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ORIGINAL RESEARCH ARTICLE

# Impact of Covid-19 Vaccination on Spontaneous Pharmacovigilance Reporting in France

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## Abstract

**Introduction** In 2021, the massive Covid-19 vaccination campaign in France was accompanied by an intensified pharmacovigilance monitoring of their potential adverse drug reactions. The importance of this reporting might have led to an important selective reporting and overloading of Pharmacovigilance Centres, delaying the recording of some reports in the national pharmacovigilance database. In this context, we aimed to evaluate the impact of the Covid-19 vaccination campaign in France and related reports on spontaneous reporting of adverse drug reactions that were not related to the Covid-19 vaccine.

**Methods** We performed time-series analyses considering the monthly number of adverse drug reactions reported between January 1, 2018 and April 30, 2022 using the French Pharmacovigilance database. The impact of the Covid-19 vaccination campaign on the monthly reporting not Covid-19 vaccine related was estimated using interrupted time-series. January 2021, marking the start of the campaign, was the intervention date in the models. Analyses were run globally first considering all adverse drug reaction reports, and second according to notifier type and to case seriousness.

**Results** We included 170,294 reports registered in the French Pharmacovigilance database between January 1, 2018 and April 30, 2022 that were not Covid-19 vaccine-related. Among these, 77,067 (45.3%) were serious and 146,683 (86.1%) had been reported by health care professionals. The campaign start was associated with a nearly 35.0% decrease in average monthly reporting that was not Covid-19 vaccine-related, with a significant level decrease in the monthly number of reports of −658.0 ($p < 10^{-3}$) immediately after the vaccination campaign start and a subsequent slope decrease of −50.0 ($p < 10^{-3}$). This decrease was mainly due to a significant level and slope decrease (level: −739.2 $p < 10^{-3}$; slope: −39 [$p < 10^{-2}$]) for health care professional reports. A similar level decrease was found for the monthly number of both serious and non-serious reports (−402.3, $p < 10^{-3}$; and −311.9, $p = 10^{-2}$, respectively). According to the ATC 1 level, the decrease in the monthly number of reports showed similar patterns for all drugs. However, a potential increase in the number of serious reports suspecting antineoplastic and immunomodulating drugs (ATC L) or drugs targeting blood was observed (ATC B).

**Conclusion** Our study showed a significant impact of the Covid-19 campaign vaccination in the reporting of adverse drug reactions that were not Covid-19 vaccine-related, of roughly 35%. This leads to a loss of information regarding the monitoring of drug safety that could have impacted the system capacity to detect safety signals for drugs other than Covid-19 vaccines.

## 1 Introduction

The last years have been marked by the Covid-19 pandemic. In January 2021, a massive Covid-19 vaccination campaign started in France, mainly with mRNA vaccines, leading in few months to a vaccine coverage of almost 80% of the adult population. The large use of these new vaccines was associated by an intensified pharmacovigilance monitoring of their potential adverse drug reactions (ADRs) [1]. This was made possible through a tremendous involvement of the French pharmacovigilance system, a system in charge of surveillance of the safety of drugs after marketing by analysing spontaneous reports of ADRs from physicians or patients. This system has proven its efficiency in the early detection of safety signals regarding drugs as used in real-world conditions, with performances that no other system has approached so far [2].

Even though it is the best available, these performances are not perfect and the system presents some limitations, the main being underreporting [3, 4]. This underreporting is well documented and estimated with a median rate of

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**Key Points**

Our study showed a significant impact of the Covid-19 vaccination campaign on the reporting of adverse drug reactions that were not Covid-19 vaccine-related, with an average decrease in monthly reporting of roughly 35%.

The decrease in reporting was mainly due to a decrease in the number of reports from health care professionals.

