverse events classified as General** adverse events were reported as free text.

- In 95 cases, an adverse event was reported of duration above 1 week
- The following graph presents the General adverse events (by Med DRA PT) reported of duration > 1 week

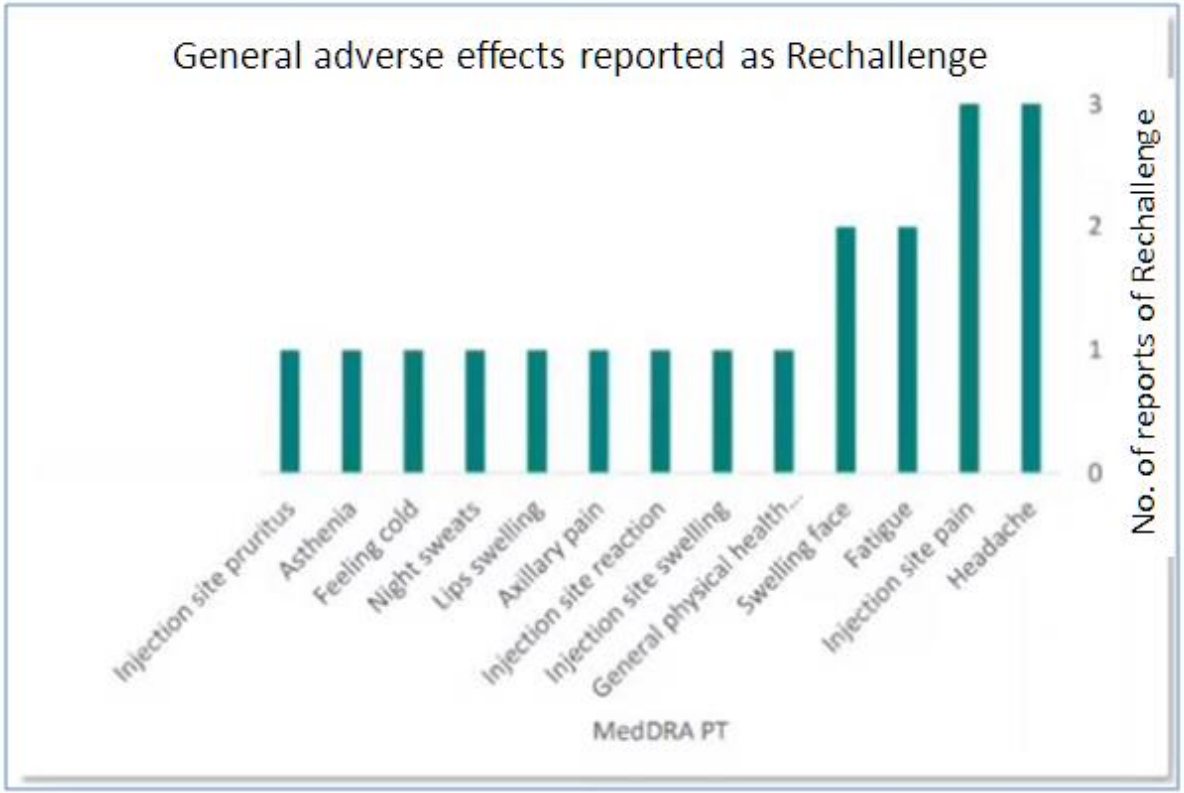


General adverse events reported in the form as free text, distribution by MedDRA PT and Rechallenge

Up to 31.5.2022, **295 adverse events classified as General** adverse events were reported as free text

Out of 295 reports, in 19 cases (6%) **Rechallenge** was reported (return / worsening of an adverse event after another dose)

