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An extension of the Benefit Risk Assessment of VaccinEs toolkit to evaluate Comirnaty and Spikevax vaccination in the European Union

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Abstract

Amid the global COVID-19 pandemic, vaccines were conditionally authorized for human use to protect against severe infection. The Benefit Risk Assessment of VaccinEs (BRAVE) toolkit, a user-friendly R Shiny application, was developed retrospectively together with the European Medicine Agency (EMA) with the aim of fulfilling the need for flexible tools to assess vaccine benefits and risks during and outside a pandemic situation. This study employed BRAVE to evaluate the impact of COVID-19 mRNA vaccines across 30 European Union (EU)/EEA countries by quantifying the number of prevented clinical events [i.e. confirmed infections, hospitalizations, intensive care unit (ICU) admissions, and deaths], using a probabilistic model informed by real-time incidence data and vaccine effectiveness estimates. The analysis assumes fixed population dynamics and behaviour. Additionally, BRAVE assesses risks associated with mRNA-based vaccines (myocarditis or pericarditis) by comparing observed incidence rates in vaccinated individuals with background incidence rates. mRNA vaccines were estimated to directly prevent 11.150 million [95% confidence interval (CI): 10.876–11.345] confirmed COVID-19 infections, 0.739 million (95% CI: 0.727–0.744) COVID-19 hospitalizations, 0.107 million (95% CI: 0.104–0.109) ICU admissions, and 0.187 million (95% CI: 0.182–0.189) COVID-19-related deaths in the EU/EEA between 13 December 2020 and 31 December 2021. Despite increased vaccination-associated myocarditis or pericarditis observed in younger men, the benefits of vaccination still outweigh these risks. Our study supports the benefit/risk profile of COVID-19 vaccines and emphasizes the utility of employing a flexible toolkit to assess risks and benefits of vaccination. This user-friendly and adaptable toolkit can serve as a blueprint for similar tools, enhancing preparedness for future public health crises.

Introduction

The SARS-CoV-2/COVID-19 pandemic originating in Wuhan, China, started in late 2019 and quickly escalated into a global health crisis. Nations worldwide responded with stringent mitigation measures to limit virus transmission, alleviate the healthcare burden, and reduce COVID-19-related fatalities. Simultaneously, substantial efforts were dedicated to prioritizing the development and widespread administration of COVID-19 vaccines as soon as they were approved and became readily available. Soon after their development (in late 2020 to early 2021), the European Medicines Agency (EMA) granted conditional marketing authorization for five vaccines to prevent severe COVID-19 disease and to lower transmission in the European Union (EU) [1]. These approved vaccines included the Comirnaty (previously known as Pfizer-BioNTech) and Spikevax (Moderna) mRNA vaccines, the Vaxzevria (Oxford-AstraZeneca), and Jcovden (Johnson & Johnson) viral vector vaccines, and the protein-based Nuvaxovid (Novavax) vaccine [2].

Large-scale clinical trials confirmed the effectiveness of these vaccines [3]. However, following their necessary rapid conditional introduction, these vaccines were subject to pharmacovigilance monitoring to identify potential rare but serious side effects [4]. In early 2021, a safety signal on the risk of Thrombotic Thrombocytopenia Syndrome (TTS), associated with the viral vector vaccine Vaxzevria was identified, followed by signals of risk of myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining surrounding the heart) associated with the mRNA vaccines (Comirnaty and Spikevax vaccines). For both signals, a careful assessment of the available evidence at the time led to warnings and an update of the product information of these vaccines [4, 5]. In response to concerns about the potential risks associated with the COVID-19 vaccines [6], the EMA highlighted

opportunities to improve several aspects of vaccine benefit-risk assessment, including data availability and methodologies to enhance contextualization. Accordingly, the Benefit Risk Assessment of VaccinEs (BRAVE) toolkit was developed to enable flexible and comprehensive assessments, thereby enhancing the understanding of the risks and benefits associated with COVID-19 vaccination in the EU. The tool utilizes real-time, virus-related clinical data (confirmed infections, hospitalizations, Intensive Care Unit (ICU) admissions, and deaths) alongside estimates of vaccine effectiveness and vaccine risk incidence rates to contrast estimated benefits and risks of vaccination. The results from the analysis using this tool confirmed the overall positive benefit-risk balance of Vaxzevria regarding the risk of TTS compared to its benefits, which include confirmed reductions in infections, hospitalizations, ICU admissions, and deaths [5].