The decrease in reporting leads to a loss of information regarding the monitoring of drug safety that could have impacted the system capacity to detect safety signals for drugs other than Covid-19 vaccines.

around 95% of all ADRs considered [4]. Per se, it does not constitute a critical limit of the system as long as the sample of reported ADRs is representative of all those that can have occurred, which thus still allows the detection of all potential signals. However, across types of ADRs or drugs, the rate of underreporting has been shown to vary depending on several factors. This implies that the ability to detect a signal could not be constant over time [3, 5, 6]. Among these factors, drug novelty and lifespan, ADR seriousness, or mediatisation and notoriety of specific drug-event association appear to influence the propensity of professionals and patients to report their potential drug-related adverse experiences [7]. For professionals the lack of time for reporting the potential ADRs they identify, can result in prioritising the reporting of some ADRs over others and consequently in differential underreporting [6]. This was particularly demonstrated in France for reports from both health professionals and patients during the so-called Mirena® and Levothyrox® crisis [8, 9]. In this last case, the massive wave of selective reporting accompanying the crisis and its mediatisation in France altered pharmacovigilance signal detection results obtained from international databases [10]. The mechanisms for these alterations are well identified and related from both notoriety bias and competition bias that can affect both the statistical signal detection performed from spontaneous reporting databases using disproportionality analyses [2, 3, 11].

The importance of the reporting that accompanied Covid vaccination campaigns might have pushed this phenomenon, not mandatorily in terms of biasing directly, but by disproportionality analysis results [12], resulting first in an important selective reporting and second by burdening Pharmacovigilance Centres and increasing their potential backlogs, and delaying the recording of some reports in the national and international pharmacovigilance databases [13]. In this context, we aimed at evaluating the impact of the Covid-19 vaccination campaign and related reports on spontaneous reporting for all other drugs in France.

## 2 Methods

### 2.1 Data Source and Study Design

We performed a repeated cross-sectional study considering the monthly number of ADRs reported between January 1, 2018 and April 30, 2022 using the French Pharmacovigilance database (BNPV) containing all ADR spontaneous reports received and considered by the 30 centres from the French Pharmacovigilance Regional Centres Network [1].

In the BNPV, for each report, receipt and registration date, ADR type and onset date, drug type and role (suspect/interacting/concomitant), dates of use and route of administration, case seriousness, reporter type, and patient characteristics are registered. A report is considered serious if the ADR led to the death of the patient, was life-threatening, led to hospitalisation or prolongation of existing hospitalisation, to a significant disability or incapacity, to a congenital malformation or all other medical situations considered significant. Spontaneous reports are continuously registered in the database allowing analysis of behavioural changes in spontaneous reporting.

Reports with at least one Covid-19 vaccine suspected were defined as "Covid-19 vaccine-related" and were excluded from the analyses. To eliminate the influence of the Levothyrox® crisis [14, 15], spontaneous reports suspecting levothyroxine were also excluded. Finally, addictovigilance reports were excluded from the analyses since the recent changes in the rules of their registration in the French pharmacovigilance database led to an increase in registered addictovigilance cases.

Drugs were considered according to their ATC (Anatomical, Therapeutic and Chemical) class as coded in the database [16]. Only suspected or interacting drugs were included in the analyses. Notifier type, originally informed as physicians, pharmacists, nurses or patients/ non-health professional were gathered into two categories: health care professionals (HCPs) and non-HCPs.

### 2.2 Statistical Analysis

Time-series analyses were performed to visualise trends in the monthly number of reports not related to Covid-19 vaccine during our study period; they considered the ADR spontaneous reports receipt date. They were detailed according to notifier type, case seriousness, and drug ATC class (Level 1 for all drugs; Level 3 for drugs showing with increased reporting).

The impact of the Covid-19 vaccination campaign on the monthly reporting for other drugs was estimated using interrupted time-series (ITS) [17, 18]. The ITS analysis, based on segmented linear regression modelling, allow estimating three regression coefficients with their 95% confidence interval (CI) to explore the impact of an intervention on time series data, i.e. repeated measurements of a given outcome at regular intervals: (i) pre-intervention slope interpreted as the change in monthly reporting associated with a time unit increase, (ii) level changes interpreted as the immediate and permanent change caused by the intervention (iii) changes between the pre- and post-intervention slopes (using the interaction between time and intervention) representing the time-dependent effect due to the intervention [17]. These changes are considered to be attributable to the intervention, in this case the start of the vaccine campaign, set for January 2021. Analyses were run first considering all ADR reports, second according to notifier type and to case seriousness. Autocorrelation was considered using the Yule-Walker method and heteroscedasticity was tested using the autoregressive conditional heteroscedasticity (ARCH) test. The SAS AUTOREG procedure was used to perform the analyses.

