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Impressum

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We would like to thank all colleagues for their contribution to producing this edition of Swissmedic Vigilance News.

Editorial

Dear Reader

Over the past few months, vigilance with regard to COVID-19 vaccines has demonstrated the important role vigilance plays in the life cycle of a medicinal product or vaccine.

Willingness to report undesirable effects directly to Swissmedic, which are then recorded in the pharmacovigilance database and evaluated by Swissmedic experts, has risen sharply among both healthcare professionals and the general population. These reports are of great importance in detecting a potential risk and implementing any risk-minimising measures.

Adverse events following immunization (AEFI) were frequently reported directly to Swissmedic by the patients affected or their relatives in connection with the COVID-19 vaccination campaign in Switzerland. The article "Experience with direct patient reporting during the COVID-19 vaccination campaign in Switzerland" covers this topic. One adverse effect of COVID-19 vaccines after booster vaccination – urticaria – came to the fore primarily through patient reports, as described in the article "Reports of urticaria (hives, nettle rash) after booster vaccination with Spikevax".

Naturally, AEFI reports were also received from healthcare professionals, and were not only related to COVID-19 vaccines, as our annual vaccinovigilance statistics show.

Authorised medicinal products such as Paxlovid® are now also being used to treat COVID-19 in adults. An article reports on "COVID-19 rebound after Paxlovid®".

To obtain pharmacovigilance data for a medicinal product or vaccine, case reports from Switzerland's regional pharmacovigilance centres (RPVC) are extremely important, in addition to direct reports from patients and healthcare professionals. One example is the article by RPVC Zurich on "Contrast-induced neurotoxicity".

In Switzerland, Safety of Medicines at Swissmedic not only covers the pharmacovigilance of medicinal products and vaccines, but also the surveillance of the entire transfusion chain. Adverse events before, during and after transfusion must be reported to Swissmedic. In this issue, Vigilance News is launching a series on haemovigilance, this time covering transfusion reactions in 2021.

You can also read a statistical overview of veterinary medicinal products.

To obtain current vigilance findings, we are continuing to encourage reporting of adverse drug reactions (ADR) and AEFI as well as haemovigilance to Swissmedic. You can find all information on submitting reports at www.swissmedic.ch.

We hope you find this an interesting read and wish you all the best for the approaching winter.

Eva Eyal

Pharmacist and editor of Swissmedic Vigilance News
Safety of Medicines division, Swissmedic

Drug safety and signals

COVID-19 rebound after Paxlovid® treatment

Thomas Schwartz, MD
Safety of Medicines division, Swissmedic

Paxlovid® (nirmatrelvir, ritonavir) is an oral antiviral that, if taken during the early phase, reduces the risk of hospitalisation and death in patients with mild to moderate COVID-19 infection.

Swissmedic granted temporary authorisation for two years to Paxlovid on 15 June 2022, prescription being already permitted in Switzerland under COVID-19 Ordinance 3.

It was noted as early as the pivotal study with Paxlovid that 1 to 2% of patients had experienced rebound after the five-day course of treatment had ended (1). The patients had recovered from COVID-19 in the meantime and had tested negative in antigen or PCR tests. The phenomenon occurred with equal frequency in the placebo group.

Rebound generally occurred between two and eight days after recovery, and affected vaccinated and non-vaccinated people equally. The patients developed COVID-19 symptoms again and tested positive once more.

The Health Alert Network of the US-Centers for Disease Control and Prevention (CDC) issued a Health Advisory on the risk of rebound in May 2022 (2).

According to the CDC, the symptoms were mild and patients recovered within a median time of three days. The CDC Health Advisory noted that there had as yet been no reports of severe disease or death. It also stated that there was generally no reason to resume Paxlovid treatment.

The cause of rebound has yet to be established. According to the CDC, there is no evidence that patients had been reinfected or that the virus had become resistant. The most likely explanation at the moment is that pockets of virus are able to stay out of reach of the active substance nirmatrelvir at certain places, re-emerging from there once the five-day treatment has ended. It is thought that the immune system of the majority of patients will by then have begun to produce antibodies to protect against serious reinfection.

It should be noted that patients who experience rebound are infectious, which is why the CDC advise affected patients to quarantine themselves again. They should only come out of quarantine once they have not experienced fever for five days. People who experience rebound should also wear a mask for a total of ten days after the start of rebound symptoms.

As at 31 August 2022, three cases of COVID-19 rebound after Paxlovid treatment had been reported to Swissmedic.

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No increased risk of stroke following SARS-CoV-2 vaccination

Thomas Schwartz, MD

Safety of Medicines division, Swissmedic

Two recently published investigations that assessed large cohorts both agree that SARS-CoV-2 vaccines do not increase the risk of a stroke.

One assessment by the French National Health Data System investigated how frequently people aged between 18 and 75 experienced a stroke, myocardial infarction or pulmonary embolism after receiving their first or second dose of vaccine against SARS-CoV-2 (1).

A total of 73,325 events were recorded in 37 million vaccinated individuals. No association was found between the Pfizer-BioNTech and Moderna mRNA vaccines and the occurrence of these severe cardiovascular complications.

However, there was an increased incidence of myocardial infarction and pulmonary embolism in the second week following the first dose of AstraZeneca vaccine, which is not authorised in Switzerland. An association between the Janssen vaccine and myocardial infarction in the second week after vaccination could not be ruled out.

However, the assessment did not identify any increased risk of stroke for any of the vaccines.

The second investigation is a meta-analysis of two randomised studies, three cohort studies and eleven registry-based studies (2). 17,481 ischaemic strokes were documented for a total of 782,989,363 vaccinations. The overall stroke rate was 4.7 cases per 100,000 vaccinations. The differences between mRNA and vector-based vaccines were not significant.

The authors conclude that the post-vaccination stroke rate is comparable to that in the general population. Moreover, they emphasise that the stroke rate in people with SARS-CoV-2 infection is significantly higher.

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Reports of urticaria (hives, nettle rash) after booster vaccination with Spikevax

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The side effect profile after booster/third vaccinations is similar to the profile after first and second vaccinations. However, more cases of urticaria were reported to Swissmedic after booster vaccinations, in particular, with Spikevax.

By 27 September 2022, 1,259 reports of urticaria in a temporal relationship with the booster vaccination with Spikevax had been received. Reports of urticaria at the injection site were not included in this analysis.

Most of the reports (N=980, 78%) were submitted by the patients themselves or their relatives. 22% of these cases (N=279) were reported by healthcare professionals. The reports were evaluated as serious in 260 cases (21%).

56% of the cases (N=707) involved women, 42% (N=528) involved men. In 2% (N=24) the gender was not known. The median age of those affected was 39 years, with an age range of 17 to 92 years.

The cases reported often relate to urticaria that appears on various parts of the body with a time lag, with an average interval since booster vaccination of around 12 days (range 0-224 days), and can cause recurring episodes over a lengthy period. The clinical picture as described in many of the reports corresponds most closely to acute (< 6 weeks) or chronic (> 6 weeks) spontaneous urticaria. (1).

The reports were submitted an average of 40 days (range 0-241 days) after the onset of symptoms. In the majority of cases (N=821, 65%) the symptoms were still present when the report was submitted; in 26% (N=322) the symptoms had improved; in 5% (N=68) they had resolved completely; and in 4% (N=48) the outcome is not known.

