Utilising the Benefit Risk Assessment of Vaccines (BRAVE) toolkit to evaluate the benefits and risks of Vaxzevria in the EU: a population-based study

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Summary

Background Several COVID-19 vaccines have been licensed. To support the assessment of safety signals, we developed a toolkit to support COVID-19 vaccine monitoring and benefit–risk assessment. We aim to show the application of our toolkit in the EU using thrombosis with thrombocytopenia syndrome (TTS) associated with the Vaxzevria (AstraZeneca) vaccine as a use case.

Methods In this population-based study, we used a model incorporating data from multiple EU sources such as The European Surveillance System and EudraVigilance, and estimated the benefits of COVID-19 vaccines by comparing the observed COVID-19 confirmed cases, hospitalisations, intensive care unit (ICU) admissions, and deaths across Europe to the expected numbers in the absence of Vaxzevria vaccination. Risks of TTS associated with Vaxzevria were calculated by comparing the observed number of TTS events in individuals who received Vaxzevria to the expected number of events based on background incidence rates. To visualise the results, we developed a toolkit with an interactive web application.

Findings 62 598 505 Vaxzevria vaccines (32 763 183 to females and 29 835 322 to males) had been administered in Europe by Feb 10, 2021. Our results showed that a first dose of Vaxzevria provided benefits across all age groups. Based on vaccine effectiveness estimates and reported coverage in Europe, from Dec 13, 2020 to Dec 31, 2021, vaccination with Vaxzevria was estimated to prevent (per 100 000 doses) 12 113 COVID-19 cases, 1140 hospitalisations, 184 ICU admissions, and 261 deaths. Women aged 30–59 years and males aged 20–29 years had the highest frequency of TTS events. The benefits of vaccination outweighed the risks of TTS in all age groups, with the highest benefits and risks observed in individuals aged 60–69 years.

Interpretation Our toolkit and underlying model contextualised the risk of TTS associated with Vaxzevria relative to its benefits. The methodology employed could be applied to other serious adverse events related to COVID-19 or other vaccines. The adaptability and versatility of such toolkits might contribute to strengthening preparedness for future public health emergencies.

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Introduction

The SARS-CoV-2 pandemic forced countries worldwide to take far-reaching measures to reduce the burden on health-care systems and to mitigate severe outcomes related to COVID-19. Several vaccines were developed and authorised at unprecedented speed, reaching a total distribution of more than 1·3 billion doses in the EU and more than 12 billion doses worldwide as of Nov 23, 2022.[1,2]

COVID-19 vaccination has been proven effective at preventing infection, hospitalisation, intensive care unit (ICU) admission, and death due to COVID-19.[3] For Vaxzevria (previously COVID-19 vaccine AstraZeneca), very rare cases of unusual blood clots with low blood platelets, including thrombosis with thrombocytopenia syndrome (TTS), occur in approximately one in 100 000 vaccinated people.[4]

In March 2021, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a safety assessment for embolic and thrombotic events after Vaxzevria administration.[5] Based on data from the European spontaneous reporting system (EudraVigilance), observed versus expected analyses, expert consultations, and literature reviews, safety signals for embolic and thromboembolic events emerged, particularly in women younger than 60 years, with onset within 2 weeks after vaccination. The PRAC concluded that a potential causal relationship between vaccination with Vaxzevria and a new clinical entity of thrombosis with thrombocytopenia, defined as TTS, was possible, and recommended warnings and updates of the product information.[5]

On April 9, 2021, the European Commission triggered an Article 5(3) procedure under Regulation (EC) number

Research in context

Evidence before this study

Putting the benefits and risks of vaccines into context requires consideration of complex dynamic interaction between infection rates, vaccine effectiveness, vaccine exposure and adverse events in the population. As part of the COVID-19 pandemic response, several COVID-19 vaccines were licensed. However, there were no dedicated digital tools to support public health and regulatory decision making based on assessing safety signals in the context of the COVID-19 vaccines' potential benefits.

We searched PubMed from inception to March 25, 2023, using the search terms [(tool* AND digital) AND (covid) AND (vaccin*) AND (effectiv* OR benefit OR risk)] for published studies in English examining the use of digital tools to evaluate benefits and risks of COVID-19 vaccines. We identified three studies focusing on digital approaches to remote data collection, including the retrieval of vaccination data, to study the impact of COVID-19 infection. Additionally, two other studies focused on supporting contact tracing, one study reported a digital health solution to support clinical management of patients with post-COVID-19 condition (also known as long COVID), and one study highlighted the valuable role digital tools might offer in supporting communication of vaccine safety information. We did not identify any studies describing a digital tool for contextualising benefits and risks of COVID-19 vaccines.

Added value of this study

This study reports on the development of the Benefit Risk Assessment of Vaccines (BRAVE), a toolkit that brings together multiple health data sources to contextualise benefits and risks of COVID-19 vaccines overall and by a subpopulation of interest. Moreover, the toolkit features an interactive dashboard for visualising and contextualising vaccine benefits and risks estimates at the EU level. Utilising Vaxzevria and thrombosis with thrombocytopenia syndrome as a use case, we show the value of BRAVE to support health emergencies. More specifically, our case study informed the vaccination strategy programmes on the positive benefit–risk balance of Vaxzevria.

Implications of all the available evidence

The BRAVE toolkit and its methodology have the potential to be extended to other vaccines, serious adverse events, and clinical outcomes, to enhance our understanding about the benefit and risk profile of any vaccine. Digital applications such as BRAVE have the potential to improve and accelerate the usefulness of health data on benefits and risks by identifying, for example, higher-risk subpopulations by age and sex. This approach might help contextualise the findings and complement informed policy decision making and might therefore play an important role in future pandemic preparedness.

726/2004, requesting the EMA's scientific opinion to guide national vaccination campaigns for Vaxzevria.[6,7] Specifically, the European Commission sought further analyses and stratification of subpopulation data (age, sex, and vaccine dose) in the context of monthly infection rates to characterise benefits and risks.

