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The role of real-world evidence for regulatory and public health decision-making for Accelerated Vaccine Deployment- a meeting report

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ABSTRACT

The COVID-19 pandemic underscored the need for rapid evidence generation to inform public health decisions beyond the limitations of conventional clinical trials. This report summarises presentations and discussions from a conference on the role of Real-World Evidence (RWE) in expediting vaccine deployment. Attended by regulatory bodies, public health entities, and industry experts, the gathering was a collaborative exchange of experiences and recommendations for leveraging RWE for vaccine deployment.

RWE proved instrumental in refining decision-making processes to optimise dosing regimens, enhance guidance on target populations, and steer vaccination strategies against emerging variants. Participants felt that RWE was successfully integrated into lifecycle management, encompassing boosters and safety considerations. However, challenges emerged, prompting a call for improvements in data quality, standardisation, and availability, acknowledging the variability and potential inaccuracies in data across diverse healthcare systems. Regulatory transparency should also be prioritised to foster public trust, and improved collaborations with governments are needed to streamline data collection and navigate data privacy regulations. Moreover, building and sustaining resources, expertise, and infrastructure in LMICs emerged as imperative for RWE-generating capabilities. Continued stakeholder collaboration and securing adequate funding emerged as vital pillars for advancing the use of RWE in shaping responsive and effective public health strategies.

1. Introduction and meeting objectives

Randomised controlled trials (RCTs) have long been the gold standard for assessing the safety and effectiveness of drugs and medical products. However, they can be resource-intensive and time-consuming, potentially limiting their feasibility for particular research questions and patient populations [1]. These limitations have prompted the search for alternative sources of reliable, interpretable data for robust, evidence-based decision-making, and real-world evidence (RWE) has emerged as a solution to many of the widely known limitations of RCTs [1–3].

RWE is clinical evidence about a medical product's usage and potential benefits or risks generated by analysing real-world data (RWD), which are data on a patient's health status or routine healthcare delivery [2,4]. The evidence from RCTs represents the outcome of a 'standardised' intervention used in an 'idealised' setting, while RWE represents the outcome of 'variable' treatment patterns in the 'real world'. Therefore, RWE complements the RCT findings and can contribute to enhanced evidence generation, especially in populations that may have been excluded from RCTs or for events too rare to be evaluated in pre-licensure studies [1].

The COVID-19 pandemic emphasised the need for quick access to new vaccines. Despite authorization of several vaccines within a year of the pandemic declaration, challenges emerged in both high-income and low-to middle-income countries (HIC/LMIC) concerning the need for rapid evidence-generation to support public health decisions, encompassing regulatory aspects as well as issues beyond what RCTs alone

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Table of abbreviations

AESI	Adverse event of special interest
AEFI	Adverse event following immunisation
ALIVE	African Leadership in Vaccinology Expertise
ACVASS	African COVID-19 Vaccine Safety Surveillance
BECOME	Beyond COVID Monitoring Excellence
CDC	U.S. Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness Innovations
CoP	Correlates of protection
DSMB	Data Safety Monitoring Board
EUA	Emergency use authorisation
FDA	U.S. Food and Drug Administration
GBS	Guillain-Barré syndrome
GP	General Practitioner
GVDN	Global Vaccine Data Network
HIC	High-income countries
IABS	International Alliance for Biological Standardization
IMI	Innovative Medicines Initiative
JCVI	Joint Committee on Vaccination and Immunisation
LMIC	Low- and middle-income countries
LRTI	Lower respiratory tract infection
MHRA	Medicines and Healthcare products Regulatory Agency
mAb	Monoclonal antibody
mpox	Monkeypox
NHS	National Health Service
NIMS	National Immunisation Management Service
O/E	Observed-to-expected
PCV	Pneumococcal conjugate vaccines
PERCH	PartnERship to Contrast HPV
PIP	Paediatric Immunisation Programme
PROMISE	Preparing for RSV Immunization and Surveillance in Europe
RCT	Randomised controlled trials
RESCEU	Respiratory Syncytial Virus Consortium in Europe
RSV	Respiratory syncytial virus
RWD	Real-world data
RWE	Real-world evidence
SPEAC	Safety Platform for Emergency vACcines
TTS	Thrombotic Thrombocytopenia Syndrome
UKHSA	UK Health Security Agency
VAERS	Vaccine Adverse Event Reporting System
VAC4EU	Vaccine Monitoring Collaboration for Europe
VSD	Vaccine Safety Data Link
VE	Vaccine effectiveness
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VMED	vaccine-mediated enhanced disease
WP	Work package

could address. It is now an opportune time to leverage stakeholders' efforts and learn how RWE can enhance vaccine decision-making for regulatory and public health purposes.