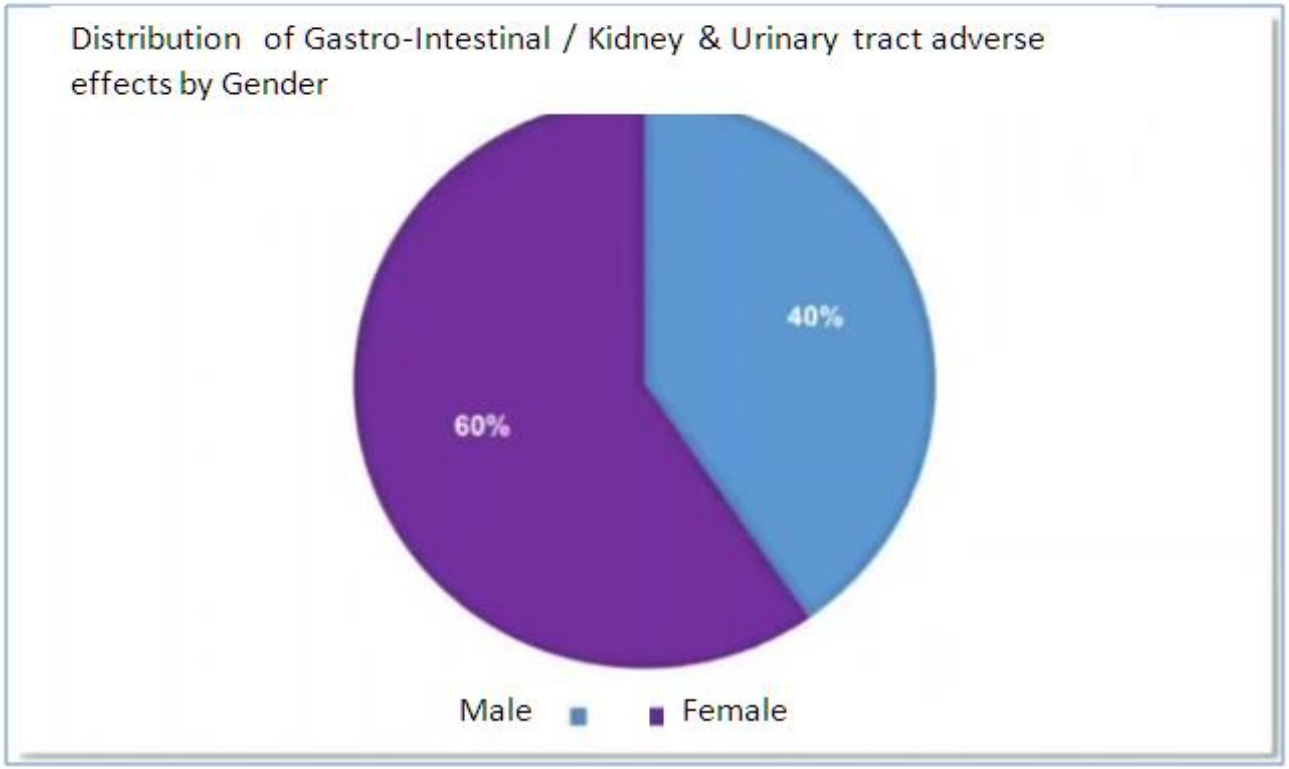
- The following graph presents the General adverse events (according to MedDRA PT) reported as Rechallenge



adverse events in the Gastro-Intestinal / Kidney & Urinary tract reported in the form as free text, distribution by Gender

- Up to 31.5.2022, **192 adverse events classified as Gastro-Intestinal / Kidney & Urinary tract were reported as free text (9% of all adverse events reported as free text)**

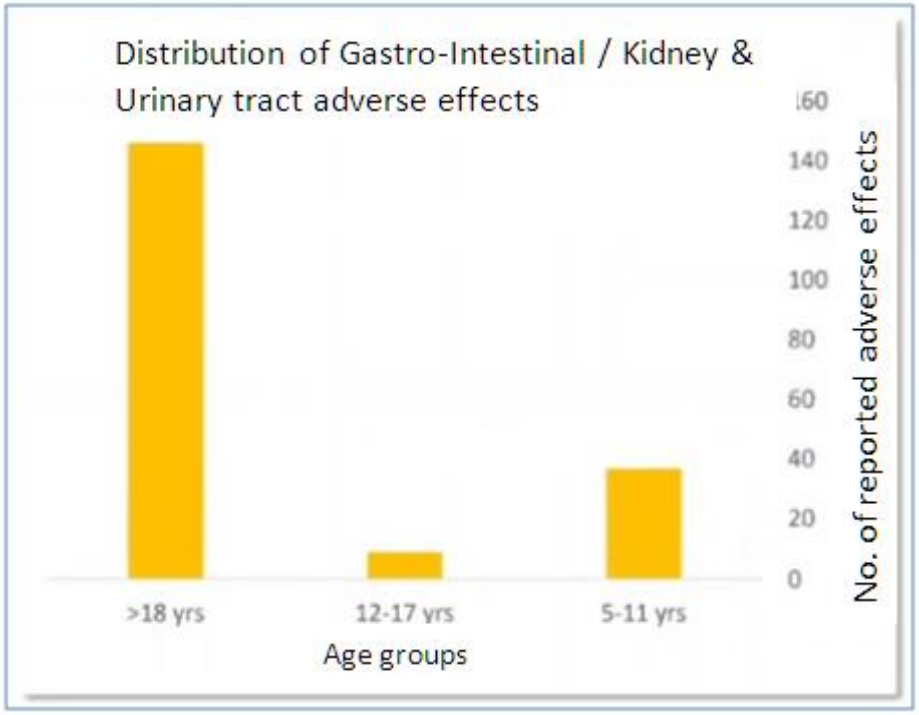
The following graph presents the distribution of these adverse events by gender