Subsequently, suspected signals of myocarditis or pericarditis risks emerged with the extensive deployment of the mRNA vaccines for COVID-19, prompting further updates and warnings [7]. These rare conditions have triggered scientific and societal debates regarding the safety of mRNA vaccines, particularly given that this marks the first large-scale utilization of the mRNA vaccine platform. Therefore, there is a pressing need for enhanced safety monitoring to address the potential occurrence of these adverse events. Given the increased risk of myocarditis and pericarditis associated with COVID-19, it is essential to compare the incidence rates of these conditions in both vaccinated individuals and those infected with COVID-19 [6]. However, unlike vaccine-associated TTS, for which no background incidence rate in an unvaccinated population was available, there is data on the background incidence of myocarditis/pericarditis. The risk assessment thus involves comparing the observed incidence rates against a reliable estimate of the expected incidence rate. This comprehensive approach ensures a balanced understanding of the benefits and risks associated with mRNA vaccination, ultimately guiding public health decisions and policy-making.

In this study, we demonstrate the use of the BRAVE toolkit for benefit–risk contextualization of the mRNA COVID-19 vaccines, Comirnaty and Spikevax. We enhance the quantification and visualization of vaccine benefits to facilitate comparison with associated risks, and illustrate how easily vaccine effectiveness parameters can be updated from those used by Dorta *et al.* [5]. We conducted a comprehensive assessment of age-specific profiles of vaccine benefits (confirmed infections, hospitalizations, ICU admissions, and deaths) and risks of myocarditis or pericarditis within 14 days after vaccine administration for these mRNA COVID-19 vaccines—Comirnaty, authorized across the EU on 21 December 2020, and Spikevax, authorized on 6 January 2021. This assessment was carried out across various age groups between 13 December 2020, and 31 December 2021. Additionally, we extended the BRAVE toolkit to include uncertainty assessments of vaccine benefits, accounting for variation in vaccine effectiveness. This extension further strengthens the toolkit's potential to support public health decision-making during future emergencies.

Methods

The BRAVE toolkit quantifies the benefits and risks of vaccination and requires information on COVID-19 clinical events (confirmed infections, hospitalizations, ICU admissions, or deaths), SARS-CoV-2 variants of concern (VoCs) and vaccine effectiveness estimates for the benefits and information on observed risk events post-vaccination and background risk incidence rates for the risk quantification. The clinical and risk events can be categorized by demographics (i.e. age, sex, geographic location). For the benefit-risk assessment of the mRNA vaccines, the risks are categorized by age and sex, whereas benefits are categorized by age only, as no sex-specific estimates of vaccine effectiveness are available. A brief explanation of the minimal required data for the benefit-risk assessment with the toolkit is summarized in Supplementary Table S1.

An extension of the probabilistic model quantifying benefit

The implementation of the probabilistic model in the BRAVE toolkit is based on the following logic. Let $n(a,t)$ denote the frequency of a specific clinical event B (i.e. either confirmed SARS-CoV-2 infections, hospitalizations, ICU admissions, or deaths) at time t and for a specific age group a. The calculation of the (counterfactual) frequency of clinical event B without vaccination is as follows:

$$n^{B^*}(a,t) = \frac{n^B(a,t)}{1-\phi^B(a,t)}$$

where $\phi^B(a,t)$ denotes the proportion of individuals in age group a protected through vaccination at time t for clinical event B. In this analysis, we assume no delay between SARS-CoV-2 infection and the occurrence of the clinical event. This simplification, though unrealistic, has a negligible impact on results due to the slow build-up of protection induced by vaccination compared to the maximum delay between infection and, e.g. confirmation of infection [5]. A complete description of the underlying equations and assumptions is provided in the Supplementary Material.