Urticaria is a relatively common disorder that can have many different causes (e.g. viral infections, allergies). This should be taken into account when evaluating the cases reported, which must be seen against the background of over 2.37 million booster vaccinations given with Spikevax in Switzerland (2, 3).

The product information for Spikevax describes the occurrence of acute and delayed urticaria as a rare (≥1/10,000 to <1/1,000) adverse drug reaction.

In a *Letter to the Editor* in the *European Journal of Clinical Pharmacology*, staff from the Regional Pharmacovigilance Centre in Lugano and from Swissmedic give account of reports of delayed urticaria following a booster (third vaccination) with Spikevax (4).

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Experience with direct patient reporting during the COVID-19 vaccination campaign in Switzerland

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The term "direct patient reporting" refers to spontaneous reports of adverse drug reactions submitted by patients (or their relatives) to an agency responsible for drug safety or to a pharmaceutical company without the direct involvement of a healthcare professional.

In the international setting, direct patient reporting has been an integral part of pharmacovigilance since the mid-1960s, e.g. in Australia, Canada, New Zealand or the USA. In Europe the Nordic countries were the pioneers in this field (1). The importance of direct patient reporting increased throughout the EU in 2012 when the new pharmacovigilance legislation entered into force.

Article 59 of the Swiss Therapeutic Products Act has also explicitly permitted individuals who are not healthcare professionals to report adverse effects to Swissmedic since 1999. In the ten years prior to the COVID-19 vaccination campaign, direct patient reports accounted for almost 14% of spontaneous reports in Switzerland. More than 85% of these reports were submitted to Swissmedic by the pharmaceutical companies, with just 15% being sent in the first instance to Swissmedic or to one of the six regional pharmacovigilance centres.

The COVID-19 vaccination campaign revealed the need for vaccination reactions to be reported directly to Swissmedic by the affected individuals. Since technical issues made it impossible to implement an electronic reporting system within a limited time span, a specific and lay-oriented PDF/Word form in three official languages and English was uploaded to the Swissmedic website. The public made active use of this form. Of the approximately 15,500 reports concerning the COVID-19 vaccines that had been submitted by mid-2022, more than half (54.9%) were sent by patients or their relatives. In contrast to the time prior to the vaccination campaign, the vast majority of these reports were sent directly to Swissmedic.

While recording and evaluating direct patient reports, several particular features and difficulties emerged that are described briefly below. The most frequently reported reactions are the known systemic reactions to vaccination such as fever, headache and tiredness and symptoms involving the injection site. There is little difference in this respect between reports from healthcare professionals and those submitted by patients. However, it has become clear that the number of reports received from patients can be influenced greatly by media reporting of the corresponding side effects. There is little evidence of this "stimulated reporting" effect among healthcare professionals.

Table 1 shows some of the differences between the reports from healthcare professionals and those from patients. The individuals affected by vaccination reactions in the direct patient reports were slightly younger and more frequently female on average, and the average number of reactions mentioned in each report was higher on average. Reports from healthcare professionals more frequently involved serious reactions.

Table 1: Differences between reports on COVID-19 vaccines from healthcare professionals (HCP) and direct reports from patients or their relatives (non-HCP)

	Total number of reports	Number of reports from HCPs	Number of reports from non-HCPs
Number of reports	15,492	6,931	8,498
Mean age of person affected (range)	50.2 (0.25-101)	54.7 (0.5-101)	46 (0.25-101)
Number of females affected (%)	9,630 (62.2)	4,142 (60.0)	5,432 (63.9)
Serious cases (%)	5,837 (37.7)	3,551 (52.2)	2,245 (26.4)
Cases with a fatal outcome (%)	213 (1.4)	178 (2.6)	33 (0.4)
Number of reactions per report (mean)		2.4	3.8
Anaphylactic reactions (%)	69	60 (87)	8 (11.6)
Myocarditis/pericarditis (%)	414	333 (80.4)	79 (19.1)
COVID arm (%)	777	407 (52.4)	369 (47.5)
Herpes zoster (%)	679	340 (50.1)	338 (49.8)
Menstrual disorders (%)	595	76 (12.8)	517 (86.9)
Urticaria (%)	1,576	425 (27.0)	1,145 (72.7)

For individual reactions that were investigated in more detail for the existence of a causal relationship with the vaccination Table 1 also shows who reported the majority of cases. While most anaphylactic reactions and instances of myocarditis/pericarditis were reported by healthcare professionals, Swissmedic received most of the reports of menstrual disorders and urticaria from the patients themselves. Reports of the so-called "COVID arm" (a delayed skin reaction on the vaccinated arm) and herpes zoster were submitted in almost equal numbers by HCPs and patients.

Other particular features of direct patient reporting during the COVID-19 vaccination campaign included the large number of reports involving different single vaccinations and different reactions at the same time. Many reports also contained questions about the cause of the reactions being reported, about treatment options and about the next course of action with respect to further vaccinations. It was not uncommon for reports to be combined with questions regarding compensation or reimbursement of illness-related costs, neither of which falls within the remit of Swissmedic.

Another striking feature was that the seriousness of a side effect was overestimated in a large number of direct patient reports. In particular, the rather unspecific criterion of "medically significant" is frequently used incorrectly. It may therefore be necessary to modify the procedure for recording and evaluating direct patient reports compared with

the procedure used for reports from healthcare professionals in order to avoid a bias in the database by a falsely high number of "serious" reports.

Overall, there has been a substantial increase in patients' and affected individuals' interest in reporting suspected adverse reactions directly to Swissmedic as a result of the COVID-19 vaccination campaign. In July 2022 Swissmedic launched an online reporting tool on its website to make direct patient reporting easier and to ensure secure data transmission. It can be assumed that the significance of direct patient reporting will continue to grow considerably in the future.

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Contrast-induced neurotoxicity

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Summary

Contrast-induced neurotoxicity is a rare, acute, and usually reversible complication of exposure to contrast media in imaging procedures. Based on the symptoms, it can often mimic a stroke. This case report concerns a 77-year-old woman who suffered aphasia and hemiparesis during coronary angiography with the contrast agent Ultravist® (iopromide). A cerebrovascular accident was initially suspected, but the symptoms were subsequently attributed to contrast-induced encephalopathy.

Introduction

Contrast-induced neurotoxicity is an often unknown adverse drug reaction (ADR) that is easily confused with a stroke due to its symptoms. It is a rare, acute, and usually reversible complication of contrast media in coronary angiography or neurological endovascular interventions, and has been documented in numerous case reports in the literature (1–3). The estimated frequency during invasive cerebral angiography is approx. 1–2% (4), whereas the incidence is probably lower after diagnostic cardiac catheterisation (4). A study in 1993 stated an incidence of 0.06% for neurological complications after diagnostic cardiac catheterisation generally (5). Contrast-induced neurotoxicity typically manifests with encephalopathy, motor and sensory disturbances, visual disturbances (including cortical blindness and ophthalmoplegia), aphasia, seizures, impaired vigilance and headache (2, 3). The symptoms usually appear shortly after contrast administration (within minutes to hours) (4). A local disruption of the blood-brain barrier and direct neuronal toxicity of the contrast agent have been suggested as possible pathophysiological causes (3). Risk factors stated in the literature include male gender, advanced age, hypertension, renal disease, large volumes of contrast media and a previous adverse reaction to a contrast agent (6). The prognosis is usually very good, and the symptoms resolve with supportive treatment, generally within 24 to 48 hours after the coronary angiography and within 72 hours after neurological endovascular procedures (2, 4, 6).