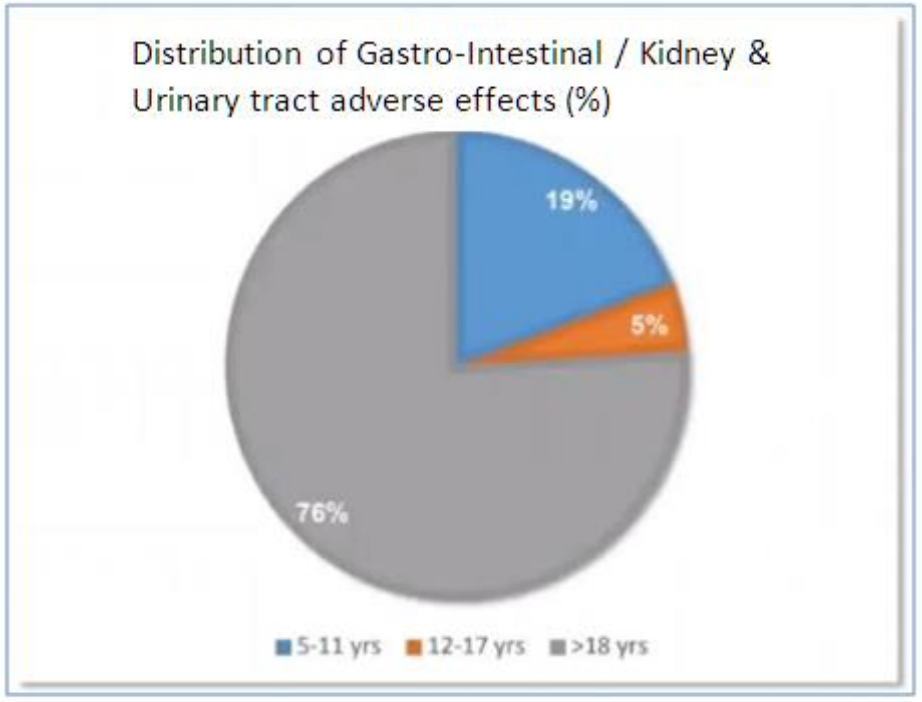


adverse events in the Gastro-Intestinal /Kidney & Urinary tract reported in the form as free text, distribution by Age groups

- Up to 31.5.2022, **192 adverse events classified as Gastro-Intestinal / Kidney & Urinary tract** were reported as free text.