Through the Article 5(3) procedure, data on COVID-19 vaccination was made available to quantify the benefits of vaccination with Vaxzevria in terms of the averted number of confirmed COVID-19 cases, hospitalisations, ICU admissions and deaths, based on country-specific age-specific, and time-specific data with respect to these endpoints, and to offset these benefits against potential risks associated with Vaxzevria vaccination.[7] Using pooled data obtained from EU–European Economic Area (EU–EEA) Member States and the European Centre for Disease Prevention and Control (ECDC), vaccine marketing authorisation dossiers, and published literature, especially observational studies on vaccine effectiveness, the assessment concluded increasing benefits with increasing age and infection rate.[7]

The aim of or study was to develop a toolkit to support benefit–risk contextualisation of COVID-19 vaccines in the EU using a comprehensive and adaptable framework methodology, demonstrated using TTS after Vaxzevria vaccination as a use case.

Methods

Study design

In this population-based study, we developed the Benefit Risk Assessment of Vaccines (BRAVE) toolkit, which is a comprehensive set of features assembled to support the benefit–risk contextualisation of vaccines. The BRAVE toolkit encompasses default datasets, a detailed framework methodology, a set of functions and code derived from the applied statistical methods, a graphical user interface, and a user manual that allows users to interpret and interact with the results through a dashboard.

The toolkit was developed for use through a dashboard to input data on COVID-19 cases, hospitalisations, ICU admissions, deaths, and vaccine-associated adverse events to inform on the benefits and the risks of vaccination. In addition to COVID-19 incidence data by population of interest, information on the emergence of SARS-CoV-2 variants of concern and vaccine effectiveness estimates for different COVID-19 vaccine brands and doses are included in the analyses.

Additional risk-communication experts and health-care professional representatives were consulted during the preparation of the visuals of the toolkit.

This study is based on secondary use of anonymised data from ECDC's The European Surveillance System (TESSy),[8] in line with established policies and data

protection regulations. Ethics approval was not required, as the data were collected for public health risk assessment under existing legal provisions. Other analysed data besides TESSy is from EudraVigilance,[9] for which ethics approval is not applicable either as no identifiable information about individuals is disclosed in the Article and all findings are reported in aggregated form. All data were processed in full compliance with General Data Protection Regulation and relevant data governance frameworks.

Data

To contextualise the benefit–risk of vaccination, the toolkit requires a minimum of input data. For our specific case study, the EMA had access to datasets covering from Dec 13, 2020 to Dec 31, 2021. The required input data for benefit dataset was the total number of people by population of interest (eg, age or sex); number of diagnosed cases, hospital admissions, ICU admissions and deaths by population of interest; number of diagnosed cases, hospital admissions, ICU admissions and deaths by population of interest aggregated by date; vaccine coverage aggregated by population of interest; and estimated distribution of variants of concern by population of interest (optional). The required input data for risk dataset was the number of observed events for the risk of interest aggregated by population of interest, background incidence rates of the reported risk of interest aggregated by population of interest, and vaccine coverage aggregated by population of interest.

The dataset on EU–EEA country demographics contains the population per country and the 10-year age group categories (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years) from EUROSTAT, as reported in December, 2021.[10]

COVID-19 case data from January, 2020, to March, 2021, were gathered directly from national health datasources in EU–EEA Member States and ECDC datasets, covering 20 EU–EEA countries. Reported by 10-year age group categories (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years), the datasets included complete information on hospitalisations, ICU admissions, and deaths for several countries. For those countries with incomplete data, the confirmed cases over time were used to fill this gap by using temporal case-to-hospital and case-to-ICU admission ratios based on daily median values over all available data for all countries that reported admissions to impute country-specific daily hospital and ICU admissions. The data availability for each country is in the appendix (p 13).

Granular COVID-19 incidence data were aggregated by country per day for cases, ICU admissions, hospitalisations, and mortality between Feb 26, 2020 and Feb 9, 2022.

The proportions of variants of concern in the sequenced SARS-CoV-2 positive samples, by day and by country, were retrieved from the GISAID EpiCOV genomic surveillance database[11] and TESSy[12] on May 11, 2020.

The vaccination coverage data were sourced from the ECDC Vaccine Tracker submissions to TESSy on Feb 10, 2021.[1] These submissions contain data on the COVID-19 vaccine roll-out within the EU–EEA by day, vaccine brand, country, 10-year age categories, and the number of doses received (first, second, or third dose). When the vaccine brand was unknown, it was replaced with the distribution of vaccine brands of other countries for which the required data were available. Additionally, when the age groups in the reported data did not match the 10-year age groups in the model, we weighted the reported vaccine uptake using fixed proportions (appendix p 10).

To perform the risk calculations of TSS, three sets of data are necessary: the number of observed events, the background incidence rates of these events, and the vaccine coverage.

The observed events after vaccination were obtained from spontaneous case reports collected in EudraVigilance, on July 25, 2021, stratified by vaccine, age, and sex (male *vs* female).[9] EudraVigilance contains individual case safety reports submitted to national competent authorities by health professionals and marketing authorisation holders. EudraVigilance manages information on suspected adverse reactions from authorised medicines in the European Economic Area. In our analysis, TTS was defined using standardised MedDRA query terms described in the safety signal assessment report.[7] Missing information on age and sex were imputed using the age and sex proportions from complete cases.

Background incidence rates of adverse events of special interest identified before vaccination help to interpret potential safety concerns associated with COVID-19 vaccines.[13]

TTS was a new clinical entity specifically associated with adenovirus-vectored vaccines and identified during real-world use.[5] Therefore, no background incidence rates had been generated from health-care databases in the prevaccination phase. As a result, the background incidence rate for TTS were assumed to be zero.[7]

Nevertheless, the toolkit was designed to include background incidence rates before vaccination from data sources such as electronic health records, administrative databases, and disease registers that provide background incidence rate in the period before the COVID-19 pandemic and during the COVID-19 pandemic before vaccination.