**Table 1** Results of the interrupted time-series analyses for the effect of Covid−19 vaccination campaign on the monthly number of adverse drug reaction reports entered in the French Pharmacovigilance database between January 2018 and April 2022 considering January 2021 as the start of the vaccination campaign

| | Estimate (CI 95%) | *P* value |
|---|---|---|
| **All reports** | | |
| Slope | −7.8 (−12.0; −3.5) | 0.1 |
| Level change | −658.0 (−681.3; −634.7) | $<10^{-3}$ |
| Slope change | −50.0 (−57.1; −42.8) | $<10^{-3}$ |
| **HCP reporting** | | |
| Slope | −7.5 (−11.7; −3.4) | 0.1 |
| Level change | −739.2 (−762.0; −716.5) | $<10^{-3}$ |
| Slope change | −39.1 (−46.1; −32.2) | $<10^{-2}$ |
| **Non-HCP reporting** | | |
| Slope | 0.1 (−1.5; +1.4) | 0.9 |
| Level change | +91.2 (+81.3; +101.2) | $10^{-3}$ |
| Slope change | −12.1 (−15.1; −9.0) | $<10^{-3}$ |
| **Serious ADRs** | | |
| Slope | −1.0 (−4.1; +2.2) | 0.7 |
| Level change | −402.3 (−421.9; −382.7) | $<10^{-3}$ |
| Slope change | +1.2 (−4.8; +7.1) | 0.9 |
| **Non-serious ADRs** | | |
| Slope | −8.1 (−11.2; −5.1) | $10^{-3}$ |
| Level change | −311.9 (−333.4; −290.4) | $10^{-2}$ |
| Slope change | −44.4 (−50.9; −37.9) | $<10^{-3}$ |

*ADR* adverse drug reaction, *CI* confidence interval, *HCP* healthcare professionals

Analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

## 3 Results

After exclusion of levothyroxine and addictovigilance reports, the number of reports registered in the French Pharmacovigilance database between January 1, 2018 and April 30, 2022 included 155,229 reports relating to Covid-19 vaccines and 170,294 reports relating to other drugs (including non-Covid-19 vaccines; Supplemental file S1). Among the reports not relating to Covid-19 vaccines included in the study, 77,067 (45.3%) were serious and 146,683 (86.1%) had been reported by HCPs. Trends in the monthly number of ADR reports related and not related to Covid-19 vaccines are represented in Fig. 1.

The monthly number of reports appeared stable before the start of the pandemic. Afterwards, a slight decrease in the number of monthly notifications was observable from the start of the pandemic that appeared to resolve over the last months of 2020 before a second and more important decreased occurred following the initiation of the vaccination campaign (Fig. 1). Overall, the mean monthly number of ADR reports was around 3670 before January 2021 and of 2385 thereafter, indicating a potential 35.0% (95% CI 29.3; 40.7) decrease. The ITS analysis confirmed and improved the estimations of this observation showing a significant level decrease in the monthly number of reports of − 658.0 immediately after the vaccination campaign start and significant slope decrease of −50.0 (Table 1).

Analyses performed according to reporter type highlighted some differences (Fig. 2). The mean monthly number of ADRs reported by HCPs was 3213 before January 2021 and 1938 thereafter, indicating a potential 39.7% (95% CI 33.7; 45.7) decrease. Conversely, the mean monthly number of ADRs reported by non-HCPs appeared stable between the two periods (around 450 reports per month for both periods). Interrupted time-series analysis of HCP reporting evidenced a significant level decrease of 739.2 after the start of the vaccination campaign and a significant slope decrease of −39.1 thereafter; whereas that of non-HCP reporting highlighted a significant initial level increase after of 91.2 and then a significant slope decrease of −12.1 (Table 1).