The following graphs present the distribution of adverse events by age groups



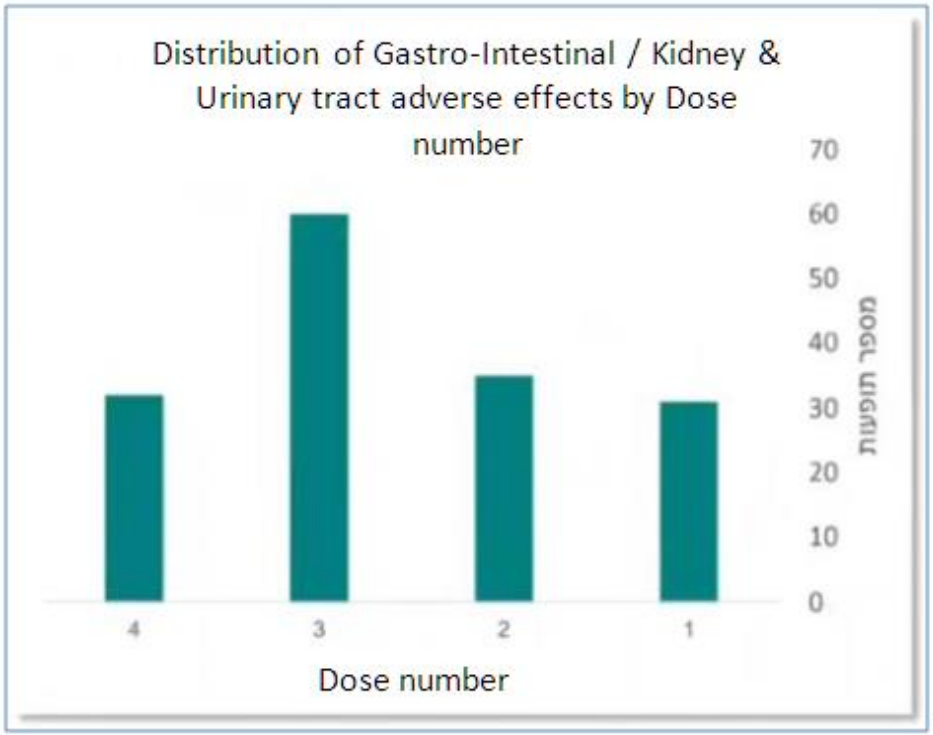


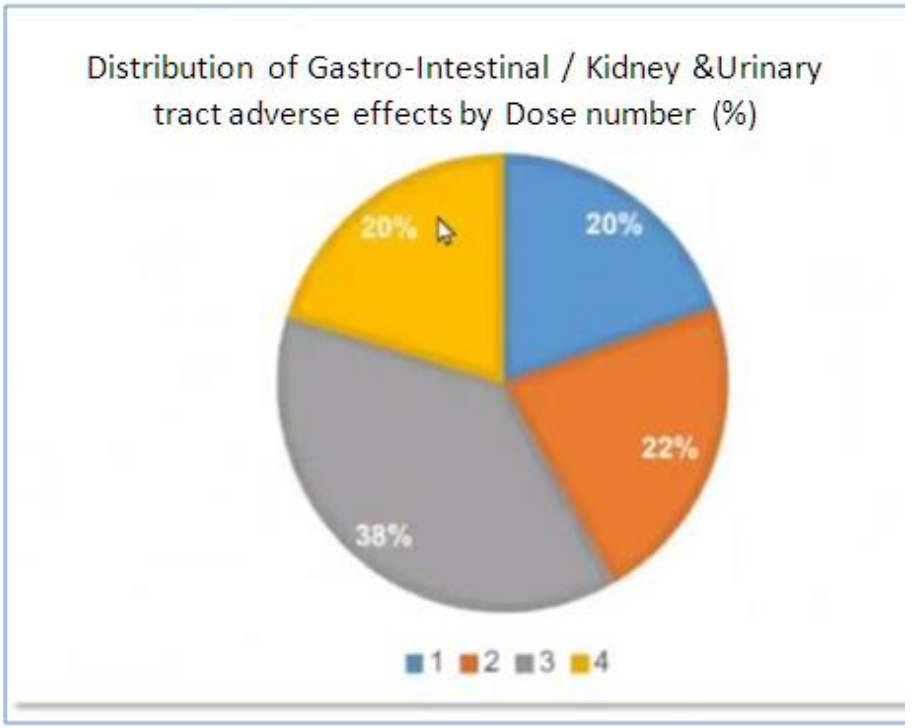
adverse events in the Gastro-Intestinal /Kidney & Urinary tract reported in the form as free text, distribution by Dose number

Up to 31.5.2022, **192 adverse events classified as Gastro-Intestinal / Kidney & Urinary tract** were reported as free text.

- Out of 192 reports, in 158 reports data were given regarding Dose number

The following graphs present the distribution of number of adverse events by Dose number