Case report

At the start of September 2022, a case of contrast-induced encephalopathy was reported to the Zurich Regional Pharmacovigilance Centre (RPVC). It concerned a 77-year-old woman who was undergoing coronary angiography with the contrast agent Ultravist® 300 (iopromide, 110 ml i.a.) for a non-ST-elevation myocardial infarction (NSTEMI). During the investigation, the patient developed aphasia and a right-sided hemiparesis, and a stroke was strongly suspected. However, since an MRI scan of the head showed no evidence of an ischaemic or haemorrhagic event compatible with the clinical presentation, the strong suspicion turned to contrast-induced encephalopathy. The neurological symptoms subsequently regressed, and the patient was discharged home in good general health after a week. At the time of the symptoms, the patient was also being treated with Heparin Sodium B. Braun (Heparin), Aspirin® Cardio (acetylsalicylic acid), Pantozol® (pantoprazole) and Padma 28 (various medicinal herbs, Tibetan medicine). Previous illnesses included a cerebrovascular accident in 2007, a myofascial pain syndrome, hypertension and knee osteoarthritis. She had no allergies and was a non-smoker.

Discussion

This case report involved the administration of the iodinated, non-ionic, low-osmolar, hydrophilic contrast agent iopromide, which is generally used for diagnostic purposes (incl. in angiographic procedures) (7). The Swiss Information for healthcare professionals for Ultravist® documents the possibility of contrast-induced encephalopathy with an unknown frequency (7). Generally speaking, any iodinated contrast medium can lead to contrast-induced neurotoxicity (1, 6). Theoretical considerations suggest that iso-osmolar and non-ionic contrast media are safer than hyperosmolar agents since they have a lower osmotic force (6), although cases of contrast-induced neurotoxicity with iso-osmolar contrast media can also be found in the literature (3, 6). In a retrospective analysis, iopromide appeared to result in contrast-induced encephalopathy more frequently compared to ioversol (8).

As in the literature (2, 3), the "Warnings and precautions" section of the Swiss Information for healthcare professionals for Ultravist® also describes how contrast-induced encephalopathy can manifest itself as neurological dysfunctions, including headache, visual disturbances, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, loss of consciousness, coma and brain oedema. It also mentions that the symptoms normally appeared within minutes to hours after administration and generally resolved within a few days (7). In the patient described in the case report, the aphasia and hemiparesis occurred already during the coronary angiography. Therefore, both the nature of the symptoms and the temporal relationship correlate with the product information and the findings reported in the rest of the literature.

Given the variability of the symptoms of contrast-induced neurotoxicity, imaging is needed in order to confirm the diagnosis and rule out haemorrhagic or thromboembolic complications of angiographic procedures (6). This was the case in the patient described above, who underwent an MRI scan. On cerebral imaging recorded shortly after the onset of the symptoms, contrast-induced neurotoxicity may mimic a subarachnoid haemorrhage or cerebral ischaemia, but it may also appear completely normal (3). Since the MRI of the patient in the case report was normal, thromboembolic and ischaemic causes could be ruled out. In an unclear situation, the MRI-derived apparent diffusion coefficient can be helpful in differentiating between contrast extravasation and cerebral ischaemia (3). In the case of ischaemia, the coefficient would be reduced as a result of the decreased diffusion of water into the affected tissue (3), whereas a normal coefficient would be shown in contrast extravasation (3). In unclear situations during CT imaging, Dattani *et al.* suggest that the Hounsfield units can be used as a density indictor to help distinguish a haemorrhage from a contrast extravasation, since contrast media show a higher attenuation of radiation compared to blood (6). It has also been reported that the contrast accumulation resolves within 25 hours in most cases (6).

The patient described in this report had two risk factors: advanced age and hypertension. According to Dattani *et al.*, chronic hypertension is the most important risk factor for the development of contrast-induced encephalopathy, because the hypertension can lead to an impaired blood-brain barrier, and this is a predisposing factor for contrast extravasation (6). According to the review by Quintas-Neves *et al.*, most of the investigated patients with contrast-induced neurotoxicity (60.4%) suffered from hypertension, which may also reflect the risk factors for the underlying vascular pathology that could have led to the angiographic procedure (2). As mentioned in the introduction, a high dose of contrast agent has been discussed in the literature as a further risk factor. According to Dattani *et al.*, a

maximum contrast dose of 170 ml has been proposed in the literature for coronary angiography procedures in order to prevent neurotoxicity (6). However, the literature also documents cases in which neurotoxicity occurred following doses as low as 25 ml when injected locally into the carotid artery (6). In our case report, a dose of 110 ml was administered, which is likewise below the proposed maximum "safe" dose of contrast medium. According to Quintas-Neves *et al.*, since the contrast volume administered in the cases described in the literature vary considerably, it is not clear whether a higher volume does, in fact, constitute a risk factor for the occurrence or severity of neurotoxicity (2). The possibility that an idiosyncratic reaction might be a more likely explanation than a dose-dependent reaction is also discussed in the literature (2).

No established, effective and evidence-based treatments currently exist for episodes of contrast-induced neurotoxicity. Most patients were monitored clinically and received, in addition to supportive therapy, specific treatment with steroids (to reduce cerebral oedema), anticonvulsants (to manage seizures), liberal hydration and mannitol (2, 6). As already described in the introduction, the symptoms usually resolve within 72 hours (2, 4, 6). In the case described above, the patient's symptoms regressed within a week. The regeneration period was therefore slightly longer in this patient than described in the product information and the literature.

A further contrast exposure basically involves the risk of recurrence of the neurotoxicity. The literature includes both cases in which re-exposure did not result in any repeated symptoms and case reports in which a further reaction occurred (1, 3). Sadiq *et al.*, for example, describe the case of a 60-year-old female patient who developed neurotoxicity after coronary angiography, with symptoms of disorientation, amnesia and cortical blindness. These symptoms did not recur during an angiographic procedure two months later with hydrocortisone premedication and a lower volume of contrast medium (1). If a re-challenge is absolutely essential, the authors therefore recommend the use of premedication with steroids, supplemented by a reduction in contrast medium to the lowest required volume (1). Spina *et al.*, on the other hand, reported on a case in which symptoms recurred during a re-challenge despite premedication with intravenous glucocorticoids (3). The effectiveness of premedication with glucocorticoids remains unclear, given the scarcity of the literature data. According to Dattani *et al.*, preventive measures include selection of the lowest possible dosage and adequate hydration of the patient prior to contrast administration (6).

Conclusion

Contrast-induced neurotoxicity is a rare, but important, complication of the administration of iodinated contrast media. Following the occurrence of suspected symptoms a few minutes or hours after contrast administration, prompt imaging is required to confirm the diagnosis and to rule out differential diagnoses such as a stroke. Although the symptoms can be serious and no specific treatment is currently available, the prognosis is very good and the symptoms usually regress within a few days. Since a further exposure to contrast media basically involves the risk of recurrence, any subsequent administration should be preceded by a careful risk-benefit assessment.