Extending this BRAVE toolkit, we employ Monte Carlo simulations to incorporate uncertainty into the probabilistic model [8], assuming independence of the vaccine benefits across countries. This means that the benefits of a country's vaccination program are not influenced by those observed in other countries. Here, we conducted 1000 independent simulations, sampling vaccine effectiveness parameters from uniform distributions within specified intervals. The results were then aggregated to construct percentile-based 95% CIs for key population quantities, such as the mean number of averted COVID-19-related confirmed infections. Additionally, we computed odds ratios (ORs) for clinical event B, comparing the odds of the event occurring under observed vaccine uptake conditions with those under the counterfactual scenario in which vaccination was not available. In this exercise, we consider the variability arising from the vaccine effectiveness of Spikevax and Comirnaty for each COVID-19 burden per dose and VoCs (Supplementary Table S2). Note that this extension is conducted outside of the publicly available toolkit due to its computational burden. Detailed information on vaccine uptake and age- and time-specific event occurrence data is crucial for determining vaccine benefits. For countries lacking specific information, we applied a multiple imputation approach within the probabilistic model framework, similar to the method used by Dorta *et al.* [5].

Risk quantification with observed-expected (O/E) ratio

The BRAVE Toolkit adopted an observed-to-expected approach to quantify the risk of adverse events following vaccination, as it enables timely signal detection using spontaneous reports and background rates [9]. The risk ratio per age group a and sex s is calculated by comparing the joined observed myocarditis and pericarditis events with the background incidence rates,

$$R_{a,s} = \frac{\mathrm{EV}_{a,s}100\ 000}{\mathrm{IR}_{a,s}N_{a,s}t},$$

where $\mathrm{IR}_{a,s}$ represents the background incidence rates for myocarditis and pericarditis per sex and age, expressed per 100 000 person-years; t denotes the time horizon in years; and $\mathrm{EV}_{a,s}$ refers to the observed myocarditis and pericarditis events associated with mRNA COVID-19 vaccination within a 14-day (0.093 years) post-vaccination time interval, as reported to the EU Drug Regulating

Authorities Pharmacovigilance (EudraVigilance) (Supplementary Table S3). A small subset of these data lacked age and/or sex information, which was remedied by imputation with referencing proportions from fully documented EudraVigilance cases. The vaccination coverage per sex and age ($N_{a,s}$) combined different data sources and required a redistribution of observed coverages to the risk-appropriate age-by-sex categories. As a sensitivity analysis, two types of adjustments were applied, namely redistribution via fixed proportions or redistribution via multiple imputation, with the latter being considered most appropriate.

The background incidence rates for myocarditis and pericarditis jointly were obtained from $m = 3$ databases ($i = 1,2,3$), one from the *Agenzia Regionale di* Sanità *della Toscana* (ARS), covering both primary and secondary care, and two from the *Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria* (BIFAP), covering primary care only [5]. In each of these datasets, three cohorts of background incidence rates were identified in the target age groups: the pre-pandemic years (2017–19), the pandemic period before introduction of vaccination, and the pandemic period thereafter. Given that COVID-19 infection may cause myocarditis or pericarditis, we focus on using the pandemic period before the introduction of vaccination as a comparator. The pooled incidence rate from the three data sources and its variance are estimated by weighting the information from these data sources [10]:

$$\bar{IR} = \frac{\sum_{i=1}^{m} IR_i w_i}{\sum_{i=1}^{m} w_i} \text{ and } \mathrm{Var}(\bar{IR}) = \frac{\sum_{i=1}^{m} x_i^2}{\left(\sum_{i=1}^{m} w_i\right)^2},$$

with $w_i = \frac{x_i}{\sigma_i 2}$ representing the inverse-variance (σ_i^2) weighting, allowing for a manually chosen contribution of the i-th data source to the mean (x_i). The weights should reflect the ability of the data source to estimate the risk incidence rate. Since myocarditis or pericarditis is mainly diagnosed in hospitals and much less in primary care settings, in this study, the ARS data source was given a 10-fold weight compared to each of the primary care BIFAP data sources (both having the same weight). The toolkit thus allows for careful consideration of the fit of purpose and the heterogeneity of the available data sources in estimating risk incidence rates.