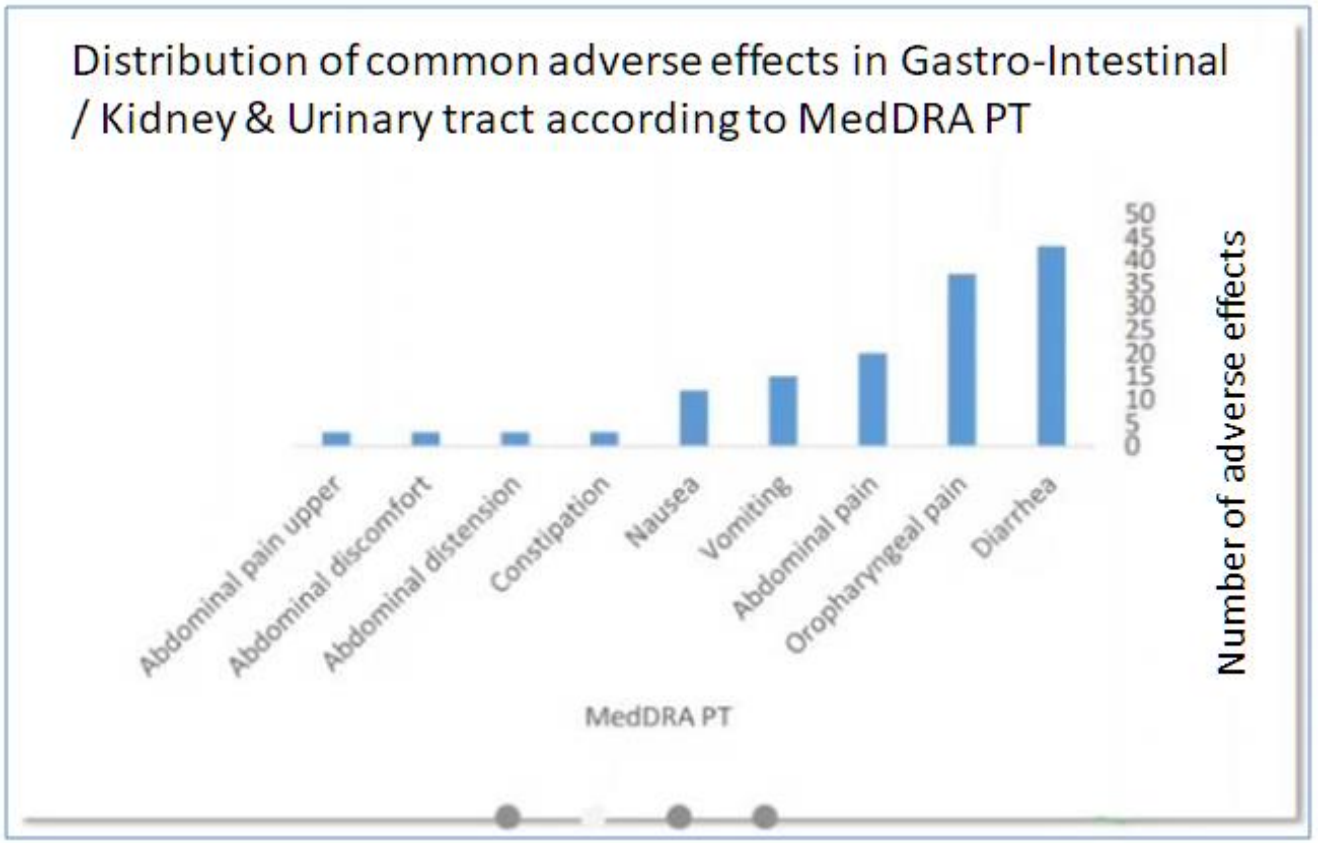




adverse events in the Gastro-Intestinal / Kidney & Urinary tract reported in the form as free text, distribution by MedDRA PT

Up to 31.5.2022, **192 adverse events classified as Gastro-Intestinal / Kidney & Urinary tract** were reported as free text.

The following graph presents the distribution of common adverse events (around 70%) in Gastro-Intestinal / Kidney & Urinary tract according to MedDRA PT



