Numbers of spontaneous reports

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Published in:
British Journal of Clinical Pharmacology

DOI:
10.1111/bcp.15024

Received: 8 July 2021 | Accepted: 28 July 2021

DOI: 10.1111/bcp.15024

SHORT COMMUNICATION

Numbers of spontaneous reports: How to use and interpret?

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Due to the high intensity of the COVID-19 vaccination campaigns and heightened attention for safety issues, the number of spontaneous reports has surged. In the Netherlands, pharmacovigilance centre Lareb has received more than 100 000 reports on adverse events following immunization (AEFI) associated with Covid-19 vaccination. It is tempting to interpret absolute numbers of reports of AEFIs in signal detection. Signal detection of spontaneously reported adverse drug reactions has its origin in case-by-case analysis, where all case reports are assessed by clinically qualified assessors. The concept of clinical review of cases—even if only a few per country—followed by sharing concerns of suspicions of potential adverse reactions again proved the strength of the system. Disproportionality analysis can be useful in signal identification, and comparing reported cases with expected based on background incidence can be useful to support signal detection. However, they cannot be used without an in-depth analysis of the underlying clinical data and pharmacological mechanism. This in-depth analysis has been performed, and is ongoing, for the signal of vaccine-induced immune thrombotic thrombocytopenia (VITT) in relation to the AstraZeneca and Janssen Covid-19 vaccines. Although not frequency or incidence rates, reporting rates can provide an impression of the occurrence of the event. But the unknown underreporting should also be part of this context. To quantify the incidence rates, follow-up epidemiological studies are needed.

KEYWORDS
AEFIs, pharmacovigilance, reporting odds ratio, signal detection, vaccines

1 | INTRODUCTION

Late 2020 to early 2021, the COVID-19 vaccination campaigns started. Multiple brands of vaccines from different manufacturers became available, at the time based mainly on two vaccine types (mRNA and viral vector). These vaccines were tested for efficacy and safety in large clinical trials.[1–3] Near real-time post-marketing pharmacovigilance was needed, because of the large-scale vaccination in a short time span.

Reports on adverse events following immunization (AEFI) can be reported to national spontaneous reporting systems (SRS). These systems have proven their worth as the backbone of post-marketing safety surveillance. SRS reporting remains one of the main methods to detect new safety signals in an efficient way once drugs are authorized on the market.[4–6] Due to the high intensity of the vaccination campaigns and heightened attention for safety issues of both healthcare professionals and the public, the number of spontaneous reports has surged. In the Netherlands, pharmacovigilance centre Lareb has received more than 100 000 reports on AEFI associated with Covid-19 vaccination by June 31, 2021, with 15.5 million vaccines administered in less than 6 months. It is tempting to interpret absolute numbers of reports of AEFIs in signal detection. How can these numbers be used and interpreted?

2 | SIGNAL DETECTION

Signal detection of spontaneously reported adverse drug reactions, or in the case of vaccines AEFI, has its origin in case-by-case analysis where all case reports containing one or more ADRs are assessed by clinically qualified assessors. Key in the assessment of the causal relationship between the vaccine and the reported AEFI is the clinical information provided by the reporter, among which information on timing and course of the reaction and other characteristics. In the case of COVID-19 vaccination, they have shown to be of irreplaceable value in finding signals, such as thrombosis with thrombocytopenia syndrome (TTS) linked to the vaccination with AstraZeneca vaccine Vaxzevria® and COVID-19 vaccine Janssen®.[7–9] The concept of clinical review of cases—even if only a few per country—followed by sharing concerns of suspicions of potential adverse reactions again proved the strength of the system.

What is already known about this subject

- Spontaneous reports are used for case-by-case signal detection. The number of reports can be used to calculate reporting rates.

What this study adds

- This study provides more insight into how to use and interpret numbers of spontaneous reports.

3 | DISPROPORTIONALITY ANALYSIS

Case-by-case signal detection by clinical experts remains important. Because of the very specific combination of clinical symptoms TTS was detected. With a triage of incoming cases, serious ADRs with clearly defined diagnosis can be quickly selected for further assessment and analysis. However, with large numbers of reports received, it is no longer possible to rely solely on case-by-case analysis because manual review of all reports is no longer feasible and, in addition, patterns in data that may reveal risk factors or other characteristics of the AEFIs are not always easily detectable. Methods for statistical signal detection were developed which help to drill down the number of associations that can be further reviewed manually. Because, in an SRS, data on the actual number of users for a drug (denominator data) are usually missing, the reports in the SRS itself are often used as a proxy. In this so-called quantitative signal detection, combinations of a drug or vaccine and a clinical event that are disproportionately highly represented in the database may represent a safety signal based upon a difference from the background frequency.[10] It should be noted that neither the absolute number of reports, nor the level of disproportionality is indicative of the occurrence of AEFIs in the population. In addition, it should be recognized that, given the use of this proxy and the likelihood of biased reporting, additional studies are needed to confirm the safety signals.

