Journal of Statistics: Advances in Theory and Applications
Volume 28, Number 1, 2023, Pages 1-10
Available at http://scientificadvances.co.in
DOI: http://dx.doi.org/10.18642/jsata_7100122279

CRITIC ASSESSMENT ON OBSERVED VS EXPECTED VACCINE-RELATED MORTALITY SHOWN IN THE 10th AIFA REPORT ON COVID-19 VACCINE SURVEILLANCE IN ITALY

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2020 Mathematics Subject Classification: 62P10.
Keywords and phrases: surveillance, vaccines, Covid-19, statistics, health services.
Received April 17, 2023

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Abstract

Since the beginning of the vaccination campaign against SARS-CoV-2, reports of postvaccination adverse events (ADRs) have raised concerns in the population, fueling doubts about vaccine safety and, consequently, producing vaccine hesitation.

The Italian national system of surveillance for drugs and vaccines is regulated by the Italian Medicines Agency (AIFA) both for the control functions at the national level and for participation in EU activities through the National Pharmacovigilance Network (RNF).

AIFA represents the national public entity responsible for guaranteeing the efficacy, safety, and appropriateness of medicines for human use in Italy, as well as for regulating their diffusion over the national territory. Since February 2021, AIFA regularly published reports on COVID-19 vaccinations in Italy. In particular, in the 5th and 10th reports, released on June 10th, 2021, and February 9th, 2022, respectively, AIFA carried out a comparative analysis between observed and expected deaths following vaccination, the results of which reassured about vaccination safety [1-2]. Unfortunately, the analysis was affected by biases which the scientific community did not notice or did not point out.

Despite the release of two public notes stating the problem highlighted by the authors of this paper [3-4] and a direct communication to the Italian Ministry of Health, AIFA never took note of its mistakes and did not make any amendments.

In this paper, we briefly focus on the methods AIFA used to perform this comparison and on the data of the 5th and 10th Reports on the Surveillance of COVID-19 vaccines. We also describe these errors discussing their implications.

1. Observed/Expected Comparison Analysis in the 10th AIFA Report on the Surveillance of COVID-19 Vaccines

The analysis carried out by AIFA aimed at calculating a Standard Mortality Ratio (SMR), as the ratio between the observed number of deaths within the first and second week after vaccine-administration (first, second or third dose) and the expected number of deaths that we would have observed in the same population during the same time window, assuming that the mortality rate was the one estimated before the COVID-19 emergency, in 2019. As pointed out by AIFA itself (2021a) [1], this analysis is only indicative of the statistical "strength" of a correlation between an event (death) and the administration of the vaccine "and does not provide direct information on the causal link" (p.24). However, the idea is that an SMR greater than 1, i.e., an excess of the observed post-vaccination deaths compared to the expected ones, could be indicative of a vaccine-related mortality. On the contrary, an SMR around 1 should reassure about the safety of vaccination. By the way it should be noticed that SMR cannot be lower than 1 as the vaccine is not expected to protect from all causes of mortality, except for random oscillations or if the individuals who receive the vaccine are healthier than the general population.

Unfortunately, the procedure used by AIFA to calculate the SMR is incorrect. The problems concern both the numerator and the denominator of the ratio.

2. The Problem Concerning the Determination of the Observed Deaths

For the purpose of the analysis in question, AIFA considers as 'observed deaths' all reports received until December 26th, 2021, in the 14 days following the administration of anti-COVID-19 vaccines, arising from the National Pharmacovigilance Network (RNF). As AIFA explains in its reports, these databases contain a collection of spontaneous reports of events temporally related to the administration of a vaccine, in which a reporter (health professional or not) thinks that there may be a suspicion of a relationship to be investigated between vaccination and adverse event. Therefore, even excluding problems of underreporting of the adverse events, the number of deaths collected in these databases is for its nature lower than the actual total number of deaths occurred in the vaccinated population within two weeks from the vaccine administration, that, conversely, represents the appropriate number to be used for the SMR calculation. The underestimation is even greater as the RNF databases are affected by a certain degree of underreporting of deaths [5-12]. In any case, such inhomogeneity between numerator and denominator of the SMR artificially unbalances the index towards the denominator and the unbalance is made bigger by the fact that the expected number of deaths appears to be overestimated by AIFA, as we show in the next section.