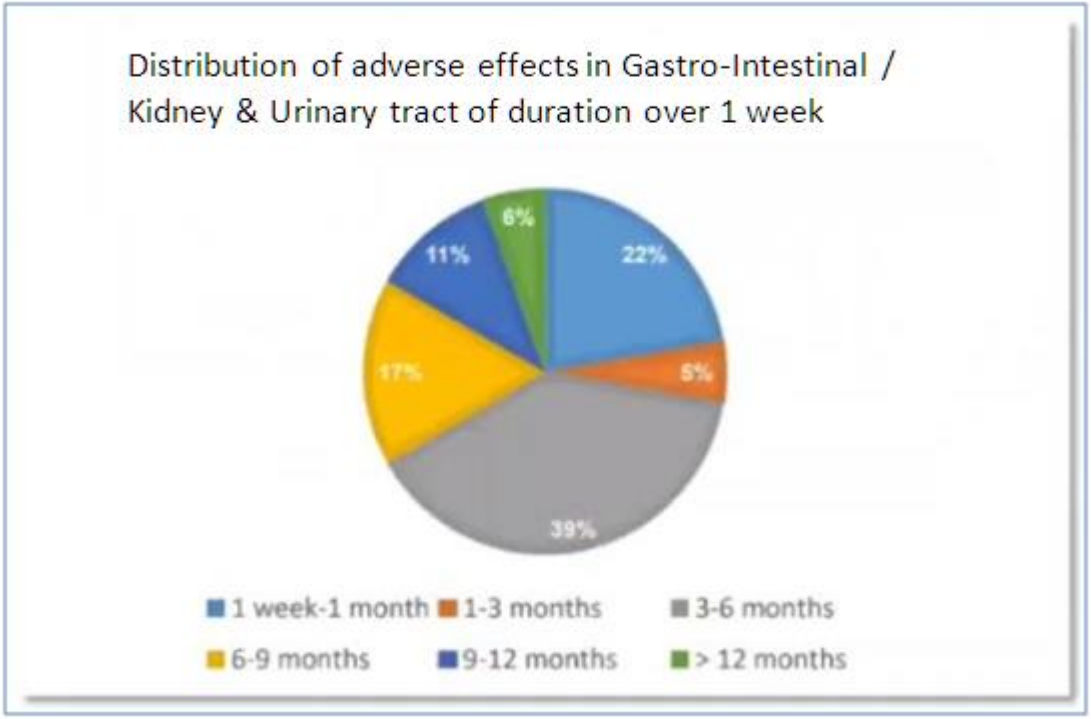
adverse events in the Gastro-Intestinal / Kidney & Urinary tract reported in the form as free text, segmentation by Duration

Up to 31.5.2022, **192 adverse events classified as Gastro-Intestinal / Kidney & Urinary tract** were reported as free text.

23 (12%) cases of these 192 reports reported **Duration** of the adverse event.

- In 19 cases out of 23 (82%) an adverse event of above 1 week duration was reported
- In 8 cases (42%) of the cases of duration longer than 1 week, the adverse event was described as ongoing, i.e. it had not disappeared, but its duration could be determined until the time of reporting

The following graph presents the distribution of Duration of adverse events of duration > 1 week