Calculations of measures of disproportionality are based primarily upon a two-by-two contingency table (Figure 1). One of the basic statistical approaches that has been in place for many years is the use of the reporting odds ratio (ROR), which is currently also in use by the European Medicines Agency.[11] The ROR compares the rate of reporting a specific adverse effect in a drug with the rate of reporting the same adverse effect in all other drugs. The ROR is calculated by the following division: the numerator is the number of cases in which the suspected drug (or vaccine) was used and a specific ADR (or AEFI) was reported divided by the number of cases using the suspected drug in which this ADR was not reported; the denominator is the number of cases using other suspected drugs, reporting a specific ADR divided by the number of cases using other suspected drugs without reporting that specific ADR. It is expressed as a point estimate with corresponding 95% confidence intervals (95% CIs).[10,12] See Figure 1.

Analysing large numbers of reports in routine signal screening by means of disproportionality analysis usually do not take into account clinical and pharmacological knowledge. This limits the capability to detect potential signals. For vaccines, statistical signal detection can be further optimized by taking into account detailed information from the reported AEFIs as well as background

	Reports with the suspected AEFI	Reports without the suspected AEFI
Reports with the suspected vaccine	a	b
All other reports	c	d

The ROR can be expressed as $ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$

The standard error of ln(ROR) and 95% confidence interval can be calculated by

$$SE\ (\ln ROR) = \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)} \text{ and } 95\%CI = e^{ln(ROR) \pm 1.96 \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}}$$

FIGURE 1 Calculation of the reporting odds ratio (ROR)

information, like the numbers of vaccines and the vaccinated populations, administered vaccines and batch numbers. Defining co-variables for stratification of disproportionality analysis, e.g., latency, age, gender, injection site, vaccination moment or vaccine brand name, may be useful.[13]

Disproportionality analysis can also be used to highlight potential batch-related issues. At Lareb, for each batch within a vaccine, local and systemic reactogenicity is compared with all other batches of the same vaccine, based on the 2 × 2 table shown in Figure 1.[14]

In addition to disproportionality analysis, other methods may be performed such as analysis of reporting patterns/clustering,[15] time-to-onset[16] and trend analyses.[17]

4 | OBSERVED/EXPECTED ANALYSIS

When a possible signal has been identified, by disproportionality analysis or case-by-case review, observed-over-expected (O/E) analyses can be performed. Numbers of reports can be used in O/E analyses that take into account background incidence rates for an event and total person–time at risk in the vaccinated population. The background incidence rate is the number of new cases occurring naturally in the population, expressed in person–time. The role of OE analyses is to refine previously detected signals when there is not enough information to determine whether further action is necessary. For instance, Lareb used this method to investigate cases of thrombosis for the different Covid-19 vaccines used in the Netherlands.[18] Stratification, for example for age and sex, can be incorporated in this method if data are present.

In this O/E method, the reported cases are considered as observed cases. However, the degree of underreporting is unknown. Even with the high reporting rate during this vaccination campaign in the Netherlands, probably not all suspected ADRs will be reported. Underestimation of the observed number of cases is therefore likely. Also, the accuracy of calculations also depends on quality of data used for background incidence and may vary according to the dataset that has been used.Nevertheless, if observed is higher than or, because of the underreporting, even close to expected, this is supportive for a signal.

5 | REPORTING RATES ARE NOT INCIDENCE RATES

Over the past few months, the number of cases suspected for TTS gradually increased. Based on a limited number of cases, a possible relationship between AZ and TTS was suspected. However, an incidence rate could not be calculated. For those working in the field of spontaneous reporting, this is obvious, but for those not so familiar with this approach, this is less obvious. Although it may give an indication, reporting rates cannot be interpreted as an incidence rate. For an incidence rate, the nominator is inappropriate, because the degree of underreporting is unknown. Media attention and increasing awareness among clinicians stimulates reporting, also known as notoriety bias.[19] Although underreporting will be reduced because of all this attention for TTS, still it is not known whether all reactions will be reported. Underreporting is obviously variable by country, time, type of drug and type of adverse events. Another problem is that spontaneous reports may lack clinical information and are not always conclusive on the event.