Results

Benefit quantification

Between 13 December 2020 and 31 December 2021, a total of 542.352 million Comirnaty and 108.165 million Spikevax vaccines were administered across 30 EU/EEA countries [11]. We estimated the benefits obtained by administering Comirnaty and Spikevax vaccines (Supplementary Table S3). In total, the mRNA vaccines prevented an estimated 11.150 million [95% confidence interval (CI): 10.876–11.345] confirmed COVID-19 infections, 0.739 million (0.727–0.743) hospitalizations, 0.107 million (0.104–0.108) ICU admissions, and 0.187 million (0.182–0.189) COVID-19-related deaths across 30 EU/EEA countries during the study period (Fig. 1). Corresponding odds ratios (OR) comparing observed events to a counterfactual scenario were 0.771 (0.768–0.776) for infections, 0.744 (0.743–0.747) for hospitalizations, 0.755 (0.753–0.760) for ICU admissions, and 0.756 (0.754–0.761) for mortality.

During the study period, the mRNA vaccines led to the greatest reduction in COVID-19-related hospitalizations and deaths in the 80+ age group (respectively 347 (339–349) per 100 000 administered vaccines and 128 (125–130) per 100 000 vaccines), while the 70–79-year-old age group had the greatest number of avoided ICU admissions [41 (40–42) per 100 000 vaccines]. Additionally, there was a substantial average number of prevented COVID-19 confirmed infections in the 20–59 years age range [1757 (1709–1789) per 100 000 vaccines] and the 80+ age group [1374 (1351–1392) per 100 000 vaccines], when combining the benefits of Comirnaty and Spikevax vaccines (Fig. 2). Vaccination was estimated to significantly reduce the number of hospitalizations, ICU admissions, and

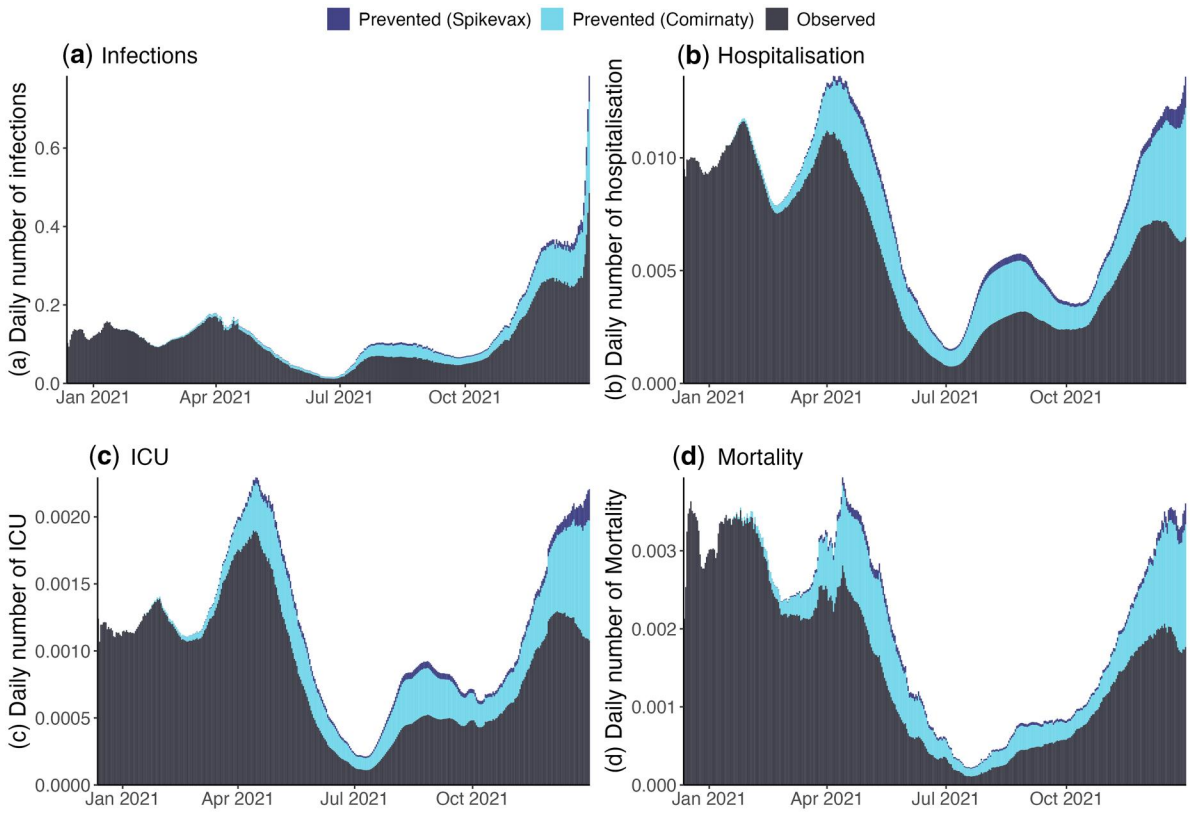

Figure 1. Daily number (in millions) of observed (black) and prevented (light blue: Comirnaty; dark blue: Spikevax) (a) COVID-19 infections, (b) hospitalizations, (c) ICU admissions, and (d) deaths across 30 countries in Europe between 13 December 2020 and 31 December 2021.