Analyses performed according to ADR seriousness highlighted lower differences (Fig. 3). The mean monthly number of serious ADR reports was 1611 before January 2021 and 1193 thereafter, indicating a potential 25.9% (95% CI 20.1; 31.8) decrease. For non-serious ADR reports, the mean monthly number of ADRs registered was 2060 before January 2021 and 1193 thereafter, indicating a potential 42.1% (34.6; 49.6) decrease. The ITS analysis indeed identified a similar level decrease for the monthly number of both

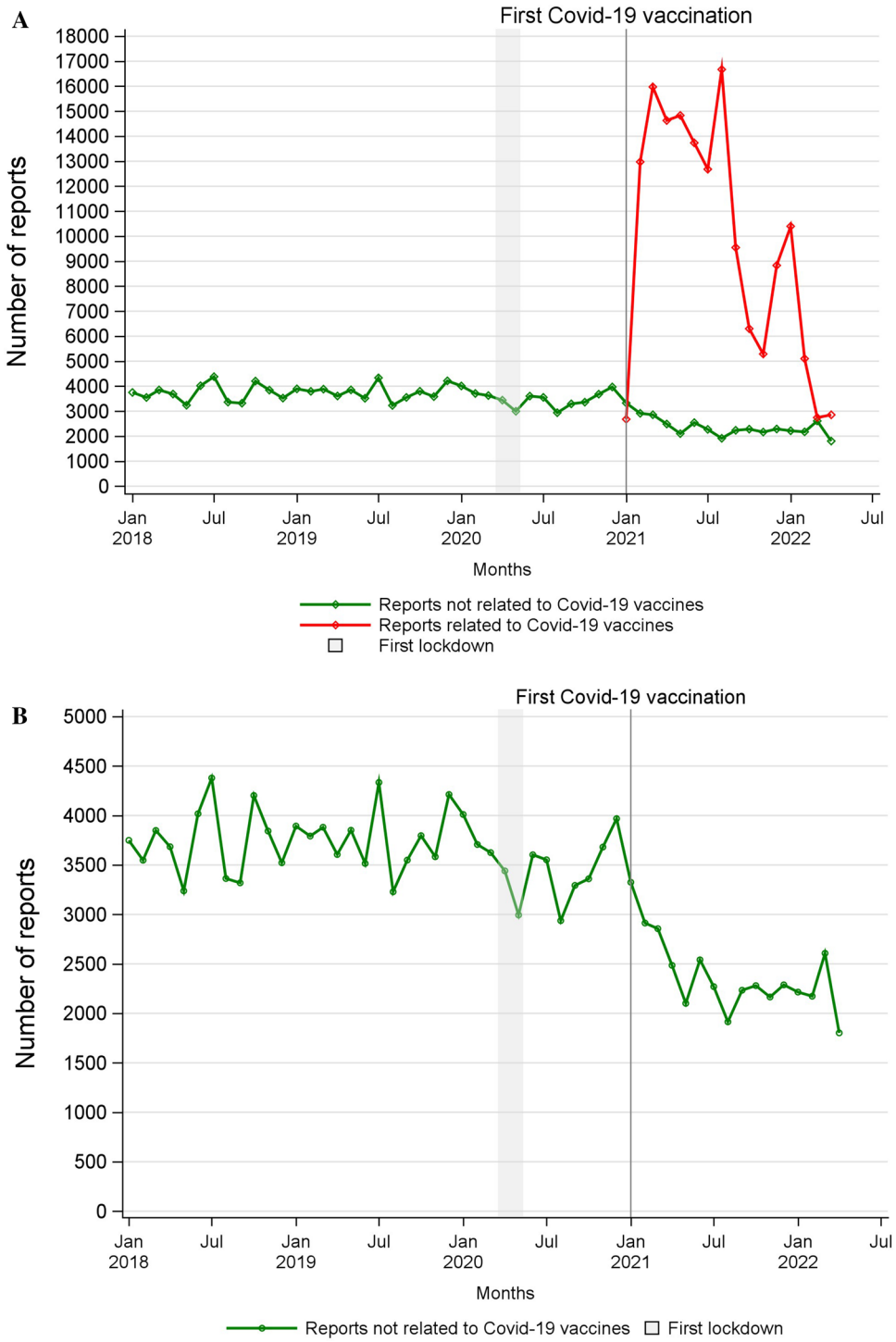



**Fig. 1** Monthly number of adverse drug reaction reports entered in the French Pharmacovigilance database between January 2018 and April 2022 (Covid-19 vaccines vs all other drugs, **A**; All drugs other than Covid-19 vaccines—adapted *x*-axis scale, **B**)

serious and non-serious ADRs (−402.3 and −311.9, respectively). However, a subsequent significant slope decrease was highlighted only for reporting of non-serious ADRs (−44.4 vs +1.2 for serious ADRs) (Table 1). These variations led to a higher number of serious reports than non-serious reports for the first time since 2018.