3. Doubts About the Calculation of the Expected Deaths

It is not clear how AIFA estimated the expected number of deaths, since the Agency did not provide any description of the procedure and did not make the data used for calculation available, in particular the distribution by age and gender of the vaccinated population and the age and gender-specific mortality rates used for standardization (assuming that AIFA accounted for age and gender in calculating the SMR). However, we suspect that some errors occurred because, when we report

the total expected number of deaths per week calculated by AIFA (18,280)[1] on an annual scale, the value we obtain (953,171) is by far higher than the total number of deaths observed in Italy in 2019 in the population over 5 years of age (643,134) and also higher than that observed in the Italian population by all ages (644,515).

In order to better check the reproducibility of the denominator of the SMR estimated by AIFA, we independently calculated the expected number of deaths, relying on the following data: (i) the person-year at risk, obtained as the product of the individual time at risk of one week (7 person-days = 7/365 person-year) by the number of vaccinated people in the three broad age classes reported by AIFA in the above mentioned report[2], (ii) the mortality rates calculated for the same age classes as the ratio between the number of deaths from all causes that occurred in 2019 and the corresponding population size (source: Italian National Institute of Statistics - ISTAT). We report these data in Table 1, whereas in Table 2 we report our estimates of the expected number of deaths after the first, the second and the third dose of vaccine and compare them with the corresponding values estimated by AIFA. The total number of expected deaths estimated by us is always lower than the one calculated by AIFA. One might think that this discrepancy may depend on the fact that, conditioned to age and gender, vaccinated people were much frailer than the general population. However, the vaccination campaign has been so extensive in Italy that this hypothesis seems to be quite unsound. Moreover, since the data considered in the AIFA report refer approximately to the whole year 2021, also a seasonality effect should be excluded.

[1]Such number is reported in Table 4 of the quoted AIFA Report (AIFA, 2022).

[2]It is possible that the age classes used by AIFA to calculate the expected deaths were narrower than these ones.

Table 1. Mortality for all causes in Italy and weekly average by age group (2019)

Age class	Total deaths	Weekly average	Population at January 1st 2019[a]
5 – 29	2,761	53	14,544,717
30 – 69	98,368	1,887	32.708.698
70 +	542,005	10,395	10.224.506
Total	643,134	12,335	57.477.921

[a]Personal elaboration based on data from ISTAT.

Table 2. Estimated number of expected deaths per week based on deaths occurred in 2019 by age and number of doses received

Age class	1 dose		2 doses		3 doses	
	Our estimates[a]	AIFA estimates[b]	Our estimates[a]	AIFA estimates[b]	Our estimates[a]	AIFA estimates[b]
5 - 29	33	91	29	80	3	9
30 - 69	1,635	3,424	1,500	3,153	514	1,358
70 +	10,014	14,764	9,601	14,199	6,349	9,875
Total	11,868	18,280	11,306	17,432	6,974	11,241

[a]Personal elaboration based on data from ISTAT.

[b]AIFA (2022) [4].

4. Discussion: AIFA Role and Responsibilities

The underestimation of the numerator and the plausible overestimation of the denominator of the SMR clearly determine a dramatic underestimation of the SMR itself in the two mentioned analyses contained in the 5th and 10th AIFA reports on COVID-19 vaccine surveillance.

According to the Italian law (Art. 14 of the Decree of the Ministry of Health of April 15, 2015), AIFA has the duty to "*subject the pharmacovigilance system to regular checks*", and to "*adopt adequate measures to obtain accurate and verifiable data for the scientific evaluation of reports of suspected adverse reactions"*. This last point emphasizes the centrality of the "scientific evaluation", as well as the methodological rigor with which AIFA should conduct such evaluations.

The analysis discussed in this article, on the other hand, reveals a substantial deficiency in methodological rigor on the part of the Agency in evaluating the possible ADRs of the vaccines. This deficiency emerges even more clearly from the comparison with other countries [13], in which greater clarity and transparency are provided in the management and display of data.