The detailed vaccination coverage described earlier was aggregated. Because the ECDC data source contained the most up-to-date information on vaccine coverage per country but did not include sex information, coverage by sex was imputed from sex proportions from datasets provided by Member States on Sept 30, 2021 (appendix p 13). Additionally, a redistribution over some age categories was required because they did not align in the

See Online for appendix

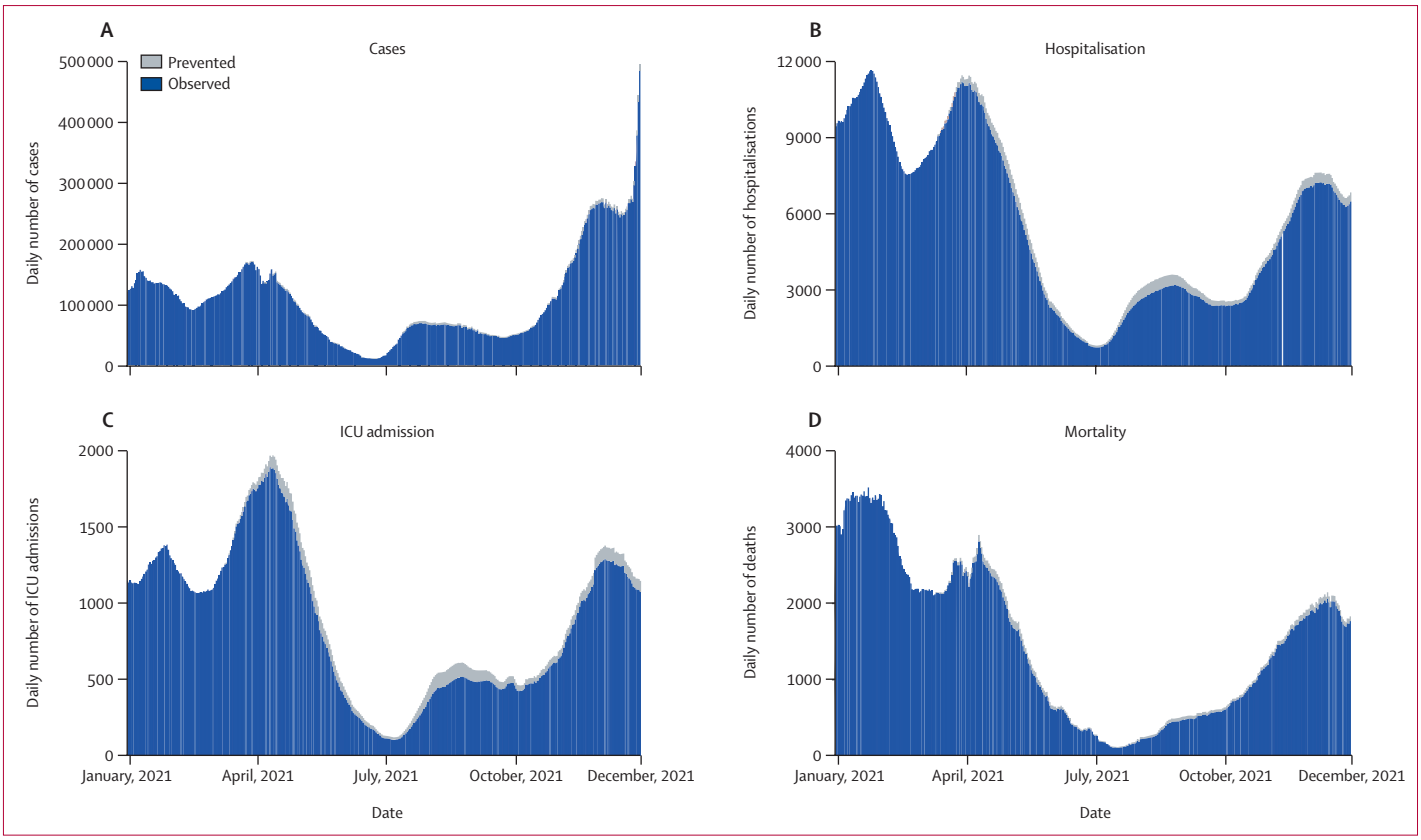

Figure 1: **Daily number of observed (blue) and prevented (grey) COVID-19 cases (A), hospitalisations (B), ICU admissions (C), and deaths (D) with Vaxzevria in the EU—European Economic Area countries between Dec 13, 2020, and Dec 31, 2021**
ICU=intensive care unit.

two data sources and differed from the ones required for the risk assessment. The coverage by sex and required age category was redistributed according to multiple imputation and fixed proportions.

Published literature on the effectiveness of the different authorised COVID-19 vaccines based on real-world evidence studies was used to obtain effectiveness estimates in terms of infection, hospitalisation, ICU admission, and death.[14,15]

Statistical analysis

The toolkit relies on a probabilistic model to quantify the benefits associated with COVID-19 vaccination by comparing the observed number of confirmed COVID-19 cases, hospitalisations, ICU admissions, and deaths with the estimated number of clinical events in the case where no COVID-19 vaccination was available. To support our use case of TTS associated with Vaxzevria, we accounted for differential vaccine effectiveness in relation to time since vaccination, variants of concern, and age-specific and temporal differences in infection and disease dynamics.

In our study we looked specifically at the direct benefits introduced by Vaxzevria vaccination, supposing the uptake of other available COVID-19 vaccines remained unchanged during the study period. Moreover, our study assumed constant case definition, testing capacity, and contact tracing, as well as vaccine effectiveness independent of time. In addition, when estimating the direct effects of COVID-19 vaccination, the method did not account for any potential indirect herd immunity effects that might exist. For example, waning of vaccine-induced immunity was incorporated through estimates based on decay in humoral immunity. However, as pointed out by Lui and colleagues,[16] cellular immunity induced by COVID-19 vaccination provides durable protection against infection with variants such as omicron, despite reduced neutralising antibody responses with time since vaccination.

We estimated the benefits, calculated as the number of prevented clinical events (ie, confirmed cases, hospitalisation, ICU admissions, or deaths), within each age stratum of interest as: benefits=observed COVID-19 cases × proportion with clinical event × vaccine effectiveness.