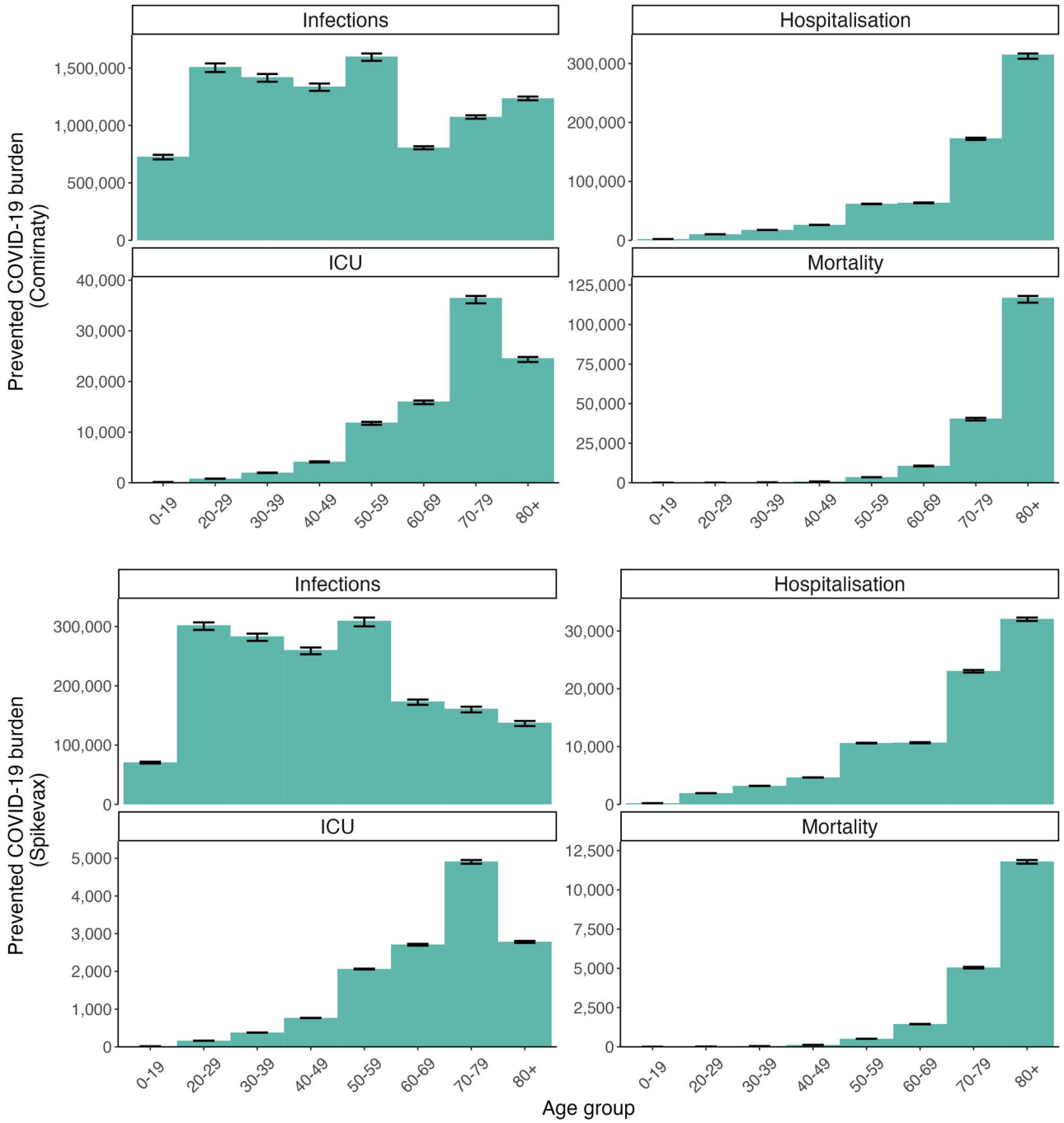

Figure 2. The estimated number (with 95% CIs depicted as error bars in black) of (a) COVID-19 infections, (b) hospitalizations, (c) ICU admissions, and (d) deaths prevented among individuals vaccinated with Comirnaty *(Top)* and Spikevax *(Bottom)* per 100 000 individuals vaccinated in Europe within the respective age categories from 13 December 2020 to 31 December 2021.

deaths caused by COVID-19 for age groups above 40 years, with individuals older than 70 years exhibiting the highest number of prevented hospitalizations and deaths due to vaccination (Supplementary Table S4).

In addition to excess burden estimates, odds ratios (ORs) comparing observed and counterfactual outcomes showed the strongest relative reductions among older age groups (Supplementary Fig. S1). For hospitalizations, the OR was 0.626 (0.625–0.631) in the 80+ age group, and 0.720 (0.720–0.723) in the 70–79 group. ICU admissions showed similar trends [80+: OR 0.620 (0.618–0.627)]. The lowest mortality ORs were found in the 80+ [OR: 0.710 (0.708–0.715)] and 70–79 [OR: 0.774 (0.772–0.779)] age groups. The OR for confirmed infections was lowest in the 80+ group [OR: 0.580 (0.577–0.585)], despite higher absolute numbers in younger adults.

Risk quantification

As of 13 October 2021, a total of 4635 cases of myocarditis or pericarditis potentially related to mRNA vaccination (3644 cases for Comirnaty and 991 cases for Spikevax) were reported to the EudraVigilance. Across most age categories and for both vaccines, there were more reported myocarditis/pericarditis cases among males than females (Supplementary Table S5). Observed-to-Expected (O/E) ratios at 14 days post-vaccination were calculated

