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Monitoring COVID-19 vaccine safety

Vaccines are a specific type of medicinal product with equally specific surveillance needs. COVID-19 vaccines are currently being administered to millions of people worldwide in a short time span. Special attention should be given to all adverse post-administration events to ascertain whether their characteristics and frequency are as expected. This calls for an intense effort for a detailed quantitative and qualitative assessment of every occurrence so that a mere post-jab coincidence in time can reasonably be separated from a causal nexus/relation between a suspected adverse reaction and a COVID-19 vaccine.

For methodological reasons, pharmacovigilance systems based on spontaneous reporting directly from healthcare professionals or patients do not allow for a head to head comparison of the safety profiles of the various COVID-19 vaccines.

On the other hand, not every adverse reaction is reported to the National Pharmacovigilance System. Actual incidence/frequency of events cannot be estimated solely based on spontaneous reporting data. Still, these data remain the main source of information for the detection of new adverse effects and they are rather sensitive for the detection of rarer cases. Hence the relevance of reporting suspected adverse reactions, especially ones that are serious or unlisted.

INFARMED, based on adverse reaction data extracted from its ADR Portal, issues a periodical COVID-19 vaccine safety monitoring report to inform the public in general. **Table 1** shows highlights from the recent July 2021 issue.

The data assessed in the report concern suspected adverse reactions that have occurred in the period of time following administration of a COVID-19 vaccine, which does not mean that there is a cause-effect relation in every case. Moreover, the number of reported cases should always be weighed against the number of vaccine doses actually given.

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Table 1
Number and time distribution of COVID-19 vaccines given and cases of total and serious adverse reactions (AR), in Continental Portugal and Islands

Data da extração de dados	30-05-2021	27-06-2021	22-07-2021
Number of vaccine doses administered (Source: DGS (Portugal General Health Directorate))	5 790 080	8 470 118	11 002 983
Total number of AR cases	6 695	8 470	11 314
Number of AR cases per 1000 vaccines administered	1	1	1
Total number of serious AR cases	2 738	3 290	4 015
Number of serious AR cases per 1000 vaccines administered	0,5	0,4	0,4

Table 2 shows data per vaccine brand. It should be noted that these data **do not allow for a comparison** of safety profiles since **different vaccines** have been used in different population subgroups (regarding age, gender, health profile, etc), as well as in varying periods of time and in diverse epidemiological contexts.

Table 2
Cumulative number of administrations and of cases of adverse reactions (AR) by brand of COVID-19 vaccine (until 22-07-2021)

Vaccine	Comirnaty	Moderna	Vaxzevria	Janssen
Number of doses administered (Source: DGS (Portugal General Health Directorate))	7 412 497	1 141 821	2 003 932	444 733
Number of AR cases	6 485	970	3 480	379
Number of AR cases per 1000 vaccines administered	0,9	0,8	1,7	0,9

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As the vaccination campaign progresses and adverse reaction reporting is promoted so the number of reports has been increasing. However, when comparing the number of cases of ARs with the total number of vaccinated individuals, it becomes apparent that the ratio has remained stable at one case per one thousand inoculations, i.e. rare.

Within the subgroup of serious ARs, the ratio has also remained relatively stable and even with a downward trend: around one case for every 2,500 jabs. Seriousness is first assessed by the reporting person (either healthcare professional or patient) and is then further assessed using World Health Organization criteria. As serious cases are prioritized over the less serious ones a bias tends to emerge, the actual proportion of serious cases being probably lower. Moreover, serious cases are also given priority by the pharmacovigilance system itself, as they user are expedited to the European database EudraVigilance within no more than 15 days, which is much shorter than the 90 days allowed for non-serious cases. This difference may additionally contribute to an artificial distortion in the proportion of serious cases.

In about 90% of serious cases, seriousness was determined from temporary unfitness (e.g., sick leave) and from other circumstances that were found significant by the reporting person (**Table 3**). Fatalities occurred in patients with a median age of 78 years and they were not necessarily related to the vaccine, since they may have alternatively to do with the usual morbidity and mortality patterns of the Portuguese population.

Table 3
Distribution of serious adverse reaction (AR) cases to COVID-19 vaccines (until 22-07-2021)

AR cases classified as serious	n	%
Clinically significant	2 408	60
Unfitness for work	1 087	27
Hospitalization	303	8
Congenital anomaly	0	0
Life threatening	116	3
Death	68	2
Total (%)	**3 982**	**100**

Table 4 shows the distribution of cases (serious vs. non-serious) by age group. Cases in the younger than 2 years group correspond to non-serious events, namely fever, regurgitation or irritability in children whose mothers may have been exposed to the vaccine.
Eleven serious cases in the 16-19-year-old age group correspond to listed hypersensitivity reactions which depend on the individual profile of the vaccinee. These cases required clinical observation and/or treatment but they all had favourable, sequela-free outcomes.

Table 4
Distribution of AR cases by age group and proportion of serious versus non-serious cases for each age group (until 22-07-2021)

Age group (years)	Serious cases	Non-serious cases
< 2	0	7
2 - 15	0	0
16 - 19	11	4
20 - 29	377	771
30 - 39	702	1359
40 - 49	842	1368
50 - 59	720	1192
60 - 69	482	800
70 - 79	345	516
80 - 89	207	166
≥90	59	51
Unknown	268	1067
Total (%)	**4 015 (36%)**	**7 299 (64%)**

Most reported ARs (Table 5)* can be ascribed to the usual patterns of reactogenicity of vaccines, including local skin reactions or systemic reactions such as fever, headache or myalgia. Because these ARs were detected earlier in pre-marketing clinical trials, they are listed in the vaccine's product information which can be accessed on INFOMED, INFARMED's medicinal product for human use database.

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Portal **RAM**

Notificação de Reações Adversas a Medicamentos

Report an adverse drug reaction here.
Find answers to your questions about the ADR Portal here.

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Table 5
The 15 most reported ARs* (until 22-07-2021)

AR *	n
Myalgia	3 044
Headache	2 927
Fever	2 830
Injection site pain	2 567
Tiredness	1 288
Chills	1 232
Nausea	1 148
Arthralgia	913
Generalized aches	711
Lymphadenopathy	642
Dizziness	638
General malaise	620
Asthenia	546
Vomiting	538
Pain in extremities	534
TOTAL	**20 178**

Most cases of discomfort caused by an adverse reaction, such as a self-limited episode of muscle aches or fever, correspond to the immune system preparing to fight a SARS-CoV-2 infection, as expected. These reactions usually resolve in a few hours or days, with no need for medical observation or intervention and leaving no sequelae. Other more serious, prolonged or unexpected (unlisted) cases may require additional clinical assessment and a physician or another adequately qualified professional should be consulted.

It is always worth remembering that only proper scientific assessment of all the data available at each moment in time (not only data from spontaneous adverse reaction reporting) allows for robust conclusions to be drawn concerning the benefits and risks of any given medicinal product, the vaccines used in COVID-19 infection prophylaxis being no exception.

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** Each case often includes more than one individual adverse reaction (AR) descriptor term. For example, a single case of fever, headache and malaise generates three individual AR terms. This explains why the number of AR terms can always be expected to be higher than the number of actual cases per se.*