Default parameters were selected based on the most conservative data from the available information. For

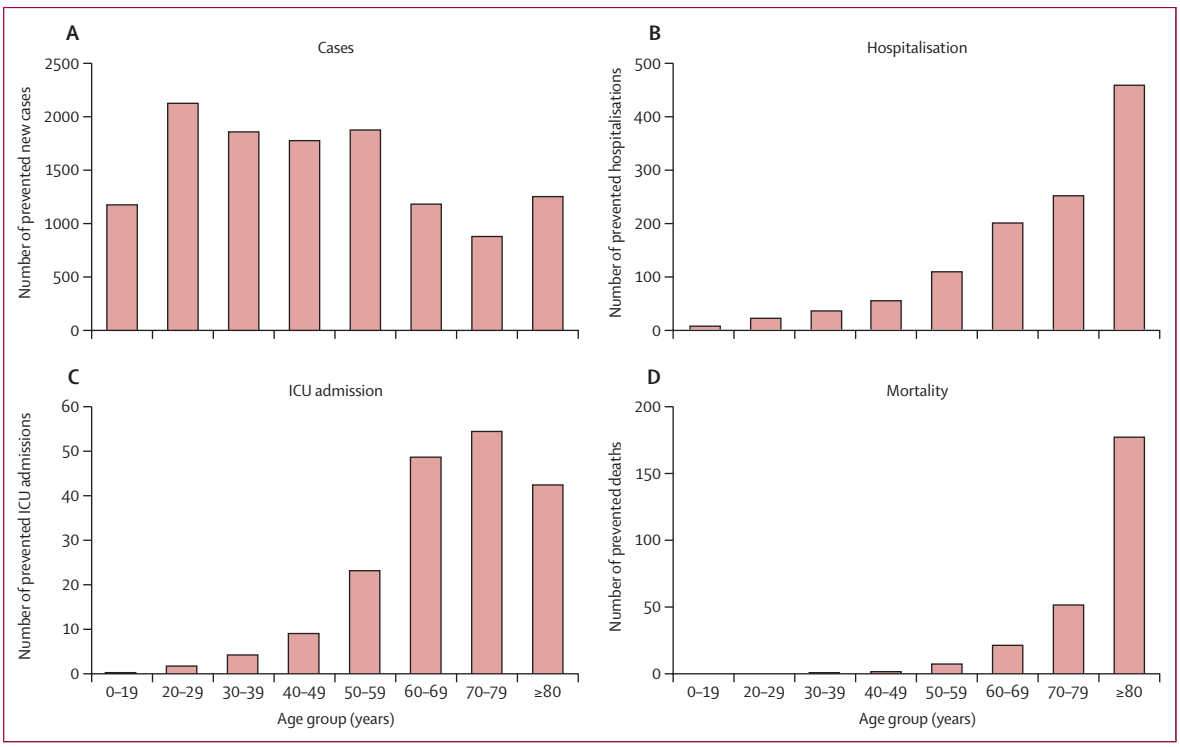

Figure 2: **Number of prevented COVID-19 cases (A), hospitalisations (B), ICU admissions (C), and mortality (D) per 100 000 individuals vaccinated with Vaxzevria in the EU by age group between Dec 13, 2020, and Dec 31, 2021**
ICU=intensive care unit.

example, in determining vaccine effectiveness, we did not choose the highest or lowest reported estimates but opted for a conservative value that falls in the middle of the range.

Missing age-specific information was imputed based on uniform weights (appendix p 10) and data from complete cases. A partially effective vaccination approach was used. For instance, 50% vaccine effectiveness against infection implies that for a vaccinated individual, the likelihood of being infected is 50% less compared with a non-vaccinated individual of the same age and at the same calendar time. Thereby, breakthrough infections after vaccination are included in our analysis. Detailed information on the modelling approach is in the appendix (pp 3–4).

The risks associated with Vaxzevria were calculated by subtracting the expected events in case of no vaccination (ie, background incidence rate×person-time at risk) from total of observed events in case of Vaxzevria vaccination (ie, TTS cases submitted to EudraVigilance) from within each stratum of interest (ie, age or vaccine brand).[13,17,18]

The number of expected events before vaccination was zero and the risk of TTS after Vaxzevria vaccination was derived from the observed cases.[7]

Information on vaccination coverage by age and sex, if missing for some cases, can be performed in the toolkit in two ways, with and without multiple imputation, where the seed for the multiple imputation of missing data is varied as a numerical sensitivity analysis. More elaborate sensitivity analyses, with the aim to explore the extent to which deviations from missing at random towards missing not at random change conclusions, are not feasible in the toolkit.

The toolkit supports simultaneous testing of scenarios, adjusting vaccine effectiveness parameters regarding clinical outcomes (ie, symptomatic infection, hospitalisation, ICU admission, and mortality) and imputation methods for missing covariate data. Finally, the toolkit's versatility allows for a benefit–risk assessment using individual estimates or pooling background rates from various real-world data sources.

The full methodological details can be found in the user manual of the BRAVE toolkit and in the appendix (pp 1–14). The study was registered in the EU PAS Register, which has now been replaced by the HMA-EMA catalogue of real-world data sources and studies (EUPAS44229).[19]

For more on the **BRAVE toolkit** see https://dsi-uhasselt.shinyapps.io/BRAVE_covid_vaccine_risks_and_benefits/

Role of the funding source
The EMA had a role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
The direct benefits of Vaxzevria in Europe were expressed in terms of the estimated number of prevented

	Female	Male
10–19 years	265 203	167 893
20–29 years	1 820 304	1 141 381
30–39 years	2 967 110	2 439 638
40–49 years	4 387 887	3 438 756
50–59 years	4 427 485	4 060 033
60–69 years	13 148 236	13 269 010
70–79 years	4 888 007	4 692 947
≥80 years	858 951	625 664
Total	32 763 183	29 835 322

Data are n. Vaxzevria coverage data sourced from the European Centre for Disease Prevention and Control on Feb 10, 2021. Age categories were adjusted and sex imputed based on Member States' data received on Sept 30, 2021.