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Statistical Review 2021

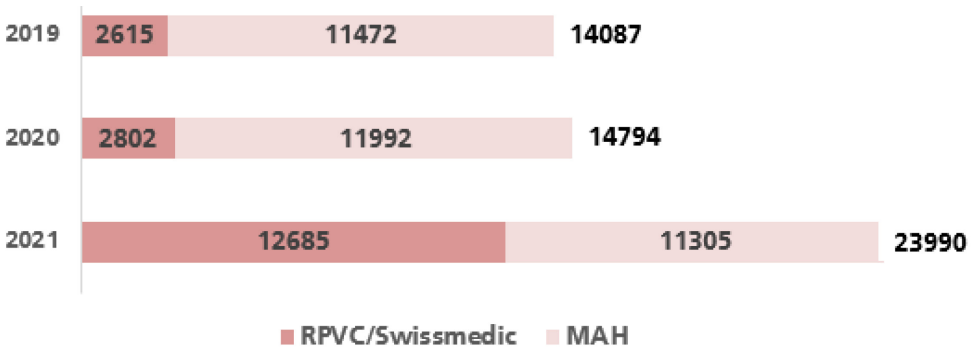
Pharmacovigilance: Human medicinal products

Swissmedic evaluates safety signals associated with medicinal products and vaccines on the basis of reports of adverse drug reactions (ADR) from within Switzerland. If its investigations confirm a new risk, Swissmedic initiates the necessary actions (for example amending the medicinal product information), often after consulting its international partner authorities. As part of the pharmacovigilance network, all reports from medical professionals and patients are entered in the national database and evaluated by specialists. Some are also assessed on Swissmedic's behalf at six regional pharmacovigilance centres (RPVC). Pharmaceutical companies also submit a large number of reports of adverse reactions from within Switzerland to Swissmedic.

Activities

The dominant activity in 2021 was monitoring COVID-19 vaccines. The substantial year-on-year increase in reports of suspected ADR is attributable to the large number of people who have been vaccinated as well as to public awareness of the importance of pharmacovigilance. Reports were submitted by medical professionals, while around half of COVID-19 vaccination-related reports came from the people affected. The VigilanceONE Ultimate database used to process ADR reports from Switzerland was upgraded to perform specialised analyses. The procedure for reporting side effects of COVID-19 vaccinations was simplified during 2021 and systems for processing these reports were optimised. International collaboration with other countries' authorities and in multinational specialist organisations was stepped up significantly in light of the COVID-19 vaccination campaign, for example as part of a regular dialogue on safety signals. Swissmedic regularly briefed the public and international partner authorities on reports connected with COVID-19 vaccinations and the findings obtained. By the end of 2021, Swissmedic had published 20 reports regarding COVID-19 vaccines.

Number of ADR reports in Switzerland per primary recipient



Vaccinovigilance

Valeriu Toma, MD

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Complete report – link:

Adverse events following immunization – annual report 2021

Summary of adverse events following immunization reported in Switzerland during 2021

During 2021, the Pharmacovigilance Unit of Swissmedic received a massively increased number of case reports of suspected adverse events following immunization (AEFI) from Switzerland, as compared to previous years. The vast majority of these reports were submitted in association with the new COVID-19 vaccines during the nation-wide vaccination campaign which was underway throughout 2021. In addition to that, 159 AEFI-reports were submitted in Switzerland for **non-COVID vaccine** during 2021, which is a significantly lower number as compared with 2020 (271 reports) or 2019 (273 reports). However, this difference is not unexpected and is probably a consequence of the new large-scale COVID-19 vaccination and information campaign, resulting in a shift of awareness and focus towards the new COVID-19 vaccines within the general population and also amongst healthcare professionals.

Firstly, the high number of reports concerning COVID-19 vaccines can be attributed to the unprecedented high exposure to these vaccines. Additionally, it illustrates the strong association between public attention and the quantity of spontaneous reports. The number could be misinterpreted as a false signal for safety concerns in association with the COVID-19 vaccines. However, most of these reports describe well-known reactions following COVID-19 immunisation such as fever, chills or administration site reactions.

This summary report has its main focus on **non-COVID vaccine** AEFI, since several COVID-19 vaccine safety reports have been regularly published as cumulative updates on Swissmedic's website and further similar reports will follow in future. Nevertheless, a brief summary of COVID-19 AEFI reports received during 2021 is presented in the final section of this document.

Similar to the previous year, AEFI-reports submitted during 2021 have been recorded, assessed and analysed in the pharmacovigilance database of Swissmedic. However, no accurate data were available regarding the number of vaccine doses administered in Switzerland during 2021 for different non-COVID vaccine groups or products and therefore a straightforward conclusion regarding AEFI reporting rates cannot be drawn.

As previously, Swissmedic is encouraging spontaneous high-quality reporting of AEFI, to enable early detection of new safety signals. Important safety issues concerning vaccines are being evaluated in international collaboration with other foreign agencies and/or with the participation of the Human Medicines Expert Committee (HMEC) of Swissmedic, if necessary. An increased AEFI reporting rate within the Swiss database, followed by an assessment of relevant cases can lead to risk minimisation measures aimed at ensuring vaccines safety.

Figure 1: Number of AEFI reports by age group and gender, 2021

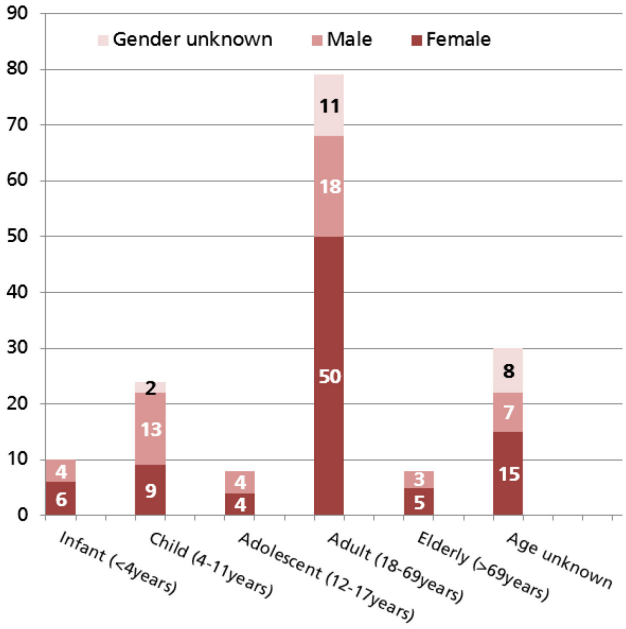

Figure 1 compares the number of reports per age group and gender. The largest number of AEFI reports involved adults (79 reports), followed by children (24 reports), infants (10 reports), adolescents (8 reports) and elderly (8 reports).

Throughout 2021, the number of reports concerning females (89 reports; 56%) exceeded the number of reports concerning males (49 reports; 30.8%). In 21 AEFI reports (13.2%), the gender of the persons remained unknown. In 30 case reports (18.8%), the age-group of the patients was not recorded.