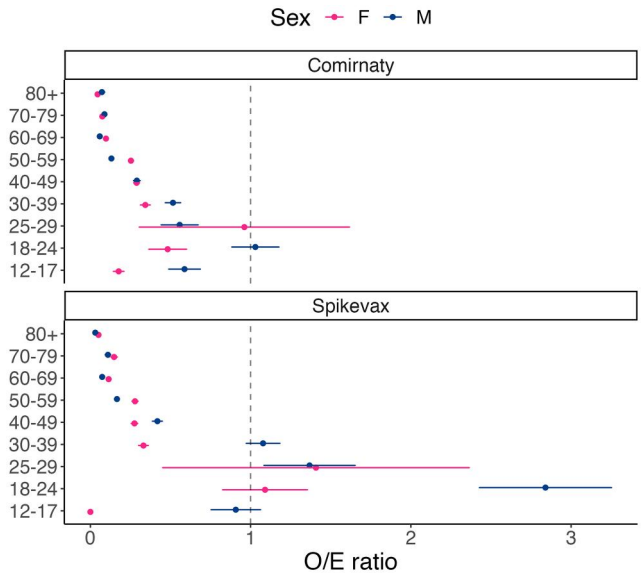

Figure 3. The O/E ratio of myocarditis/pericarditis cases by age group, sex, and vaccine type [i.e. Comirnaty *(Top)*, Spikevax *(Bottom)*], using the pooled background incidence rate during COVID-19 prior to vaccination with weights (1, 0.1, 0.1) and relying on multiple imputation.

using pooled background incidence rates from the COVID-19 period (prior to vaccination), incorporating multiple imputation to address missing data. These O/E ratios were relatively higher in individuals under 40 years of age compared to older individuals, for both sexes and vaccine types (Fig. 3). However, only for Spikevax, the O/E ratio exceeded 1, suggesting that more myocarditis/pericarditis cases were observed than expected in the absence of vaccination. The highest O/E ratio was seen in males aged 18–24 years [O/E ratio: 2.840 (2.428–3.251)]. A moderate elevation was also observed in males aged 25–39 years, with O/E ratios of 1.367 (1.083–1.652) for those aged 25–29 years and 1.077 (0.972–1.180) for those aged 30–39 years. In general, males under 40 years showed a slightly higher risk than females in the same age groups. Notably, a large variability in the O/E ratio was observed among females aged 25–29 years [O/E ratio: 1.407 (0.451–2.363)]. This is likely due to zero background incidence estimates in two of the three data sources used. Applying a fixed proportion redistribution did not alter the results significantly. However, the multiple imputation approach led to reduced variance in older age groups and increased uncertainty in younger ones (Supplementary Fig. S2).