On the other hand, the observed/expected analysis discussed in this article seems to reveal a substantial deficiency in methodological rigor on the part of the Italian Agency in evaluating the possible ADRs of the vaccines.

This emerges even more clearly from the comparison with other countries, in which a greater clarity and transparency in data management/exposure are provided. As an example, in the first US Report published by the Centre for Disease Control (CDC), 113 deaths are reported by the VAERS (a monitoring system comparable to the Italian RNF) out of 13,794,904 doses administered, less than expected according to statistical estimates. In that case, the Control Authority has highlighted some possible limitations due to reporting biases. As a consequence, the number of deaths may have been underestimated [14].

A similar issue is also addressed in another document by the Advisory Committee on Immunization Practices (ACIP) in which, summarizing the statistical discrepancies highlighted, the CDC reports that observed death following vaccine administration were lower than expected on a statistic basis [15]. AIFA is undoubtedly aware of the above reports, since the First Month of COVID-19 Vaccine Safety Monitoring is cited by AIFA on page 17 of the report relating to the period 27/12/2020 - 26/02/2021 [16].

There is no doubt that the pharmacovigilance is hampered by the reporting systems used of adverse events (in Italy, the RNF), characterized by excessive capillarity and the impossibility of verifying the work of operators encharged to report ADRs. However, this cannot exempt AIFA from the need of conducting a scientific rigorous evaluation of its data which, if partial, should be clearly described as such and, when they are not sufficient to conduct a complete assessment, this should lead AIFA not to draw any conclusions and not to perform inappropriate and misleading analyses.

AIFA has the duty to make up for the shortcomings of the RNF system, integrating the data collected by the latter with those extracted from any available database. If AIFA is unable to perform this linkage operation, it would be advisable for it to declare it and explain its reasons.

A satisfactory estimate of the SMR could be only obtained with active pharmacovigilance or, in any case, if datasets containing information on the mortality of the vaccinated individuals were accessible.

5. Conclusions

In our opinion, it is a serious matter that a public agency, which is entrusted with an important and delicate task of information, publishes a statistical analysis flawed by evident biases. Moreover, throughout these months AIFA does not seem to have noticed these mistakes and, consequently, did not correct them.

It is also surprising that, in the Italian scientific community, as far as we know, no one else has pointed out these serious errors or has felt the need to discuss them openly. Perhaps this happened because the AIFA reports on COVID-19 vaccines surveillance are not read carefully enough or because of an overconfidence in the agency's work.

The role of health regulatory agencies such as AIFA represents an important element in protecting the community health. We hope that this paper will stimulate AIFA to always operate in a scientifically correct and transparent way so as to avoid similar problems in the future.

References

[1] AIFA, Rapporto AIFA sulla Sorveglianza dei vaccini COVID-19, no. 5, 27/12/2020 - 26/05/2021, (2021a).

https://www.aifa.gov.it/documents/20142/1315190/Rapporto_sorveglianza_vaccini_COVID-19_5.pdf

[2] AIFA, Rapporto Annuale Sulla Sicurezza dei Vaccini Anti-COVID-19, 27/12/2020 - 26/12/2021, (2022).

https://www.aifa.gov.it/documents/20142/1315190/Rapporto_annuale_su_sicurezza_vaccini%20anti-COVID-19.pdf

[3] M. Baccini, B. Cheli, R. Foschi, A. Iodice, L. Melacarne, B. Pinto and E. Serravalle, Considerazioni critiche sul confronto tra decessi osservati e attesi dopo la vaccinazione nel 10° Rapporto AIFA sulla Sorveglianza dei vaccine COVID-19, Discussion Papers del Dipartimento di Economia e Management, Universita di Pisa, 286 (2022).

http://www.ec.unipi.it/ricerca/discussion-papers

[4] B. Cheli, R. Foschi, A. Iodice and E. Serravalle, Considerazioni critiche sul confronto tra decessi attesi e osservati dopo la vaccinazione contenuto nel 5° Rapporto AIFA sulla Sorveglianza dei vaccini COVID-19, Discussion Paper Dipartimento di Economia e Management, Universita di Pisa, 285 (2022).

http://www.ec.unipi.it/ricerca/discussion-papers

[5] L. Hazell and S. A. Shakir, Under-reporting of adverse drug reactions, Drug Safety 29(5) (2006), 385-396.