Table 1: **Vaxzevria coverage by age group and sex**

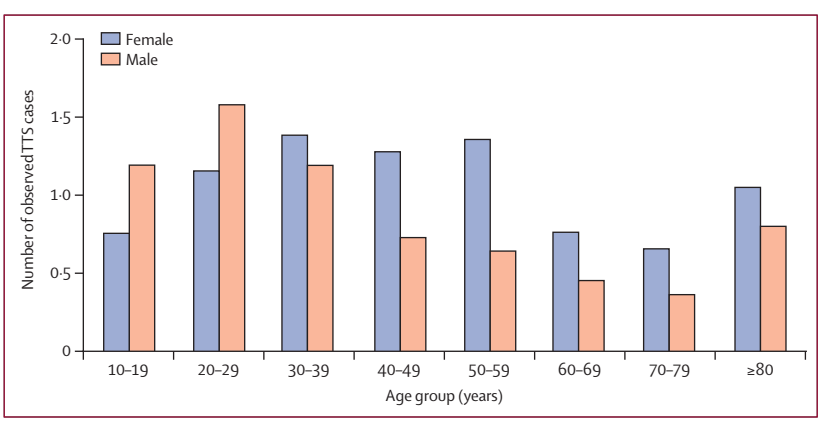

Figure 3: **Number of observed cases of TTS reported for Vaxzevria for males and females**
The data were sourced from EudraVigilance and were extracted on July 25, 2021. TTS=thrombosis with thrombocytopenia syndrome.

COVID-19 cases, hospitalisations, ICU admissions, and COVID-19 related deaths (figure 1) since the start of the vaccination campaign (Dec 13, 2020) to Dec 31, 2021. Using default model parameters, Vaxzevria prevented an estimated total of 855 105 confirmed COVID-19 cases during the study interval in the EU–EEA, alongside 87 243 COVID-19 hospitalisations, 18 493 ICU admissions, and 14 234 COVID-19 related deaths under the assumption that the vaccination coverage for the other COVID-19 vaccines remained constant and without accounting for herd immunity, which is likely to have occurred with the COVID-19 vaccines.

To enable a direct comparison of the vaccination impact across age groups, we expressed the estimated number of prevented COVID-19-related events per 100 000 individuals vaccinated with Vaxzevria by age. Overall, vaccination with Vaxzevria was estimated to prevent (per 100 000 people vaccinated) 12 113 COVID-19 cases, 1140 hospitalisations, 184 ICU admissions, and 261 deaths. When comparing the benefits of Vaxzevria, we observed the largest reduction in COVID-19-related hospitalisations (572 per 100 000 vaccines) and deaths (215 per 100 000 vaccines) in the 80 years or older age group, and the highest number of prevented ICU admissions was observed for the 70–79 years age group (59 per 100 000 vaccines; figure 2). The number of prevented COVID-19 confirmed cases was consistent for all age groups between 20 years and 59 years (mean of 2111 per 100 000 vaccines).

62 598 505 Vaxzevria vaccines (32 763 183 to females and 29 835 322 to males) had been administered in the EU–EEA countries on Feb 10, 2021 (table 1).

By July 25, 2021, EudraVigilance received reports of 503 TTS events within 30 days after Vaxzevria vaccination. The highest frequency of events was found for females in the 30–39, 40–49, and 50–59 years age groups along with males in the 20–29 years age group (figure 3).

Because TTS was a new clinical entity,[5] background rates were not available. Consequently, the number of expected TTS risk cases in the absence of vaccination was zero and we only considered the number of observed cases (appendix p 14).

Contextualising the benefits (ie, prevented clinical events and therefore prevented burden) of Vaxzevria vaccination against the risk of TTS (ie, additional burden) highlighted that the estimated benefits outweigh the risks in all age categories (figure 4; table 2). The number of prevented hospitalisations, ICU admissions, and deaths were highest in the 60–69 years age group (figure 4).

Discussion

We developed a toolkit using an interactive web application to quantify the benefits and risks of COVID-19 vaccines across the EU and tested it to evaluate the benefits and risks of Vaxzevria in the EU. To better contextualise the benefits and risks associated with vaccination, the dashboard was designed to integrate data from multiple sources, including incidence of confirmed cases, hospitalisations, ICU admissions, deaths, vaccination coverage information (through age-specific and time-specific uptake of different vaccines), and vaccine-related risk events.

In our use case of TTS with Vaxzevria, we estimated that Vaxzevria prevented a total of 855 105 confirmed COVID-19 cases, 87 243 COVID-19 hospitalisations, 18 493 ICU admissions and 14 234 COVID-19 related deaths between the start of the COVID-19 vaccination programme in the different European countries (Dec 13, 2020) and Dec 31, 2021, at least in the presence of unchanged vaccine uptake regarding the other COVID-19 vaccines. The benefits were compared to the potential risks of developing TTS within 30 days after Vaxzevria vaccination, and the results supported the positive overall benefit–risk balance despite the recognised risk of TTS.

During the past decade, several initiatives within and outside Europe have characterised and developed recommendations for quantitative benefit–risk assessment. In 2009, two initiatives started in Europe with the aim of providing recommendations for a quantitative