Nevertheless, reporting rates are useful. The ratio of the number of reports of TTS divided by the number of vaccines administered gives an impression of the rarity of this adverse reaction.

6 | CONCLUSION

Disproportionality analysis can be useful in signal identification, and comparing reported cases with expected cases based on background incidence can be useful to support signal detection. However, they cannot be used without an in-depth analysis of the underlying clinical data and pharmacological mechanism. This in-depth analysis has been performed, and is ongoing, for the signal of vaccine-induced immune thrombotic thrombocytopenia (VITT) in relation to the AstraZeneca and Janssen Covid-19 vaccines.[4,5]

Although not frequency or incidence rates, reporting rates can provide an impression of the occurrence of the event. But the unknown underreporting should also be part of this context. To quantify the incidence rates, follow-up epidemiological studies are needed.

COMPETING INTERESTS

The authors have no competing interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed.

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REFERENCES

1. Baden LR, el Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
3. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet*. 2021;397(10277):881-891.
4. Lester J, Neyarapally GA, Lipowski E, Graham CF, Hall M, Dal Pan G. Evaluation of FDA safety-related drug label changes in 2010. *Pharmacoepidemiol Drug Saf*. 2013;22(3):302-305.
5. Pacurariu AC, Coloma PM, van Haren A, Genov G, Sturkenboom MCJM, Straus SMJM. A description of signals during the first 18 months of the EMA pharmacovigilance risk assessment committee. *Drug Saf*. 2014;37(12):1059-1066.

6. Raine J. Risk management: a European regulatory view. In: Mann RM, Andrews EB, eds. *Pharmacovigilance*. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2007:553-558.
7. European Medicines Agency. AstraZeneca's COVID-19 vaccine: benefits and risks in context. 2021. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context. Updated April 23, 2021. Accessed June 6, 2021.
8. European Medicines Agency. Vaxzevria: further advice on blood clots and low blood platelets. 2021. https://www.ema.europa.eu/en/news/vaxzevria-further-advice-blood-clots-low-blood-platelets. Updated May 21, 2021. Accessed June 6, 2021.
9. European Medicines Agency. COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 2021. https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood. Updated April 20, 2021. Accessed June 6, 2021.
10. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf*. 2002;11(1):3-10.
11. European Medicines Agency. Screening for adverse reactions in EudraVigilance. 2016. https://www.ema.europa.eu/en/documents/other/screening-adverse-reactions-eudravigilance_en.pdf. Updated December 19, 2016. Accessed June 16, 2021.
12. Haarman MG, van Hunsel F, de Vries TW. Adverse drug reactions of montelukast in children and adults. *Pharmacol Res Perspect*. 2017;5(5):e00341.
13. Hilgersom W, van Hunsel F, van Puijenbroek E. A systematic step-by-step approach to vaccine signal detection. *Drug Saf*. 2018;41:1103-1273.
14. Scholl J, van Hunsel F, Hilgersom W, van Puijenbroek E. Vaxbatch: a stratified disproportionality analysis tool for batch-related AEFI monitoring in vaccines. *Pharmacoepidemiol Drug Saf*. 2020;29(S3):650-684.
15. Chandler RE, Juhlin K, Fransson J, Caster O, Edwards IR, Norén GN. Current safety concerns with human papillomavirus vaccine: a cluster analysis of reports in VigiBase®. *Drug Saf*. 2017;40(1):81-90.
16. Scholl JHG, van Puijenbroek EP. The value of time-to-onset in statistical signal detection of adverse drug reactions: a comparison with disproportionality analysis in spontaneous reports from the Netherlands. *Pharmacoepidemiol Drug Saf*. 2016;25(12):1361-1367.
17. Pinheiro LC, Candore G, Zaccaria C, Slattery J, Arlett P. An algorithm to detect unexpected increases in frequency of reports of adverse events in EudraVigilance. *Pharmacoepidemiol Drug Saf*. 2018;27(1):38-45.
18. Dutch Pharmacovigilance Centre Lareb. Overview of thrombo-embolic events with COVID-19 vaccines. 2021. https://www.lareb.nl/media/yhbp4bxl/signal_oe_thromboembolic_events_j07bx_20210426_finalc.pdf. Published April 26, 2021. Accessed August 17, 2021.
19. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. *Drug-Safety*. 2007;30(10):891-898.

How to cite this article: Kant A, van Hunsel F, van Puijenbroek E. Numbers of spontaneous reports: How to use and interpret? *Br J Clin Pharmacol*. 2022;88(3):1365-1368. doi: 10.1111/bcp.15024