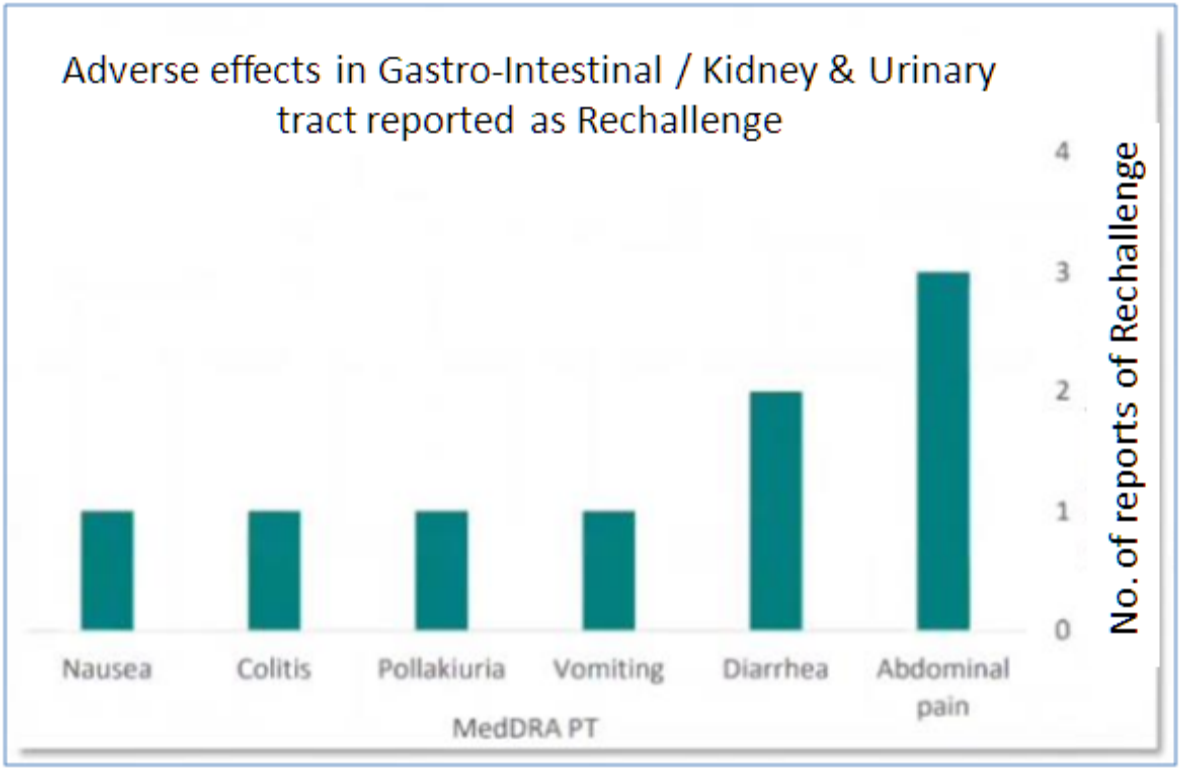


Adverse events in the Gastro-Intestinal / Kidney & Urinary tract reported in the form as free text, segmentation by MedDRA PT and Rechallenge

Up to 31.5.2022, **192 adverse events classified as Gastro-Intestinal / Kidney & Urinary tract** were reported as free text

Out of 192 reports, 9 cases (5%) were reported as **Rechallenge** (recurrence / worsening of a side effect after a repeated dose)

- The following graph presents the adverse events in the Gastro-Intestinal / Kidney &Urinary tract (according to MedDRA PT) reported as Rechallenge



Summary of findings collected via the predetermined fields and the open fields of the reporting form

- **Distribution of the reports by gender, predetermined field effects / free text:**
  a distribution of 60:40%-70-30% in favor of female can be seen (except for reports regarding menstrual change) that remains, regardless of the manner of reporting.

- **Distribution of the reports by vaccine doses, closed field effects / free text:**
  a distribution of around 10% : 40% : 30% : 20% is seen for doses 4:3:2:1 respectively. The distribution remains, regardless of manner of reporting. Notably the distribution of doses regarding the menstrual change adverse events is exceptional because the fraction of the forth dose is reduced to 5% while the fractions of doses 2 and 3 are wider.

  It appears that the explanation is that the population that received the forth dose was older (not in reproductive age) and therefore did not experience such effects.

Summary of findings collected via the predetermined fields and the open fields of the reporting form

Distribution of the reports by age groups, predetermined field adverse events / free text

1. In general (excluding the exceptions specified in the following slides), consistency can be seen in the distribution of reports according to age groups (85-90% report in the adult group; 2-5% in the adolescent group; 5-10% in the pediatric group), regardless of the manner of reporting.
2. It is appropriate to note here that consistently, less effects are reported in the adolescent group in comparison with the other age groups, despite higher vaccination rates in this group compared to the pediatric group
3. Additionally, side effects related to the gastrointestinal system are reported more in the pediatric age group (widens to 19% versus 10% in other effects) at the expense of reduction in the adult age group (75% instead of 85-90% in other effects).
4. Naturally, the opposite phenomenon was seen on side effects related to menstrual changes – the fraction of adults widens to 90% while the pediatric fraction shrinks to 1%

Summary of findings collected via the open fields of the reporting form

Advantages and shortcomings of collection and analysis of data from free text

- Identification and gaining of additional knowledge regarding unknown adverse events, that are not included in the predetermined fields.
- The manner of data delivery (in natural language including details) enables characterization of the adverse event clinically, onset, duration, Rechallenge, etc. Collection of such information may contribute, significantly, to establishment of causal relationship between the vaccine and the side effect.
- Data documented in the open fields were delivered voluntarily and in an undirected way, i.e. it is unsolicited. This characteristic raises its research value.
- Enables identification of signals/adverse events with DDR (Disproportionate Reporting Rate), such as menstrual changes, neurological disorders, etc.
- Adding knowledge regarding characterization and identification of adverse events that do not appear in the Comirnaty preparation's physician's leaflet, but have raised the scientific community's interest.