The graphical representation of reporting according to the ATC 1 level showed similar patterns for all drugs (Supplemental file S2). Therefore, no additional ITS analysis was performed according to ATC level. However, some potential discrepancies were visible when results were stratified by seriousness and especially for the most serious. A potential increase in the number of reports suspecting antineoplastic and immunomodulating drugs (ATC L) or drugs targeting blood could then be observed (ATC B) (Fig. 4). For ATC L, the mean monthly number of ADR reports was 246

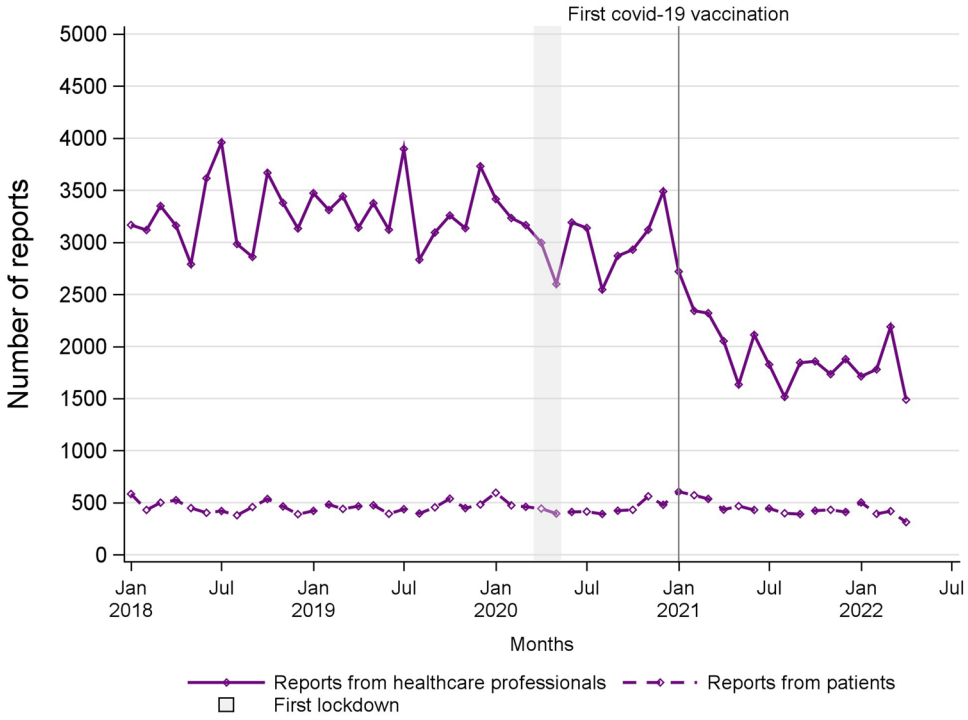



**Fig. 2** Monthly number of adverse drug reaction reports not related to covid-19 vaccines and entered in the French Pharmacovigilance database between January 2018 and April 2022 according to reporter type