Figure 2: Number of reports by vaccine group (ATC code) and seriousness, 2021

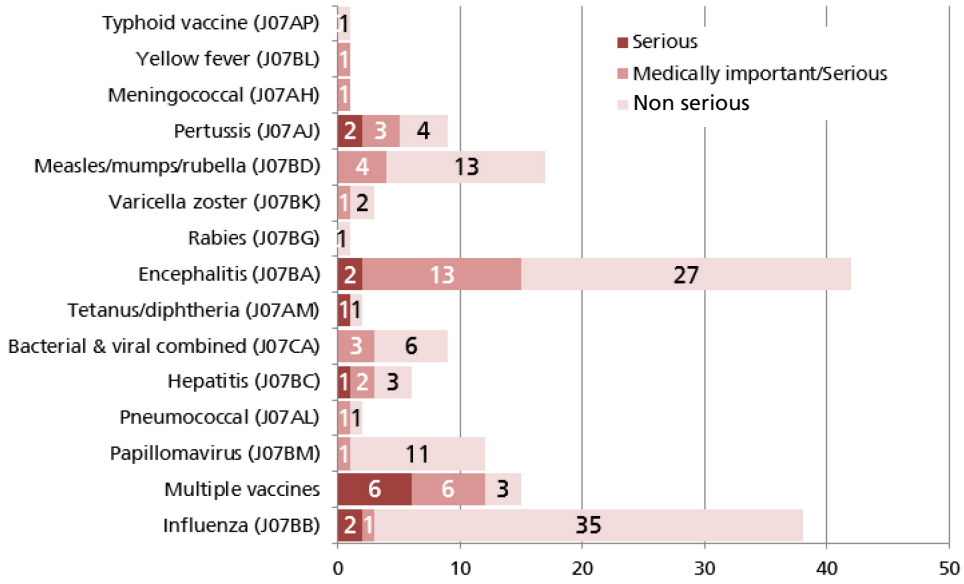

Figure 2 shows the number of spontaneous AEFI reports by vaccine group (ATC code) and seriousness. There are no accurate data available to Swissmedic regarding the number of doses administered in each particular non-COVID 19 vaccine group in 2021 and therefore this figure does not indicate which vaccine group displayed a higher AEFI rate (e.g. as number per 100,000 doses).

Generally, a safety report is assessed as "serious" if it involves an adverse event leading to death, to hospitalisation or to prolongation

of an existing hospitalisation, if it was life-threatening or resulted in a significant or persistent disability or a congenital anomaly. Furthermore, a report is assessed as "medically important" (and therefore, also as "serious") even if it does not fulfil the criteria for "seriousness" mentioned, but it involves an event considered to be significant by medical judgement. All other reports are assessed as "non serious" (e.g. self-limiting adverse events with good recovery). Of the 159 spontaneous reports received in 2021, 108 (67.9%) were non-serious, 37 (23.3%) included only medically important events and 14 (8.8%) of the reports involved AEFI with serious consequences.

Generally, by considering all vaccines in 2021, the relative frequency (percentage) of "serious" cases including "medically important" cases (51 reports, i.e. 32.1%) was equal to that recorded in the previous year 2020 (29.9%) and lower as compared to 2019 (35.2%).

Case reports where several (n>1) different vaccines were administered and were reported in association with suspected AEFI, are shown in Figure 2 as "Multiple vaccines".

During 2021, a higher number of cases was submitted in association with the tick-borne encephalitis vaccination and are shown in Figure 2 as ATC code "Encephalitis (J07BA)". However, the majority of these case reports were assessed as "non-serious", whereas the number of "serious" and/or "medically important" cases regarding encephalitis vaccines (n=15) was comparable with those received for other vaccine groups. Among the serious/medically important reports, a few cases of "vaccination failure"/"drug ineffective" and consecutive "tick-borne viral encephalitis" or "meningitis" were received for this vaccine-group (see also further below).

Figure 3: Number of AEFI reports by reporter qualification and seriousness, 2021

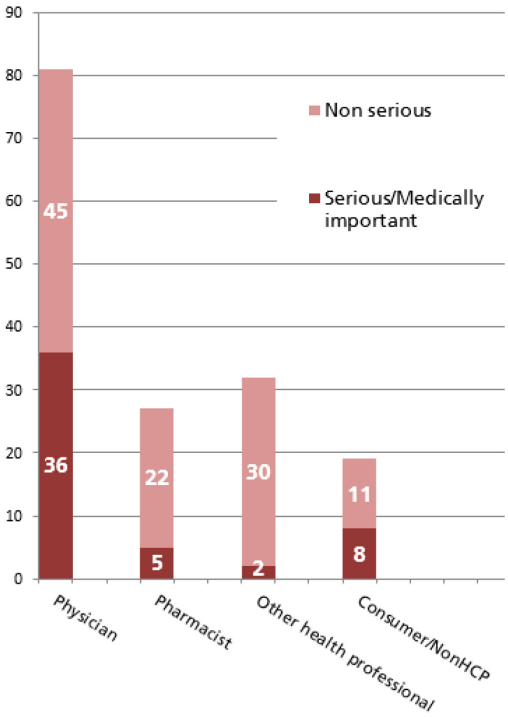

Figure 3 shows the number of Swiss AEFI reports in 2021 grouped by primary reporter and seriousness. Healthcare professionals – generally providing medically confirmed data and good quality individual AEFI reports – were primary reporters in the vast majority of cases. Physicians reported the largest group of AEFI reports (81 of 159), also comprising a higher number of reports assessed as serious or medically important (36 of 81 reports). Notably, consumers/patients submitted to Swissmedic the lowest number (19) of non-COVID AEFI reports during 2021.

Figure 4: Number of AEFI reports by age group and seriousness, 2021

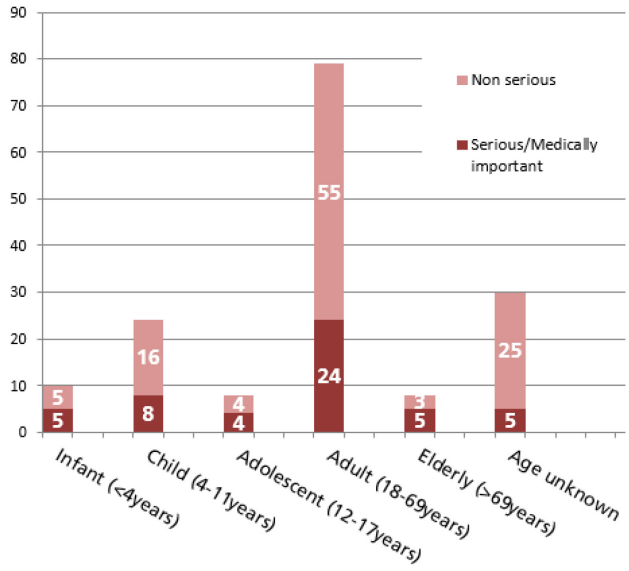

Figure 4 shows the number of spontaneous AEFI reports grouped by age group and seriousness. It becomes apparent that the highest number of "serious" or "medically important" cases (24 AEFI reports in total) have been recorded in the age group "adults". However, during 2021 the "elderly" age group shows the highest percentage of "serious" or "medically important" cases taken together (with 5 of 8 reports, 62.5%) as compared with the other age groups specifically recorded: "infants" (5 of 10 reports, 50%), "adolescents" (4 of 8 reports, 50%), "children" (8 of 24 reports, 33.3%) and "adults" (24 of 79 reports, 30.4%).

AEFI reports received by Swissmedic in 2021 following COVID-19 vaccinations

In Switzerland, the COVID-19 vaccine rollout and vaccination campaign were started in late December 2020 and only a single AEFI report was submitted in 2020 for these new vaccines. Hence, AEFI reports received in 2021 reflect the spontaneous safety reporting on COVID-19 vaccines during the first year of the nationwide immunisation campaign.