Summary of findings collected via the open fields of the reporting form

New findings:

- Menstrual irregularities:
  1. Characterization of the 5 common adverse events (Menorrhagia, Menstrual disorder, Menstruation irregular, Amenorrhea) described in around 80% of the reports (for details see slides 44-45)
  2. Studies performed on this topic noted short irregularities (up to a few days) in the menstrual cycle. However, over 90% of the reports that detail duration of the adverse event, point at long-term adverse events. Over 60% note a duration of over 3 months (details in slides 46-47)

- Neurological adverse events:
  1. Identification and characterization of neurological adverse events that are not mentioned in the physician's leaflet of the Comirnaty preparation, such as hypoesthesia, paresthesia, tinnitus, dizziness and more (details in slide 38)
  2. In addition to identification of new neurological adverse events, the findings raise a suspicion of long-term neurological adverse events. In 68% of the reports that included a feature of duration of the adverse event, duration was longer than one month. In 88% of these reports duration longer than 3 months was documented (details in slides 39-40)

Summary of findings collected via the open fields of the reporting form

New findings:

- Musculoskeletal adverse events:
  1. Excluding a significant number of reports of Back pain (which has been identified as a new adverse event), the findings in the current analysis are identical to the findings reported in the physician's leaflet. In both cases adverse events of Myalgia, Arthralgia, Pain in extremity were identified as the most common adverse events in this category (see slide 52)
  2. Despite much overlap between the leaflet and the common adverse events, a significant disparity has been recognized in the duration of these aforementioned adverse events. The leaflet states a duration of several days until the adverse event disappears. However, the current analysis demonstrates that in 79% of the reports that included data regarding duration of the side effect, the mentioned duration was longer than two weeks. Of these, around 50% of the reports reported a duration of more than 6 months (for details see slide 53)
- Gastrointestinal/Kidney & Urinary tract adverse events :
  1. There is some overlap between the common adverse events (diarrhea, nausea and vomiting) mentioned in the manual, and the findings in the current analysis. In addition to these adverse events, analysis of the free text identified adverse events of stomach ache and sore throat that appeared in high incidence (20% and 10% respectively)
  2. Over 80% of the reports that included information about duration stated duration longer than a week. In 30% of these reports, duration of over 6 months was reported (see details in slide 67)

Summary of findings collected via the open fields of the reporting form

Limitations of the collection and analysis of data from the free text

- Conversion of free text to valid MedDRA nomenclature involves translation from Hebrew (occasionally Hebrew slang) to English. This process might be subjective and could impair the precision of the conversion.
- Inference of conclusions regarding Duration, Rechallenge, Onset, is based on reports that include these data. A small sample size of reports that include the relevant information may cause bias and lead to Over/Underestimation. Additionally, there is a likelihood of Selection bias towards a longer duration and positive Rechallenge, since it is likely that there would be a higher tendency to report these cases.
- The reports were collected in the middle of the Covid-19 pandemic. Therefore it is likely that some of the subjects reporting were sick or infected – which could be a co-factor to the reported adverse events.

Summary of findings collected via the open fields of the reporting form

Suggested future activity

- Due to findings that suggest the existence of long-term adverse events, and taking into account multiple reports that testify that the adverse events are ongoing, it is highly important to continue following and collecting the safety data – in order to widen Core Safety information and to consolidate a Risk Management plan.
- Analysis of data reported as free text (that include vital information such as clinical details, Duration, Onset, Rechallenge) may be a central tier not only in identification of new signals, but in establishing the causal relationship between the adverse events and the vaccine. It is very important to continue the development of advanced tools (Artificial Intelligence based) for effective and systematic identification, categorization, prioritization and reporting.
- Cooperation with the Military Unit 8200 with focus on continuing the development of a module to convert natural language to MedDRA terminology: Onset, Duration, Rechallenge.

Summary of findings collected via the open fields of the reporting form

Suggested future activity

- Development of a tool based on Artificial Intelligence will enable its assimilation in various projects including collection, analysis and classification of social media reports/ handling incoming reports from medical crews, etc.
- During the current project, significant adverse events were reported among the adult population (such as hospitalization, damage to vital organs, etc.). These cases were not discussed by a professional committee. Widening the project in this population will enable medical data collection from the “Ofek” system and evaluation of these cases by a professional committee.
- So far, a primary analysis relating only to the adverse events in the five most frequent categories has been performed. We estimate that there is valuable information in the reports relating to adverse events in less common categories as well. Delving into the additional data will enable identification and characterization of rare adverse events that were not discovered in the clinical trial phase / in the predetermined fields.