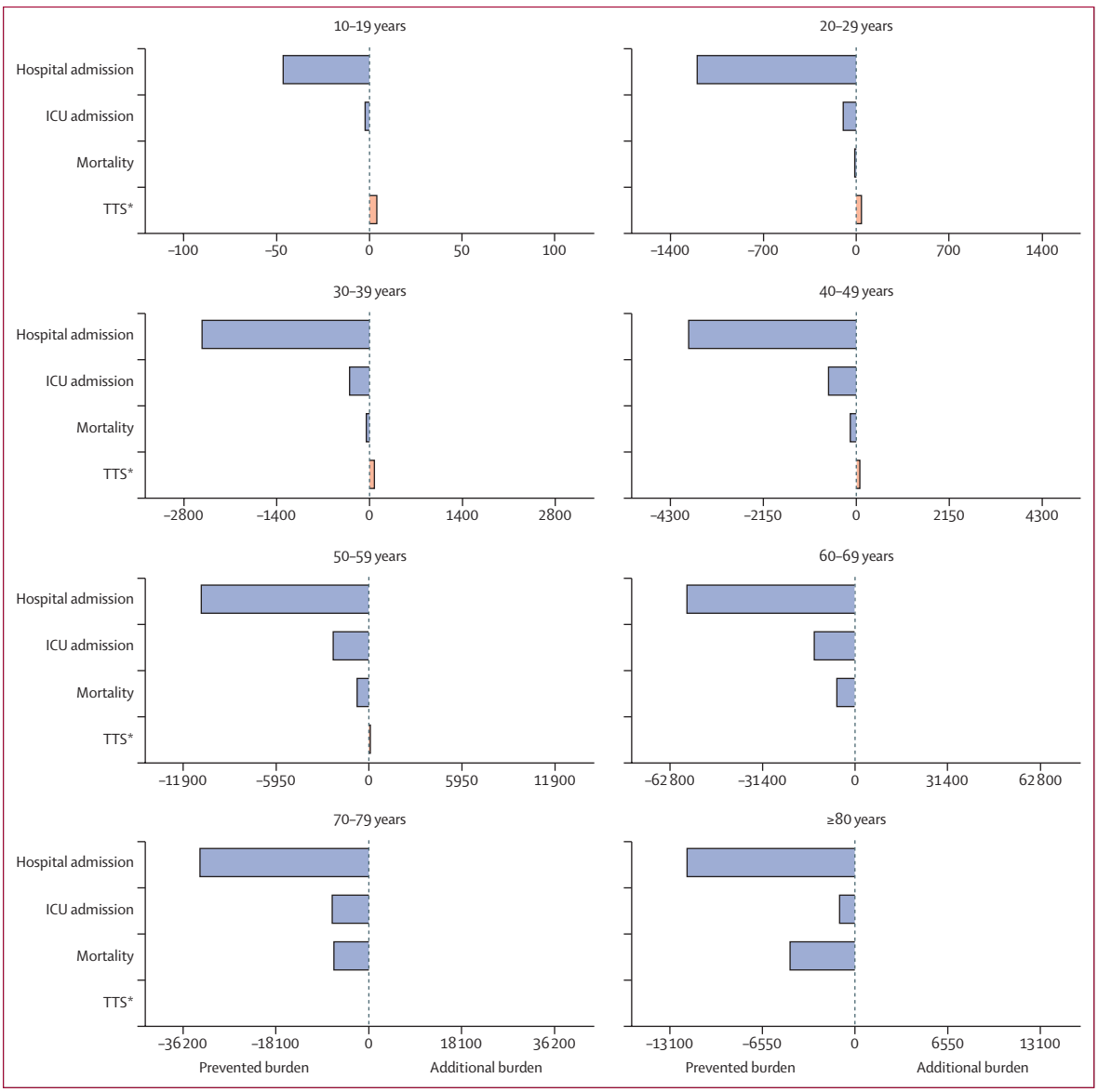

Figure 4: **Contextualisation of the benefits (prevented burden) and risks (additional burden) of thrombosis with thrombocytopenia syndrome associated with two doses of Vaxzevria per age category**

Note that the scales for benefits and risks in each age group are different. ICU=intensive care unit. TTS=thrombosis with thrombocytopenia syndrome. *Expected additional cases compared with the intrapandemic background rate.

benefit–risk assessment: the Benefit–Risk Methodology Project led by the EMA and the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI-PROTECT).[20,21] In 2012, the Center for Innovation in Regulatory Science started the Unified Methodologies for Benefit–Risk Assessment project, with their guidelines adopted by Canada, Australia, Switzerland, and Singapore.[22] Following these first initiatives, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Risk–Benefit Management Working Group further developed promising general quantitative benefit–risk assessment methods,[23] and between 2013 and 2019, the Accelerated Development of Vaccine Benefit–Risk Collaboration in Europe (IMI-ADVANCE) project revisited all methodologies described in systematic reviews of IMI-PROTECT and ISPOR and evaluated their suitability specifically focusing on benefit–risk assessment in the context of vaccines.[24,25] An output from IMI-ADVANCE was the development of an interactive dashboard to assess the incremental net health benefit and benefit–risk ratio using different sets of preference weights with simulated data.[26]

Another tool, using Bayesian modelling, calculates COVID-19 vaccine benefits and risks.[27] Our tool stands out as it is designed for easy updates based on changing case numbers reported to regulatory authorities during

	Thrombosis with thrombocytopenia syndrome	Hospitalisations	Intensive care unit admission	Mortality
10–19 years	4	46·5	2·3	0·2
20–29 years	39	1198·2	98·5	12·2
30–39 years	70	2527·4	303·3	50·9
40–49 years	81	3880·1	642·1	140·1
50–59 years	86	10738·5	2286·7	758·2
60–69 years	160	57015·8	13853·7	6183·2
70–79 years	49	32894·6	7120·5	6780·8
≥80 years	14	11881·1	1102·1	4598·3

Table 2: **Number of additional risks (in absolute numbers) and benefits (ie, prevented clinical events per 100 000) associated to Vaxzevria vaccination per age group**

pharmacovigilance monitoring. Our tool offers greater flexibility with input parameters based on data availability. Both tools complement each other, and have the potential to contribute to evidence-based decisions in regulatory and public health settings.

The US Food and Drug Administration used a similar methodological approach to inform and to support the Advisory Committee for Immunization Practices in several COVID-19 vaccine policy decisions in the USA.[28] Although benchmarking our results against other models would have provided valuable reference points, the lack of more granular and rich data limits the possibility of using alternative, refined models for comparison. Also, within the EMA, a related exercise using the BRAVE toolkit was conducted, focusing on myocarditis and pericarditis associated with mRNA vaccines.[19]

We acknowledge some limitations in our study. The proposed model used for quantifying the benefits did not directly account for uncertainty in the number of prevented cases or other clinical endpoints (eg, standard error estimates), which would arise from incorporating uncertainty about specific model parameters. However, this uncertainty can be addressed externally, outside of the toolkit, through Monte Carlo methods, by running the model multiple times for different sets of parameter values. More specifically, in each simulation run, the input values are drawn from a (multivariate) probability distribution, representing uncertainty with respect to these population-level input parameters. Under the assumption of independence of these parameters, this approach comes down to drawing values for different univariate sampling distributions for vaccine effectiveness estimates, variant prevalence in study populations, waning immunity rates, and incidence rates. Although this method explicitly acknowledges the precision with which input parameters are estimated and how uncertainty with regard to these parameters translates into interval estimates for the model output and therefore enhances the robustness of the analysis, standard Monte Carlo methods are typically time-consuming, particularly for high-fidelity, complex models.[29] Consequently, their direct integration into the tool might be impractical. An extension of the toolkit, which allows for the calculation of uncertainties, has been developed and is currently under peer review. This extension could further support the use of the tool. The model also did not consider the build-up of natural immunity in the population because estimating country-specific natural immunity from previous COVID-19 infection is computationally burdensome. We could further improve the methods by using a stochastic compartmental model to refine benefit estimation by incorporating disease dynamics, uncertainty propagation, indirect vaccination effects, and accounting for recipients of multiple vaccine brands.[19] However, due to limited data granularity and computational complexity, informing such a model and achieving convergence for all countries and parameters would be challenging.

