Drug Safety (2023) 46:813–815
https://doi.org/10.1007/s40264-023-01311-6

LETTER TO THE EDITOR

Authors' Reply to Juergen O Kirchner's Comment on "Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project"

Corinne Willame[1] · Daniel Weibel[1] · Miriam C. J. M. Sturkenboom[1]

Accepted: 17 April 2023 / Published online: 27 May 2023
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2023

Dear Editor,

We appreciate the opportunity to reply to the letter to the editor from Dr. Kirchner pertaining to our publication [1] in which we have computed background incidence rates of autoimmune diseases in European healthcare data sources as part of the IMI-ADVANCE project [2].

The author of the letter to the editor criticized the methodology that was applied in our background incidence rates study and highlighted possible misidentification of a vaccine safety signal. Following this, it is of importance that we reiterate the context in which this study has been conducted and we provide additional clarity on data interpretation and contextualization for vaccine safety signal assessment.

Our background incidence rate study demonstrated that the ADVANCE system can identify specific autoimmune events, generate rapid estimation of rates, and detect age-specific patterns. In our manuscript, we emphasized the heterogeneity of the various data sources that were used and attempted to demonstrate that the type of care that is captured in the data sources (general practitioners versus record-linkage data sources) should be cautiously considered when data are used, for instance, in observed-to-expected analysis. The heterogeneity across European healthcare data sources has been further assessed in ACCESS [3], a project funded by the European Medicines Agency leveraging expertise in the European Pharmacoepidemiology and Pharmacovigilance research network, and the VAC4EU, in which we highlighted the importance of the nature of the events and the setting in which it is diagnosed. We demonstrated that data sources containing exclusively general practitioner data may not be suitable to identify events requiring immediate care at hospital level.

Regarding background incidence rate of acute disseminated encephalomyelitis (ADEM), the author of the letter pointed out that rates from our ADVANCE study are largely above rates from other published sources. Although we acknowledge the numerical differences, we would like to stress the importance of the clinical definitions that were used across the listed studies in Table 1 of the letter to the editor. Study design, the use of different medical codes, narrow or broad clinical definitions, and the implementation of a case validation process through medical chart review impact the generated evidence. Among the nine studies listed in Table 1 below, seven applied a case ascertainment process, which makes more robust the validation of the outcome under assessment. Regarding the two studies from Willame et al. (2021 [4] and 2023 [3]), the major difference resides in the applied clinical definitions. The Willame et al. 2021 [4] paper used a broad clinical definition (ICD-10: G35-G37.9; G04; G04.3; G04.9; G36.9) compared with the Willame et al. 2023 [3] paper (ICD-10 narrowed to: G04.00; G04.01; G04.02), which led to higher incidence rates in the ADVANCE background rate study.

The author of the letter mentioned that, in the minutes of the PRAC meeting held on 5–8 July 2021 concerning the Pfizer/BioNTech COVID-19 mRNA-vaccine BNT 162b2 [12], the PRAC recommended to use background incidence rates from the ACCESS study [3] to evaluate a potential safety signal for ADEM, but the author of letter stated that ACCESS data were not available. This statement is incorrect as the ACCESS data including broad and narrow clinical definitions were made immediately available to the scientific community in February 2021 on the ENCePP website (https://www.encepp.eu/phact_links.

This reply refers to the comment available online at https://doi.org/10.1007/s40264-023-01310-7.

✉ Corinne Willame
c.willame@umcutrecht.nl

[1] Department Datascience and Biostatistics, University Medical Center Utrecht, Heidelberglaan 100, Utrecht, The Netherlands

Table 1 Heterogeneity in clinical definitions for ADEM across nine studies

References	Computable algorithm search (yes/no) (coding system)	Case ascertainment process (yes/no)
Willame et al. [4]	Yes (ICD-9; ICD-10; ICPC; READ)	No
Willame et al. [3]	Yes (ICD-9; ICD-10; CIM-10; ICD-10-GM; SCTSPA; READ)	No
Dubey et al. [5]	Yes (not available)	Yes
Xiong et al. [6]	NA	Yes
Pavone et al. [7]	NA	Yes
Torisu et al. [8]	NA	Yes
Banwell et al. [9]	NA	Yes
Pohl et al. [10]	NA	Yes
Leake et al. [11]	Yes (ICD-9)	Yes

NA (not applicable): prospective or hospital-based study including cases that were medically reviewed and confirmed with access to laboratory and/or imaging data

shtml), far before the PRAC request. Updated background incidence rates were also made publicly available on the VAC4EU dashboard (https://vac4eu.org) and Zenodo platform (https://www.zenodo.org/record/5255870#.ZA7sTuyZP0o).