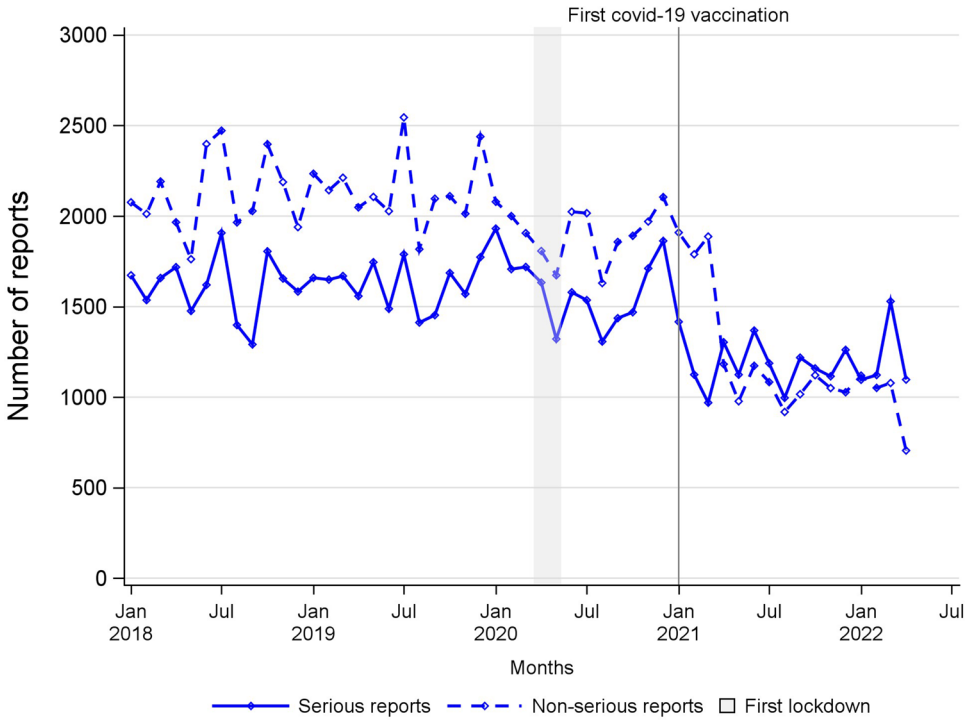
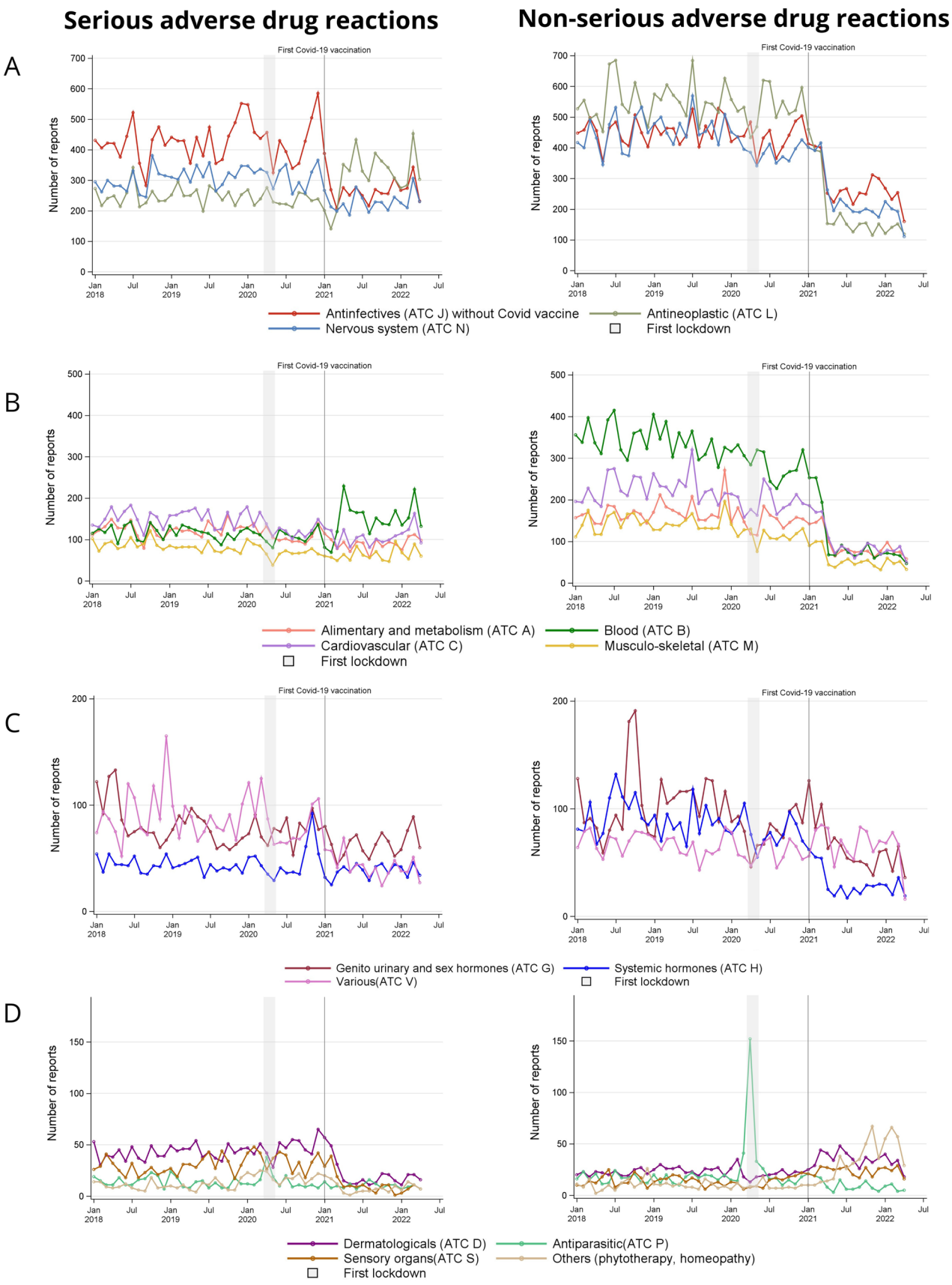