As published by Swissmedic in "Update 20 – Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland" (1), up to 14 December 2021 Swissmedic evaluated 10,842 reports on suspected adverse drug reactions to COVID-19 vaccinations that occurred with a temporal link to the vaccinations. At 6,915 (64%), most of the reports were classified as non serious, while 3,927 (36%) reports were classified as serious. About half of the reports were submitted by medical professionals, while 5,478 or 50.5% came directly from those affected, i.e. the patients. The average age of those affected was 52 years, with 13.1% aged 75 or over. In the cases classified as serious, the average age was 54.5 years, and for reports temporally linked to a death it was 79.7 years. The majority of the reports concerned women (64%) and there were a few cases where no gender was specified.

In 178 serious cases, the people concerned died at different time-intervals after receiving the vaccine. Despite a chronological association, there is no concrete evidence indicating that the COVID-19 vaccination was the cause of death.

7,426 (68.5%) reports involved Moderna's COVID-19 vaccine Spikevax (for approx. 64% of the vaccine doses administered – this was the most widely used COVID-19 vaccine in Switzerland), while 3,141 (29%) were associated with Pfizer/BioNTech's Comirnaty® (with approx. 36% administered vaccine doses).

The reports of adverse reactions received and analysed by 14.12.2021 did not alter the positive benefit-risk profile of the COVID-19 vaccines used in Switzerland, largely confirming their known side effects profile. Known adverse reactions of COVID-19 vaccines are listed in the continually updated Swiss product information texts published (2).

As important safety topic, "myocarditis/pericarditis" was particularly addressed in this "Update 20", since very rare cases of myocarditis and pericarditis have been reported following vaccination with the COVID-19 mRNA vaccines. These cases generally occurred within 14 days of vaccination and more frequently after the second dose and in younger men. By 14.12.2021, 267 cases of myocarditis and/or pericarditis with a suspected relation to vaccinations had been reported and evaluated out of a total of more than 12.75 million vaccine doses administered in Switzerland. Of these, 52 were linked with Comirnaty and 206 with Spikevax. The large majority of cases involved males (n = 199, 74.5%) and the mean age was 37 years (median: 51, range: 14 to 88 years). The persons affected received medical treatment and most had recovered by the time of reporting. Considering the national safety data and available international study results, the Swiss Federal Commission for Vaccination (FCV) has made the vaccination recommendation for persons under 30 years of age more specific.

Further cumulative Safety Updates on COVID-19 vaccines have been published by Swissmedic on the website on a regular basis, most recently on 26 August 2022 (3).

References

(1) Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – Update 20; Swissmedic website, 17.12.2021

(2) AIPS (www.swissmedicinfo.ch)

(3) Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – Update 27; Swissmedic website, 26.08.2022

Vigilance for veterinary medicinal products

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Adverse reactions reported in 2021

A summary of the main points:

- Slight decrease in reports received (down 3.4%)
- Most frequently affected species: 218 dogs, 85 cats, 23 cows/cattle/calves
- Most frequent medicinal product types: antiparasitics (127), hormone products (83) products to modulate the nervous system (43), anti-infectives (30)
- 95 cases of suspected lack of efficacy, largely for antiparasitics and hormone products
- 35 cases passed on by Tox Info Suisse
- 19 cases of accidental ingestion of flavoured tablets by dogs/cats
- 104 cases of human exposure to veterinary medicinal products
- 13 signal procedures concluded

A total of 343 reports were received by Swissmedic in 2021, representing a decrease of around 3.4% compared with 2020. As in previous years, the majority of these reports were submitted by marketing authorisation holders. The distribution as regards the species concerned is virtually unchanged from previous years. Small animals make up the largest group (88% of all reports), with 218 adverse reaction reports in dogs and 85 in cats. They are followed in descending order by cattle/cows/calves with 23 reports, and by reports concerning horses or adverse reactions in users, each accounting for 5 reports. Fewer than 5 reports were received for each of the other species in 2021.

The classification of reports by medicinal product type has had a consistent pattern over the years. Antiparasitics dominate, with 127 reports (37% of the total). In this group, 36 reports concerned a suspected lack of efficacy against ticks. Veterinary medicinal products containing hormones were the second-largest group, with 83 reports. A considerable proportion (43%) of the reports in this group also concerned a suspected lack of efficacy of a veterinary medicinal product, in this case for temporary reduction of fertility in male dogs. Veterinary medicinal products for treatment of the nervous system constituted the third-largest group. A large number of cases (15) in this group concerned two monoclonal antibodies for the treatment of osteoarthritis-related pain in dogs and cats.

It was possible to establish a clear relationship between the use of a product and the adverse reaction ("probable" causality) for 62 reports; in 76 cases at least one possible alternative cause was identified ("possible" causality); and in 68 cases it was possible to unequivocally rule out a relationship between the product and the adverse reaction. For the remaining 97 cases, there was too little information to definitively determine causality.

35 of the 343 reports were passed on by Tox Info Suisse. 19 of these cases involved the excessive ingestion of flavoured veterinary medicinal products by dogs and cats. Tox Info Suisse also reported 104 cases of human exposure to veterinary medicinal products. 36 of these cases describe consumption of veterinary medicinal products by children, 25 accidental contact with a veterinary medicinal product by adults, and 34 cases concerned a mix-up of a human and a veterinary medicinal product. In addition, there were 7 cases of accidental self-injection.

From the cumulative reports and periodic safety update reports, 13 signal procedures were concluded with modification of the medicinal product information.

The complete report for 2021 will be published shortly on the Swissmedic website.

Swiss Haemovigilance System in Switzerland

Regulatory Aspects and Transfusion Reactions

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Abstract

In Switzerland, haemovigilance is mandatory under federal law. It includes the reporting of undesirable or unexpected events related to the administration of labile blood products, known as transfusion reactions (TR), to Swissmedic. In 2021, the vast majority of reported TR corresponded to non-severe cases (80.7%) with allo-immunisations, febrile, non-haemolytic transfusion reactions (FNHTR) and allergic reactions being the most frequently reported events. Transfusion-associated circulatory overload (TACO) remains the major cause of life-threatening or fatal TR.

Introduction

Haemovigilance is the set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood to the epidemiological follow-up of patients (1). In a haemovigilance system, reports of adverse events before, during and after the transfusion are collected in order to take adequate measures, prevent their recurrence and – ultimately – increase patient safety.

The beginnings of haemovigilance can be traced back to the early 1990s when France introduced the first blood transfusion monitoring system following the spread of the human immunodeficiency virus (2). Soon after, the United Kingdom and the Netherlands followed a similar path, creating the basis for a new era in blood surveillance and regulation in Europe (3).

Within the Swiss jurisdiction, Swissmedic monitors the safety of therapeutic products, including blood and blood products, according to Art. 58 of the Therapeutic Products Act. Since its founding in 2002, the Agency has been responsible for the Swiss haemovigilance system, a passive reporting system. Swissmedic receives and processes reports from different types of events associated with transfusions such as transfusion reactions, near misses and transfusion errors, as well as reports related to donor safety, screening and testing and quality defects of blood products (Table 1). The obligation to report events, to establish an adequate quality control system and to ensure traceability throughout the entire transfusion chain from donor to recipient is stipulated by Swiss law. All manufacturers and users of labile blood products must appoint a person responsible for compliance with haemovigilance requirements.

Table 1: Reported events in 2021

Type	Number of reports
Transfusion reactions (TR)	1,873
Near misses (NM)	2,585
Transfusion errors / incorrect blood component transfused (IBCT)	49
Quality defects and protective measures	149
Donor reactions	3,245

In this edition, we focus on transfusion reactions and present an overview of the most frequently reported events in Switzerland.