We relied on data from EudraVigilance spontaneous reports, which, while valuable, have limitations such as potential under-reporting and data incompleteness, possibly resulting in an underestimation of adverse events, including TTS associated with the Vaxzevria vaccine. Active safety surveillance systems would ideally offer more accurate risk estimates. Moreover, the absence of individual-level data on the time between vaccine doses and the approximation of vaccine-induced protection at the population level might introduce constraints affecting the precision of benefit–risk estimates, particularly in scenarios with varying dose schedules. The toolkit accounts for the gradual build-up of vaccine protection but does not explicitly consider dose schedules and time intervals between doses. The benefits quantification is based on a time-invariant age distribution, estimated separately for each endpoint over the pandemic, potentially underestimating the prevented burden in age groups with high vaccine uptake. Detailed age-specific and time-specific information is crucial for future versions of the toolkit. Additionally, the availability and quality of data related to COVID-19 incidence and vaccination coverage, in terms of data completeness, granularity, and accuracy, introduce limitations that impact the precision and comprehensiveness of the benefit–risk analysis. Enhancing data quality and adopting common data models can yield more precise estimates of prevented clinical events, facilitating analysis of heterogeneity in background incidence rates.[30] Standardised surveillance systems that collect granular data are crucial for pandemic preparedness and continuous monitoring of vaccine benefits and risks, necessitating high-quality real-world data.[31] Leveraging the European Health Data Space and the Data Analysis and Real-World Interrogation Network can contribute to achieving these needs.

Our toolkit was developed to include information about the emergence of new variants of concern and to specify different age groups, harmonised with age groups for the risk in question. Moreover, new vaccines can be included in the toolkit by specifying parameters governing the

vaccine properties in the context of the different variants of concern. However, adding additional booster vaccinations and examining subpopulations (eg, sex) would require further development of the source code and access to sex-stratified data.

Users are encouraged to identify the benefits and risks pertaining to their particular use case, which might vary from the parameters selected in our study. Users might focus on a single or multiple benefits or risks. Furthermore, subgroups of interest can also be assessed such as sex, age, and underlying comorbidities. We recommend collecting data on the benefits and risks of vaccines over the same time period and if possible since the start of the vaccination campaign. Notably, some input datasets might not be required for all questions of interest (eg, background incidence rates or variants of concern).

Although the toolkit was developed in the context of a specific use case, its flexibility allows for the assesment of benefits and risks for other vaccines and interventions when data are available (eg, benefits in terms of prevention of post-COVID-19 condition [also known as long COVID]). However, extending the toolkit to the context of other vaccine types would require further work because the nature (ie, airborne) and transmission dynamics of the pathogen of interest might differ. In addition to the methodological improvements, further work is required to evaluate user-driven improvements of digital tools and their implementation with stakeholders, such as the EU Vaccine Monitoring Platform and national regulatory agencies.

The COVID-19 pandemic has catalysed improvements in crisis response and pandemic preparedness both in Europe and internationally and has also strengthened the collaboration within the EU. In particular, the role of real-world data in emergency settings has been emphasised, because there is a need to effectively support and provide recommendations in the decision-making process based on the latest data available at population level.[5]

We have developed a toolkit to contextualise the benefit–risk of COVID-19 vaccines, potentially providing insights to support vaccination policy decisions, that will be important for enhancing preparedness in responding to future public health emergencies. However, the results rely on the timely availability of high-quality data across different countries, where data collection often differs in terms of granularity and uniformity. Approaches to improve data collection and its standardisation at the European and international level, such as using common data models, would enable future development and improvement of such digital health tools.

Further research could involve a systematic comparison between the information originally used to develop the toolkit and any new data that has emerged since then. For example, the toolkit could be enhanced by incorporating new findings that address conflicting literature, such as updated parameters on vaccine effectiveness or vaccine-related risks. This ongoing updating process would ensure that the toolkit remains a robust and up-to-date resource, thereby improving the accuracy of its estimates.

Contributors

CQ, CC and XK conceived the research question. All authors participated in the design of the study and analysis plan. JV, JC, NL, LW, GM, NH, and SA developed the model and tool, and performed the initial analysis. HGD, CQ, and DRM drafted the initial and final versions of the manuscript. All authors critically reviewed early and final versions of the manuscript and results. All authors had access to all data, and HGD, CQ, JV, and SA have verified the data. All authors have seen and approved the final text. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

HGD, DRM, CC, XK, and CQ were employees of the EMA at the time that this work was conducted. HGD is co-founder and holds stock options of Rynd Biotech, a startup company for the rapid detection of sexually transmitted infections. NH holds a grant sponsored by MSD, Janssen Vaccines & Prevention, and GSK; has received consulting fees for participation in an advisory board for Janssen Global Services; and has received payment for expert testimony for MSD. LW is the Principal Investigator of a research project on COVID-19 modelling funded by Research Foundation–Flanders (FWO Belgium). GM declares participation on a data safety monitoring board for COVID-19 vaccines trials for Janssen Pharmaceutical. These potential conflicts of interests have not influenced the design, conduct, or reporting of the work presented in this manuscript. All other authors declare no competing interests.

Data sharing

The default datasets can be accessed at the BRAVE toolkit (https://dsi-uhasselt.shinyapps.io/BRAVE_covid_vaccine_risks_and_benefits/). The full study protocol and report related to this study can be consulted at EUPAS4429.[19] The source code behind the BRAVE toolkit can be shared upon request to the corresponding author.

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References

1 European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. 2022. https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html (accessed Feb 10, 2025).

2 WHO. WHO Coronavirus (COVID-19) Dashboard. 2022. https://covid19.who.int/ (accessed Nov 21, 2022).

3 Sacco C, Mateo-Urdiales A, Petrone D, et al. Estimating averted COVID-19 cases, hospitalisations, intensive care unit admissions and deaths by COVID-19 vaccination, Italy, January–September 2021. *Euro Surveill* 2021; **26:** 2101001.