DOI: https://doi.org/10.2165/00002018-200629050-00003

[6] F. R. Varallo, S. de Oliveira Paim Guimarães, S. Abjaude and P. de Carvalho Mastroianni, Causes for the underreporting of adverse drug events by health professionals: A systematic review, Revista da Escola de Enfermagem da USP 48(4) (2014), 739-747.

DOI: https://doi.org/10.1590/s0080-623420140000400023

[7] O. Mahaux, V. Bauchau and L. Van Holle, Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines, Pharmacoepidemiology and Drug Safety 25(2) (2016), 215-222.

DOI: https://doi.org/10.1002/pds.3918

[8] M. Gahr, J. Eller, B. J. Connemann and C. Schönfeldt-Lecuona, Underreporting of adverse drug reactions: Results from a survey among physicians, European Psychiatry 41(S1) (2017), S369.

DOI: https://doi.org/10.1016/j.eurpsy.2017.02.377

[9] A. Patrignani, G. Palmieri, N. Ciampani, V. Moretti, A. Mariani and L. Racca, Under-reporting of adverse drug reactions, a problem that also involves medicines subject to additional monitoring, Preliminary data from a single-center experience on novel oral anticoagulants, Journal of Italian Cardiology 19(1) (2018), 54-61.

DOI: https://doi.org/10.1714/2852.28779

[10] A. Dutta, A. Banerjee, S. Basu and S. Chaudhry, Analysis of under-reporting of Adverse Drug Reaction: Scenario in India and neighbouring countries, IP International Journal of Comprehensive and Advanced Pharmacology 5(3) (2020), 118-124.

DOI: https://doi.org/10.18231/j.ijcaap.2020.025

[11] J. Inch, M. C. Watson, S. Anakwe-Umeh, Patient versus Healthcare Professional Spontaneous Adverse Drug Reaction Reporting, Drug Safety 35(10) (2012), 807-818.

DOI: https://doi.org/10.1007/BF03261977

[12] A. Sandberg, V. Salminen, S. Heinonen and M. Sivén, Under-Reporting of Adverse Drug Reactions in Finland and Healthcare Professionals' Perspectives on How to Improve Reporting, Healthcare 10(6) (2022); Article 1015.

DOI: https://doi.org/10.3390/healthcare10061015

[13] T. T. Shimabukuro, M. Nguyen, D. Martin and F. DeStefano, Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine 33(36) (2015), 4398-4405.

DOI: https://doi.org/10.1016/j.vaccine.2015.07.035

[14] Julianne Gee, Paige Marquez, John Su, Geoffrey M. Calvert, Ruiling Liu, Tanya Myers, Narayan Nair, Stacey Martin, Thomas Clark, Lauri Markowitz, Nicole Lindsey, Bicheng Zhang, Charles Licata, Amelia Jazwa, Mark Sotir and Tom Shimabukuro, US Department of Health and Human Disease Control and Prevention (2021) "First Month of COVID-19 Vaccine Safety Monitoring – United States, December 14, 2020 – Jan 13, 2021". MMWR Morbidity and Mortality Weekly Reports, Feb 26 70(8) (2021), 283-288.

DOI: https://doi.org/10.15585/mmwr.mm7008e3

[15] T. Shimabukuro, COVID-19 Vaccine safety updates - Advisory Committee on Immunization Practices (ACIP), June 23, 2021, Tom Shimabukuro, MD, MPH, MBA, Vaccine Safety Team, CDC COVID-19 Vaccine Task Force, 2021.

https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html

[16] AIFA, Rapporto AIFA sulla Sorveglianza dei vaccini COVID-19, no. 2, 27/12/2020 - 26/02/2021 (2021b).

https://www.aifa.gov.it/en/-/secondo-rapporto-aifa-sullasorveglianza-dei-vaccini-covid-19

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