Transfusion reactions 2021

Transfusion reactions (TR) are undesirable or unexpected events related to the administration of labile blood products. Art. 63 para. 2 TPO (Therapeutic Products Ordinance) requires these events to be reported to Swissmedic. Swissmedic follows the definitions of transfusion reactions set by the International Society of Blood Transfusion (ISBT) and further classifies them by severity (non-severe, severe, life-threatening, fatal) and imputability (i.e. causal connection between transfusion and reaction) (Table 2) (4). For more detailed information concerning grading, please refer to the Annual Haemovigilance Report 2021 and our website (https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/market-surveillance/haemovigilance.html).

Table 2: Classification of transfusion reactions

Immunologically-related TR	Cardiovascular and metabolic problems	Infections
• Transfusion-related acute lung injury (TRALI)*	• Circulatory overload (TACO)	• Bacterial
• Allergic TR	• Hypotensive TR	• Parasitic
• Febrile, non-haemolytic TR (FNHTR)*	• Transfusion-associated dyspnoea (TAD)	• Viral
• Allo-immunisations	• Haemosiderosis	• Prions
• Haemolytic TR (HTR), acute and delayed	• Hyperkalaemia, hypocalcaemia	• Fungal
• Post-transfusion purpura (PTP)	• Other	
• Transfusion-associated graft-versus-host disease (Ta-GvHD)		

**non-immunological mechanisms for these transfusion reactions are also under consideration*

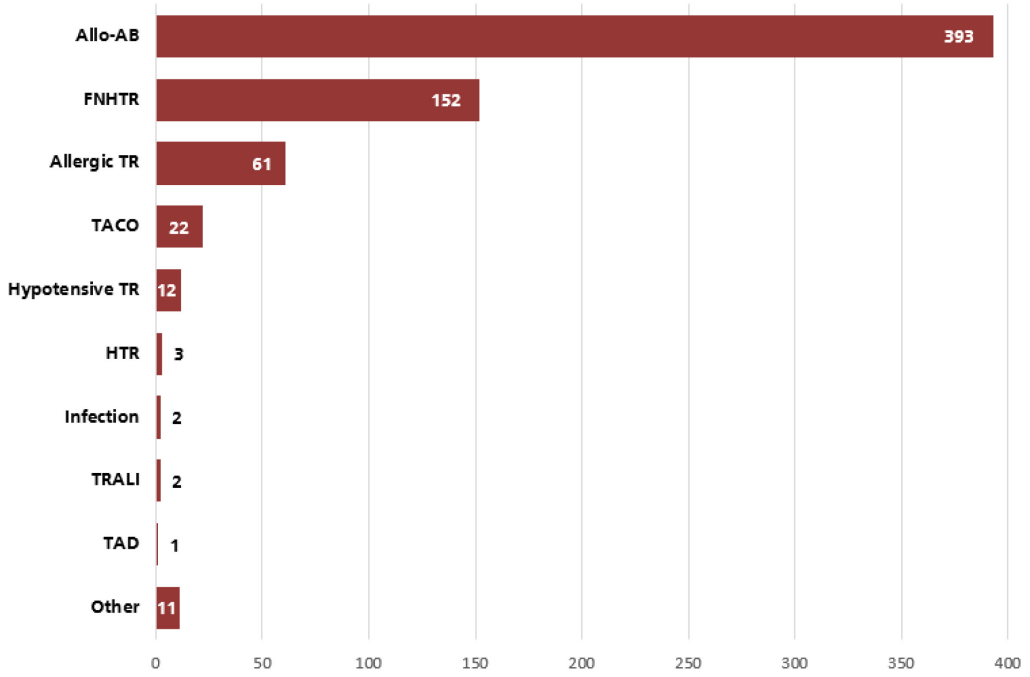
Reported events and patient characteristics

A total of 1,873 TR were submitted in 2021, leading to a reporting rate of 6.6/1,000 transfusions (7.8% lower than in 2020). Looking at all reported TR, the most frequent adverse events were allo-immunisations (1,116 in total, 393/100,000 transfusions), followed by FNHTR (febrile, non-haemolytic transfusion reaction) (432 total, 152/100,000) and allergic reactions (174 total, 61/100,000) (Figure 1). This observation was also made in previous years. The causal relationship between transfusion and reaction (imputability) was considered unlikely in 5%, possible in 25%, probable in 32% and certain in 37% of cases.

Similar to previous years, the absolute occurrence (all grades and imputabilities) of TR was higher in men, and the number of reported TR increased after the age of 50 years – a finding that applies to all types of transfusion reactions. However, the distribution patterns are different for each type of TR. For example, transfusion-associated circulatory overload (TACO) occurred predominantly in older patients (>70 years, 69% of TACO), while 77% of allergic reactions were experienced by patients <70 years (<50 years: 47%).

Figure 1 and Table 3: Reported transfusions reactions in 2021 by category and severity (all imputabilities)

Transfusion reactions by category per 100,000 transfusions



Transfusion reactions by severity (absolute number)

	1	2	3	4	Total
Allo-immunisation	0	1,116	0	0	**1,116**
FNHTR	413	17	2	0	**432**
Allergic TR	131	30	13	0	**174**
TACO	15	33	13	1	**62**
Hypotensive TR	13	18	2	0	**33**
HTR	2	7	0	0	**9**
Infection	6	0	1	0	**7**
TRALI	0	2	4	0	**6**
TAD	2	0	2	0	**4**
Other	29	0	0	1	**30**
Total	**611**	**1,223**	**37**	**2**	**1,873**

Severity 1: non-severe, 2: severe/permanent damage, 3: life-threatening, 4: death.

If allo-immunisations are not taken into account, the majority of the 757 TR were accounted for by FNHTR (57%), allergic TR (23%), TACO (8%) and hypotensive TR (4%).

Severity

Allo-immunisations represent a permanent damage to the patient and are therefore classified as severe TR (grade 2). Of the remaining TR, 80.7% were non-severe, 14.1% severe, 4.9% life-threatening and 0.3% fatal (Table 3). Focusing on life-threatening or fatal TR, 31 TR (grade 3: 29, grade 4: 2) with an imputability of at least "possible" were graded as such. Of these, TACO (total: 13) and allergic TR (total: 12) made up the largest share; TRALI (transfusion-associated acute lung injury, total: 3), hypotensive TR (total: 2) and "other" (total: 1) were further causes (Table 4). Compared to previous years, TACO remains the major cause of life-threatening or fatal TR with one fatal incident (imputability: certain) in 2021. This is of particular significance, as TACO is – to some extent – considered a "preventable" TR with certain patient-dependent risk factors and preventive measures (e.g. transfusion rate and diuretic therapy) (5). The incidence of TACO (all severities and imputabilities) was 22/100,000 in 2021 and 32/100.000 in 2020, remaining largely stable over the last 5 years. Overall, the incidence of death associated with transfusions was 0.7/100,000 transfusions in 2021, which is comparable to international data (6). A further description of the reported TR, including details on allo-immunisations and case reports for the 2 fatal TR, is provided in the Annual Haemovigilance Report.