The ADVANCE background rate study paved the way for further improvements to generate background incidence rates through a benefit–risk system at the European level, which has been made successful with ACCESS. Variations in background incidence rates are often observed across different sources owing to differences in data sources, years of the study conduct, study populations, and clinical case definitions. In vaccine safety signal assessment, it is our recommendation to consider several sources of data for background incidence rates depending on availability of age-stratified data and the validity of study outcomes.

Declarations

Funding Not applicable.

Conflict of interest Corinne Willame is conducting a Ph.D. at the University Medical Center Utrecht. She works full time for Janssen Pharmaceutica and allocated working time to finalize the submitted work; this should be considered an in-kind contribution. Miriam Sturkenboom and Daniel Weibel are salaried employees by University Medical Center Utrecht, which receives institutional research funding from pharmaceutical companies and regulatory agencies, administered by University Medical Center Utrecht. All these studies follow the ENCePP code of conduct. Miriam Sturkenboom is a consultant to the Task Force for Global Health for the Safety Platform for Emergency vACcines (SPEAC) project.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

Availability of data and material Not applicable.

Authors' contribution All authors contributed equally to the work submitted. All authors read and approved the final version.

References

1. Kirchner J. Comment on "Rates of autoimmune diseases in European healthcare databases: a contribution of the ADVANCE project". Drug Saf. 2023. https://doi.org/10.1007/s40264-023-01310-7
2. Sturkenboom M, Bahri P, Chiucchiuini A, Grove KT, Hahné S, Khromava A, Kokki M, Kramarz P, Kurz X, Larson HJ, de Lusignan S, Mahy P, Torcel-Pagnon L, Titievsky L, Bauchau V, ADVANCE consortium. Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines. Vaccine. 2020;38(Suppl 2):B1–7. https://doi.org/10.1016/j.vaccine.2019.07.081. (**Epub 2019 Oct 31. PMID: 31677952**).
3. Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, Paoletti O, Wang L, Ehrenstein V, Kahlert J, Haug U, Schink T, Diez-Domingo J, Mira-Iglesias A, Carreras JJ, Vergara-Hernández C, Giaquinto C, Barbieri E, Stona L, Huerta C, Martín-Pérez M, García-Poza P, de Burgos A, Martínez-González M, Bryant V, Villalobos F, Pallejà-Millán M, Aragón M, Carreras JJ, Souverein P, Thurin NH, Weibel D, Klungel OH, Sturkenboom M. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases—an ACCESS cohort study. Vaccine. 2023;41(1):251–62. https://doi.org/10.1016/j.vaccine.2022.11.031. (**Epub 2022 Nov22. PMID: 36446653; PMCID: PMC9678835**).
4. Willame C, Dodd C, van der Aa L, Picelli G, Emborg HD, Kahlert J, Gini R, Huerta C, Martín-Merino E, McGee C, de Lusignan S, Roberto G, Villa M, Weibel D, Titievsky L, Sturkenboom MCJM. Incidence rates of autoimmune diseases in European Healthcare Databases: a contribution of the ADVANCE Project. Drug Saf. 2021;44(3):383–95. https://doi.org/10.1007/s40264-020-01031-1. (**Epub 2021 Jan 19. PMID: 33462778; PMCID:PMC7892524**).
5. Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018;83(1):166–77. https://doi.org/10.1002/ana.25131.
6. Xiong CH, Yan Y, Liao Z, et al. Epidemiological characteristics of acute disseminated encephalomyelitis in Nanchang, China : a retrospective study. BMC Public Health. 2014;14:111.
7. Pavone P, Pettoello-Mantovano M, Pira AL, Giardino L, Pulvirent IA, Giugno R, et al. Acute disseminated encephalomyelitis: a long-term prospective study and meta-analysis. Neuropediatrics. 2010;41(06):246–55.
8. Torisu H, Kira R, Ishizaki Y, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev. 2010;32:454–62. https://doi.org/10.1016/j.braindev.2009.10.006.
9. Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology.

2009;72:232–9. https://doi.org/10.1212/01.wnI.0000339482.84392.bd.
10. Pohl D, Hennemuth L, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr. 2007;166:405–12.
11. Leake JAD, Albani S, Kao AS, et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J. 2004;23:756–64. https://doi.org/10.1097/01.inf.0000133048.75452.dd.
12. Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (PRAC), Minutes of the meeting on 05-08 July 2021. https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-5-8-july-2021_en.pdf. Accessed 23 May 2013.