**Fig. 3** Monthly number of adverse drug reaction (ADR) reports not related to covid-19 vaccines and registered in the French Pharmacovigilance database between January 2018 and April 2022 according to ADR seriousness

before January 2021 and 312 thereafter, indicating a potential 26.9% (95% CI 14.8; 39.1) increase. For ATC B, the mean monthly number ADR reports was 115 before January 2021 and 147 thereafter, indicating a potential 28.1% (14.4; 41.9) increase. This mainly concerned monoclonal antibodies (not indicated in Covid-19 treatment) amongst antineoplastic agents (Supplemental file S3) and antithrombotic agents amongst drugs targeting bloods (Supplemental file S4).


Serious adverse drug reactions
Non-serious adverse drug reactions
A
B
C
D
First Covid-19 vaccination
Number of reports
Antinfectives (ATC J) without Covid vaccine
Antineoplastic (ATC L)
Nervous system (ATC N)
First lockdown
Alimentary and metabolism (ATC A)
Blood (ATC B)
Cardiovascular (ATC C)
Musculo-skeletal (ATC M)
Genito urinary and sex hormones (ATC G)
Systemic hormones (ATC H)
Various(ATC V)
Dermatologicals (ATC D)
Antiparasitic(ATC P)
Sensory organs(ATC S)
Others (phytotherapy, homeopathy)

◂**Fig. 4** Monthly number of adverse drug reaction (ADR) reports not related to Covid-19 vaccines entered in the French Pharmacovigilance database between January 2018 and April 2022 according to the Anatomical, Therapeutic and Chemical (ATC) classification and to ADR seriousness (**A**: ATC class J, L, N; **B**: ATC class A, B, C, M; **C**: ATC class G, H,V; **D** ATC class D, P, S and others)

## 4 Discussion

In this study, we aimed to evaluate the impact of the Covid-19 vaccination on the reporting for ADR not related to these vaccines. We highlighted a significant decrease in global reporting of ADRs both in terms of level and slope, especially affecting reporting from HCPs. Additionally, the changes that occurred resulted, over the months following the start of the vaccination campaign, in a reporting consisting mainly of serious ADRs, which is the opposite to what is usually observed.

These findings raise an important question. The global level decrease that we quantified could have impacted drug safety monitoring and the ability of the system to detect safety signals for drugs other than Covid-19 vaccines during the studied period. As long as the underreporting that was potentially increased during the period has not been selective across non-Covid-19 vaccines, drugs and ADRs, then resulting in no loss of representation of the reporting over all occurring ADRs, this would only be of concern in terms of power and potentially time to detection for signals. Theoretically, given the remaining high volume of reporting, the impact would then probably be limited to the ability to detect signals for very rare ADRs or exposure. In this context, some studies have evaluated the risk of masking effect due to Covid-19 vaccine spontaneous reporting [19–21]. A masking effect was detected for 5 of the 52 signals studied in Eudravigilance [19] and for 132 adverse drug reactions in the worldwide pharmacovigilance database Vigibase [20]. The masking effect also affected Covid-19 vaccine and others, as demonstrated by Harpaz et al in an analysis performed on the US Vaccine Adverse Event Reporting System (VAERS) [21]. In any case, the massive wave of reporting for the Covid-19 vaccination had a detrimental impact on reporting for other drugs. This would need to be communicated to reporters, both HCPs and non-HCPs in order to preserve as much as possible of the reporting for all drugs in the context of extraordinary attention surrounding one drug or ADR [8, 9].