Discussion

We extended the BRAVE toolkit to account for variability in vaccine effectiveness and demonstrated the benefits of COVID-19 mRNA vaccination compared to the risk of myocarditis or pericarditis in 30 EU/EEA countries [5]. We estimated the benefits of vaccination while accounting for varying vaccine effectiveness as a function of time since vaccination, variant emergence, as well as age-specific and temporal differences in disease dynamics. These benefits were assessed relative to vaccination risks, which were stratified by age and sex. While acknowledging that the results for Comirnaty and Spikevax vaccines may vary because of differences in the timing of vaccination roll-out across countries and in the initial target populations, the analysis shows that benefits still far outweigh the potential risks associated with myocarditis and pericarditis within 14 days following vaccination, across all age groups and sexes.

In general, COVID-19 vaccines have shown significant benefits across various age groups [12, 13]. Our findings are in alignment with existing research, which consistently shows that COVID-19 vaccination has a beneficial effect in older age groups [14–16], as reflected in both the high number of averted clinical events (excess estimates) and the substantial reduction in relative odds of adverse outcomes (ORs). These age groups are at higher risk of experiencing severe COVID-19-related clinical events, and vaccination has played a crucial role in mitigating the impact of the virus in these age groups. Furthermore, younger age groups may also benefit from vaccination by reducing the frequency of infections, thereby reducing the risk of upward transmission to more vulnerable individuals, and protecting themselves from potential long-term effects of the disease [17]. Despite the benefits of COVID-19 vaccination, it is imperative to acknowledge and address the potential risks associated therewith. The findings of the current study align with established evidence from other studies and earlier benefit-risk assessments by the EMA, highlighting that COVID-19 mRNA vaccine-induced myocarditis or pericarditis is more common among younger males [18, 19]. The Observed-to-Expected (O/E) ratio for Spikevax consistently exceeded that of Comirnaty, suggesting a potentially higher risk of myocarditis and pericarditis following Spikevax vaccination [20–22]. While background incidence rates of myocardial infarction declined over the observation period, the number of observed cases of myocardial infarction following vaccination remained significantly higher than expected across all age groups. Notably, our comparison involved the background incidence rate during the COVID-19 period before vaccination, which may have influenced the reporting of myocarditis/pericarditis cases, e.g. changes in healthcare-seeking behaviour or diagnostic practices [23].

The toolkit potentially aids users in quantifying the risks and benefits associated with COVID-19 vaccines. By virtue of its flexibility, the toolkit can be readily augmented and complemented with various functionalities, such as the uncertainty assessment included in this study. Acknowledging uncertainty with respect to input parameters provides a more nuanced perspective on benefits and risks estimated from the data at hand. It also enhances understanding by providing a comprehensive overview of vaccine-related risks and benefits, encompassing a robust methodology, both visually and through direct quantification. Secondly, it facilitates decision-making by presenting the results in a clear and accessible format [24]. Furthermore, this toolkit can serve as a foundation for developing practical digital monitoring applications to monitor the benefits and risks of currently available vaccines in real-life scenarios. By providing population-level insights, this interactive toolkit may ultimately support public health planning for prioritizing and optimizing interventions and informing regulatory decision-making, making it a valuable asset for assessing COVID-19 vaccination benefits and risks while promoting effective public health communication.