4 The European Medicines Agency. Vaxzevria (previously COVID-19 Vaccine AstraZeneca): EPAR - Product information. 2022. https://www.ema.europa.eu/en/documents/product-information/vaxzevria-epar-product-information_en.pdf (accessed March 13, 2025).

5 Durand J, Dogné J-M, Cohet C, et al. Safety monitoring of COVID-19 vaccines: perspective from the European Medicines Agency. *Clin Pharmacol Ther* 2023; **113:** 1223–34.

6 The European Parliament and the Council of the European Union. Regulation (EC) no 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. 2004. https://eur-lex.europa.eu/eli/reg/2004/726/oj/eng (accessed March 13, 2025).

7 Committee for Medicinal Products for Human Use. Vaxzevria assessment report. Procedure under Article 5(3) of Regulation (EC) No 726/2004. 2021. https://www.ema.europa.eu/en/documents/opinion-any-scientific-matter/use-vaxzevria-prevent-covid-19-article-53-procedure-assessment-report_en.pdf (accessed March 13, 2025).

8 European Centre for Disease Prevention and Control. The European Surveillance System (TESSy). 2021. https://www.ecdc.europa.eu/en/publications-data/european-surveillance-system-tessy (accessed March 18, 2025).

9 The European Medicines Agency. EudraVigilance. 2022. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/pharmacovigilance-research-development/eudravigilance#:~:text=From%2030%20June%202022%2C%20it,and%20analytical%20capabilities%20in%20EudraVigilance (accessed March 13, 2025).

10 Eurostat. Population on 1 January by age group and sex. 2021. https://ec.europa.eu/eurostat/databrowser/view/demo_pjan/default/table?lang=en (accessed March 13, 2025).

11 Khare S, Gurry C, Freitas L, et al. GISAID's role in pandemic response. *China CDC Wkly* 2021; **3:** 1049–51.

12 European Centre for Disease Prevention and Control. Weekly COVID-19 country overview. 2021. https://www.ecdc.europa.eu/en/covid-19/surveillance/weekly-surveillance-report (accessed March 13, 2025).

13 The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on methodological standards in pharmacoepidemiology (revision 10). 2022. https://encepp.europa.eu/newsroom/news/10th-revision-encepp-guide-methodological-standards-pharmacoepidemiology-published-2022-07-01_en (accessed March 13, 2025).

14 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; **385:** 585–94.

15 Vasileiou E, Simpson CR, Shi T. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021; **397:** 1646–57.

16 Liu J, Chandrashekar A, Sellers D, et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 Omicron. *Nature* 2022; **603:** 493–96.

17 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) product- or population-specific considerations i: vaccines for prophylaxis against infectious disease. 2013. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-or-population-specific-considerations-i-vaccines-prophylaxis-against-infectious-diseases_en.pdf (accessed March 13, 2025).

18 Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. *Pharmacoepidemiol Drug Saf* 2016; **25:** 215–22.

19 Molenberghs G, Hens N, Abrams S, et al. Benefit risk contextualisation of COVID-19 vaccines in the EU. 2022. https://catalogues.ema.europa.eu/node/3141/administrative-details (accessed March 13, 2025).

20 European Medicines Agency. Benefit-risk methodology project. Work package 3 report: field tests. 2011. https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-work-package-3-report-field-tests_en.pdf (accessed March 13, 2025).

21 Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT). PROTECT benefit-risk. 2014. https://protectbenefitrisk.eu/index.html https://imi-protect-eu.cc.ic.ac.uk/ (accessed March 13, 2025).

22 McAuslane N, Leong J, Liberti L, Walker S. The benefit-risk assessment of medicines: experience of a consortium of medium-sized regulatory authorities. *Ther Innov Regul Sci* 2017; **51:** 635–44.

23 Guo JJ, Pandey S, Doyle J, Bian B, Lis Y, Raisch DW. A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. *Value Health* 2010; **13:** 657–66.

24 Arlegui H, Bollaerts K, Bauchau V, Nachbaur G, Bégaud B, Praet N. Benefit-risk assessment of vaccines. Part II: proposal towards consolidated standards of reporting quantitative benefit-risk models applied to vaccines (BRIVAC). *Drug Saf* 2020; **43:** 1105–20.

25 Bollaerts K, Vincent BV, Ledent E, Levitan B, Verstraeten T, Zhong Y. Accelerated development of vaccine benefit-risk collaboration in Europe. Work package 4, D4.3 report on appraisal of vaccine benefit-risk methodology. 2014. https://vac4eu.org/wp-content/uploads/2019/03/ADVANCE_D4.3appraisal_benefit_risk-methods.pdf (accessed March 13, 2025).

26 Bollaerts K, De Smedt T, Donegan K, Titievsky L, Bauchau V. Benefit-risk monitoring of vaccines using an interactive dashboard: a methodological proposal from the ADVANCE project. *Drug Saf* 2018; **41:** 775–86.

27 Mayfield HJ, Lau CL, Sinclair JE, et al. Designing an evidence-based Bayesian network for estimating the risk versus benefits of AstraZeneca COVID-19 vaccine. *Vaccine* 2022; **40:** 3072–84.

28 Wallace M, Rosenblum HG, Moulia DL, et al. A summary of the Advisory Committee for Immunization Practices (ACIP) use of a benefit-risk assessment framework during the first year of COVID-19 vaccine administration in the United States. *Vaccine* 2023; **41:** 6456–67.

29 Zhang J. Modern Monte Carlo methods for efficient uncertainty quantification and propagation: a survey. *Wiley Interdiscip Rev Comput Stat* 2021; **13:** e1539.

30 Russek M, Quinten C, de Jong VMT, Cohet C, Kurz X. Assessing heterogeneity of electronic health-care databases: a case study of background incidence rates of venous thromboembolism. *Pharmacoepidemiol Drug Saf* 2023; **32:** 1032–48.

31 Keusch GT, Amuasi JH, Anderson DE, et al. Pandemic origins and a One Health approach to preparedness and prevention: solutions based on SARS-CoV-2 and other RNA viruses. *Proc Natl Acad Sci USA* 2022; **119:** e2202871119.