Reassuringly in this context, the results we herein report support the hypothesis of a prioritisation of the reporting of serious ADRs. This appears to be represented most in the post-vaccination period, which is unusual in terms of reporting. This hypothesis would indeed be consistently supported by the observation that the return to a regular level of reporting after the drop observed during the first year of the pandemic was observed only for the serious ADRs and not for the non-serious ADRs. The disparities observed in changes between serious and non-serious ADRs might nonetheless have been overestimated owing to the differences in reglementary requirements for their recording in pharmacovigilance spontaneous reporting databases (15 days for serious ADRs vs 90 days for non-serious ADRs). It would be very interesting to obtain information on the evolution of spontaneous declarations, excluding those related to Covid-19, in other countries to compare the reporting behaviours during the pandemic.

Second, we observed a smaller decrease in reporting by non-HCPs than by HCPs. The huge mobilization of HCPs during all the phases of the Covid pandemic could explain why they could not dedicate more time to reporting, in a context where they were required to report ADRs of Covid-19 vaccines. The discontinuation of routine collections in hospitals during the pandemic could also have an impact on the number of reports. However, this discontinuation began from the start of the pandemic, not from the start of the vaccination campaign. It may, however, explain part of the decline that began at the start of the pandemic. In this context, the lower impact on patient reporting appears of interest to help maintain the system ability for signal detection [22, 23]. This reinforces the importance of involving patients in ADR report activities.

Third, the increased number of serious reports suspecting antineoplastic and immunomodulating drugs or drugs targeting blood should be discussed. The Covid-19 pandemic led to delays in identifying new cancers and/or initiating treatment [24]. We can thus suppose that the increase in antineoplastic and immunomodulating drug reports was the reflection of an increased use of these drugs in the post-lockdown period to compensate for the delayed care. Nevertheless, the global decrease in the monthly number of reports even for these two drug classes could provide more ADRs considered serious, due to a change in the coding rules. It would have been of interest to investigate these changes according to drug indication. However, this information is considered of limited reliability in spontaneous reporting databases. A more detailed study of these reports would be interesting to better understand these reporting changes over time.

The main strength of our study is the use of the French Pharmacovigilance Database containing all the adverse reactions reported in France. The continuous implementation of the database allows the realisation of chronological series based on the registration date. Another strength was the exclusion in our study of situations that may bias the interrupted time series interpretation like levothyroxine or addictovigilance reports.

In addition to the massive reporting wave, the Covid-19 pandemic itself may also had a direct and indirect (via the

decrease in drug utilisation [25, 26]) impact on spontaneous reporting. Actually, some studies highlighted the impact of the Covid-19 pandemic [27] and resulting lockdowns [28] on spontaneous reporting. The decrease in spontaneous reporting found in our study may therefore be partly linked to the Covid-19 pandemic, independently of the vaccination campaign, explaining the slight decrease in the number of monthly notifications between the start of the pandemic and the start of the vaccination campaign.

Finally, a last limitation concerns the 90-day period allowed for the recording of non-serious ADRs and potential backlog remaining of cases remaining in pharmacovigilance centres. However, this should mainly have concerned 2021 and should have been resolved when data were obtained in June 2022.

## 5 Conclusion

In conclusion, our study showed a significant impact of the Covid-19 campaign vaccination in the reporting of ADRs for other drugs, of roughly 35%. This leads to a loss of information regarding the monitoring of drug safety that could have impacted the system capacity to detect safety signals for drugs other than Covid-19 vaccines at a time when these were especially important. Such a potential detrimental impact needs to be prevented in the future by educating both HCPs and non-HCPs of the importance of preserving all reporting, even in periods of limited availability.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40264-023-01359-4.

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## Declarations

**Funding** This research received no funding.

**Conflict of interest** The authors declare no conflict of interest.

**Ethics approval** In accordance with French regulations, formal approval by an investigational review board is not required for this type of study.

**Consent to participate** As all data recorded in the French Pharmacovigilance database are anonymous, informed consent is waived.

**Consent to publication** Not required.

**Availability of data and material** The approval to access the anonymised data maintained by the French Network of Pharmacovigilance requires the data to be treated as confidential with protected and secure access. For this reason, the data cannot be shared publicly.

**Code availability** The code will be made available upon reasonable request.

**Author contributions** All authors contributed to the study conception and design. Validation of the data and analysis were performed by SG and AS. SG drafted the manuscript which was commented and reviewed by all authors. All authors read and approved the final manuscript.

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