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Table 4: Life-threatening and fatal TR (severity 3 and 4) with causality possible, probable or definite

Life-threatening and fatal transfusion reactions (severity 3 and 4) with causality ≥2				
	Possible	Probable	Certain	Total
TACO	5	6	2	**13**
Allergic TR	5	5	2	**12**
TRALI	2	0	1	**3**
Hypotensive TR	0	1	1	**2**
Other	1	0	0	**1**
Total	**13**	**12**	**6**	**31**

Conclusions

In 2021, the overall risk of transfusion reactions in Switzerland remained low and the pattern of reaction types as well as affected patient groups was consistent with previous years. Although TR are rare and mostly mild, careful evaluation before and monitoring during and after transfusions remain important. All transfusion reactions (regardless of the assumed causality) must trigger an investigation and are reportable to Swissmedic.

In the next edition of Vigilance News, we will provide an overview of incorrect transfusions and near misses from 2021.

References

(1) EDQM. CD-P-TS Guide to the preparation, use and quality assurance of blood components. Council of Europe; 2020.

(2) De Vries RRP. Haemovigilance: recent achievements and developments in the near future. 2009;4(1):60-2.

(3) Faber J-C. The European Blood Directive: a new era of blood regulation has begun. 2004;14(4):257-73.

(4) ISBT ISoBT. Haemovigilance Resources 2022 [Available from: https://www.isbtweb.org/isbt-working-parties/haemovigilance/resources.html.

(5) Bosboom JJ, Klanderman RB, Migdady Y, Bolhuis B, Veelo DP, Geerts BF, *et al.* Transfusion-Associated Circulatory Overload: A Clinical Perspective. Transfusion Medicine Reviews. 2019;33(2):69-77.

(6) S Narayan (Ed) D Poles eaobotSHoTSSG. The 2021 Annual SHOT Report 2021. Available from: https://www.shotuk.org/wp-content/uploads/myimages/SHOT-REPORT-2021-FINAL-bookmarked.pdf.

Information on the Swissmedic website

In focus

COVID-19 Pandemic

Information on the new coronavirus (SARS-CoV-2)

Side effects of COVID-19 vaccines in Switzerland

26.08.2022

Reports of suspected adverse reactions to COVID-19 vaccines

15,781 reports of suspected adverse vaccination reactions evaluated

01.07.2022

Reports of suspected adverse reactions to COVID-19 vaccines

15,578 reports of suspected adverse vaccination reactions evaluated

Healthcare Professional Communication

The links are available in German/French only

17.11.2022
DHPC – Alle Allergovit® und Novo-Helisen Depot® Präparate
Mögliche Falschetikettierung von Allergovit und Novo-Helisen Depot Produkten

16.11.2022
DHPC – Imbruvica® (Ibrutinib)
Neuaufnahme von Leitlinien zur Dosisanpassung aufgrund kardialer Toxizitäten sowie Aktualisierung der Leitlinien bei nicht-kardialen Toxizitäten

15.09.2022
DHPC – Sabril® (Vigabatrinum)
Vorübergehender Lieferengpass

19.08.2022
DHPC – Xalkori® (Crizotinib)
Sehstörungen, einschliessich des Risikos schweren Sehverlusts, Notwendigkeit der Überwachung bei pädiatrischen Patienten

15.08.2022
DHPC – Besponsa (Inotuzumab Ozogamicin)
Haarrisse im Boden einer Durchstechflasche

21.07.2022
DHPC – Paxlovid® (Nirmatrelvir [PF-07321332] / Ritonavir)
Dosisanpassung bei Nierenfunktionsstörung und Interaktionspotential von Paxlovid mit anderen Arzneimitteln

15.07.2022
DHPC – Palexia® (Tapentadolum)
Vorübergehende Auslieferung von Palexia® retard mit fehlerhaften Patienteninformation

02.06.2022
DHPC – Zinforo (ceftarolinum fosamilum)
Änderung der Haltbarkeitsdauer für verdünntes Zinforo 600mg/Vial

Announcements

Some of the links are available in German/French only

07.11.2022
Update – Warning about supposedly herbal products
Swissmedic is issuing an urgent warning regarding slimming products and other supposedly natural products

04.11.2022
Formation of bubbles in Comirnaty Bivalent Original/Omicron BA.1 vaccine: Swissmedic analysis reveals no indications of risk
Results from laboratory analyses now available

31.10.2022
Die neue Pharmacopoea Helvetica 12
Die neue Pharmacopoea Helvetica ist publiziert. Der Institutsrat hat beschlossen, die 12. Ausgabe der Schweizerischen Pharmakopöe auf den 1. April 2023 in Kraft zu setzen.

24.10.2022
Umfrage Public Summary SwissPAR
Kennen Sie das Public Summary SwissPAR? Nehmen Sie an unserer Umfrage teil.

10.10.2022
Swissmedic approves bivalent COVID-19 booster vaccine from Pfizer
Comirnaty Bivalent Original / Omicron BA.1 (tozinameran / riltozinameran) from Pfizer authorised from age 18

10.10.2022
Adverse events following immunization – annual Vaccinovigilance report
Summary of adverse events following immunization reported in Switzerland during 2021

30.09.2022
Link between fertility and COVID-19 vaccination investigated

26.09.2022
Update on the replacement of the medical professions register MedReg
by the new Health Professions Platform (HealthReg)

02.09.2022
COVID-19 vaccine Nuvaxovid: temporary authorisation from 12 years of age and as booster
Swissmedic authorises indication extension and booster

01.09.2022
Guidance document Authorisation according to Art. 14 para. 1 abis-quater TPA HMV4 updated
Clarification of safety-relevant updates to medicinal product information for authorisations according to Art. 14 para. 1 let. abis TPA

01.09.2022
Update of the information sheet on notification of suspected illegal trading in medicinal products products
Clarification of the criteria for cases notified in connection with mandatory notification where there is a suspicion of illegal trading in medicinal products

29.08.2022
Swissmedic approves first bivalent COVID-19 booster vaccine in Switzerland
Moderna's Spikevax Bivalent Original/Omicron (mRNA-1273.214) authorised from age 18

26.08.2022
Haemovigilance Annual report 2021
Evaluation of haemovigilance reports in 2021

16.08.2022
Benchmarking study 2021
International comparison of Swiss approval times

03.08.2022
Empfehlung bezüglich COVID-19 für die autologe Blutstammzellspende
Beschluss Vorschriften SBSC – Blutstammzellspende

01.08.2022
Changes to Guidance document Authorisation procedures for COVID-19 medicinal products during a pandemic HMV4
Filing of Submission Plans to evaluate the efficacy of existing COVID-19 medicinal products against new SARS-Cov-2 variants

20.07.2022
Operation PANGEA XV: International campaign against falsified and illegally imported medicinal products
Authorities checked shipments of medicinal products worldwide from criminal online sales

14.07.2022
Reporting side effects electronically: new online reporting form for those affected or their relatives
Private individuals can now report suspected adverse drug reactions to Swissmedic via a web form

04.07.2022
New website – complementary and herbal medicines (CHM)
The website for authorisation of complementary and herbal medicines has been completely revised and updated

01.07.2022
Changes to the Guidance document Product information for human medicinal products HMV4
Clarifications on boxed warnings and other topics

01.07.2022
Swissmedic position paper on the use of real-world evidence
Swissmedic considers real world data (RWD) as all data other than those collected through a clinical trial conducted as per ICH GCP

15.06.2022
Swissmedic approves Paxlovid for COVID-19 patients
Paxlovid from Pfizer AG granted temporary authorisation in Switzerland

14.06.2022
International cooperation on therapeutic products
First application reviewed by all five Access Consortium Authorities

10.06.2022
Annual Report 2021

The complete list is available at the following web address www.swissmedic.ch/updates-en