While we have accounted for the uncertainty arising from vaccine effectiveness, variability from other sources, such as variant circulation, waning immunity, and incidence rates, can also be substantial [25, 26]. However, incorporating additional uncertainty would significantly increase computational burden, and our ability to model these complexities is limited by data availability. Moreover, as comprehensive and comparable background incidence data are not available across all 30 EU/EEA countries, we relied on two large, high-quality sources (i.e. ARS and BIFAP), with greater weight assigned to ARS, which predominantly captures data from secondary care, where diagnoses of myocarditis and pericarditis are more reliably recorded [27]. However, we acknowledge that using data from only two countries may limit the generalizability of the background rates to the entire EU/EEA region, particularly in younger age groups where the incidence of myocarditis and pericarditis shows considerable variability across age, sex, and geographic regions [28]. This concern aligns with findings from a recent study on venous thromboembolism, which observed notable heterogeneity in incidence rates across EU healthcare databases, despite methodological consistency [29]. Factors such as differences in healthcare-seeking behaviour, diagnostic coding practices, availability of diagnostic technologies, and population demographics may lead to heterogeneity in incidence rates across countries [27, 30]. While we

have employed best practices and generated valuable results with the available data, further improvements will depend on more comprehensive and granular data quality. In this regard, initiatives such as DARWIN EU (EUPAS1000000254) [31], which is currently expanding the database of real-world healthcare data by integrating information from multiple EU countries, are expected to enhance the representativeness of background incidence rates for vaccine adverse events across the region. Moving forward, standardized case definitions and harmonized data collection across countries will be key to achieving consistent and comparable incidence assessments. We also note that while the model incorporates waning immunity as a function of time (e.g. loss of humoral protection), it does not account for natural immunity acquired through prior infection, which may lead to underestimation of population-level immunity [32]. This limitation implies that the benefits of vaccination may, in reality, be even greater due to indirect protection effects. Lastly, risk calculations based on spontaneous reports from EudraVigilance may result in an underestimation of the occurrence of myocarditis or pericarditis in the population under study, and no consideration is given to disease severity.

In conclusion, our analysis extending the BRAVE toolkit further emphasizes the substantial benefits of COVID-19 mRNA vaccines relative to their risks. This reinforces the significance of developing user-friendly and flexible toolkits like BRAVE. Such a toolkit enhances the quantification and visualization of vaccine benefits and associated risks and facilitates extrapolation to guide future decision-making and public health planning initiatives.

Author contributions

Chantal Quinten, Catherine Cohet, and Xavier Kurz conceived the research questions. All authors participated in the design of the study and analysis plan. Johan Verbeeck, Jonas Crèvecoeur, Neilshan Loedy, Lander Willem, Geert Molenberghs, Niel Hens, and Steven Abrams conducted different parts of the study. Neilshan Loedy, Johan Verbeeck, and Steven Abrams drafted the initial and final versions of the manuscript. All authors critically reviewed the early and final versions of the manuscript and results. All authors had access to all data, and Hector G. Dorta, Chantal Quinten, Johan Verbeeck, and Steven Abrams have verified the data. All authors had final responsibility for the decision to submit for publication.

Supplementary data

Supplementary data are available at *EURPUB* online.

Conflict of interest: H.G.D., D.R.M., C.C., X.K., and C.Q. were employees of the EMA at the time of elaboration of this work and have no conflict of interest. H.G.D is a co-founder and holds stock options in Rynd Biotech, a startup company for the rapid detection of sexually transmitted infections. N.H. holds a grant sponsored by MSD, Janssen Vaccines & Prevention, GSK—Glaxo SmithKline, and has received consulting fees for his participation in the advisory board for Janssen Global Services, and payment for expert testimony for MSD. L.W. and S.A. are PIs of a research project on COVID-19 modelling funded by the Research Foundation—Flanders (FWO Belgium, G059423N). G.M. declares his participation on a data safety monitoring board or advisory board for COVID-19 vaccine trials of Janssen Pharmaceutica. These potential conflicts of interest have not influenced the design, conduct, or reporting of the work presented in this manuscript. All other authors declare no competing interests.

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Data availability

The default datasets can be accessed in the BRAVE toolkit [5]. The full study protocol and report related to this study can be consulted at EUPAS4429 [27]. Upon request to the authors, the source code behind the BRAVE toolkit can be provided.

Ethical statement

Not applicable.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Key points

- The mRNA vaccine benefits outweigh the potential risks of myocarditis and pericarditis within 14 days after vaccination, across all age groups and sexes.
- Developing a flexible, interactive tool like the BRAVE Toolkit allows vaccine-related risks and benefits to be presented in a clear and accessible format.
- The development of practical digital monitoring applications for vaccines and other interventions could improve preparedness for future public health emergencies.

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