To facilitate this learning, the International Alliance for Biological Standardization Europe (IABS-EU), in collaboration with Flanders Vaccine, organised a hybrid conference entitled: *"The Role of Real-World Evidence for Regulatory and Public Health Decision Making for Accelerated Vaccine Deployment*". The two-day event was held on 19–20 September 2023 in Leuven, Belgium, and brought together key stakeholders, including renowned vaccine experts from national and international public health authorities, regulatory bodies, industry, academia, and research organisations.

The meeting objectives were to discuss RWE derived from RWD for vaccine development and deployment while sharing experiences and ultimately developing recommendations on the best use of RWE to assist both regulatory and public health decision-makers in future decisions around policies, healthcare services, and the rollout of therapeutics and vaccines. This report summarises the discussions and lessons learned from the participants.

2. The role of RWE in accelerating vaccine deployment

2.1. Accelerated vaccine development in pandemic situations

Helen Rees (WITS Research Health Institute) delved into the use of RWE evidence for accelerated vaccine development in emergency situations.

RWD and RWE generated in outbreak or pandemic situations can inform vaccine development, research agendas, vaccination strategies and dosage adjustments. Several examples support their value in public health emergencies. During the COVID-19 pandemic, RWE was central to helping establish vaccine effectiveness (VE). Data from RWE studies of COVID-19 vaccine rollouts in Denmark [5] and Israel [6] revealed new insights into VE against different variants, hospitalisation, and the impact of additional doses, thus providing complementary data that could not be obtained from clinical trials. In the mpox outbreak, a German study evaluated the MVA-BN vaccine [7], and RWE led to recommendations for prioritising vaccination in high-risk individuals.

Further examples of outbreak-related RWE have come from LMIC; for example, the 2016 yellow fever outbreak in Angola and the Democratic Republic of the Congo was also a significant concern due to a shortage of vaccine doses. A fractional dose was used to manage the outbreak, and the decision was based on the results of limited safety and immunogenicity data from clinical trials, including a prospective study in Brazil [8]. The RWD prospectively collected during this outbreak has allowed for the development of WHO's recommendation on the use of fractional doses of the yellow fever vaccine and informed the WHO 2017 research agenda on remaining gaps in knowledge, e.g., the suitability of fractional doses for different yellow fever vaccines, age groups, and populations, as well as their long-term effectiveness and safety [9]. The 2013–2016 West African Ebola outbreak saw the successful use of the rVSV ZEBOV vaccine, driven by limited data from animal challenge models and clinical studies [10]. Based on vaccine efficacy and VE data generated during the outbreak, this vaccine has been widely used in Ebola outbreak response rollouts and allowed the drafting of a secondary research agenda, looking at long-term protection and use in other groups.

Using RWD instead of RCTs in emergencies raises ethical considerations. Key issues include defining exceptional circumstances, determining the specifications for unproven interventions, assessing the risk-benefit ratio, and clarifying whether the research focuses on individual or collective interests. RWD can provide valuable evidence. Still, its utility depends on data quality and a well-functioning public health system. Concerns about data protection, privacy, and sharing persist, and timing is crucial. Additionally, questions about comparators and the contribution of generated data to new research agendas must be addressed in the context of RWE utilisation.

Jakob Cramer (Coalition for Epidemic Preparedness Innovations (CEPI)) broached the issue of the approach in pandemic or outbreak situations. The choice between RCTs and RWE for generating vaccine-related data depends on two key factors. Firstly, the outbreak dynamics, such as pathogen characteristics, outbreak size (small outbreak, epidemic or pandemic), speed of transmission, duration, and the quality of existing evidence, will inform the study design. Importantly, RWE and RCTs can generate evidence of vaccine effectiveness/efficacy when the incidence is high (e.g., COVID-19). Still, neither can do so when the

incidence is very low (e.g., Nipah virus). The benefit-risk profile is the second factor and depends on the risk appetite of regulators, populations, and political authorities to use a vaccine with limited data. The absence of a control group poses challenges for both RWE and RCTs, as the requirement for well-controlled substantial evidence cannot be generated without an appropriate comparator.

Moreover, ethical considerations arise in some cases when randomly assigning individuals to a control group where no intervention is administered. Ultimately, there is no blueprint strategy. The approach is not an either-or choice between RWE and RCTs but a combination of both or something in between, determined by the unique circumstances of the outbreak.

Time is critical, but much depends on the urgency of evidence generation. Furthermore, scenario-specific approaches are necessary. CEPI's 100-day mission exemplifies that pandemic preparedness requires a paradigm shift to accelerate vaccine development [11]. This shift entails significant front-loading preparedness efforts, breaking barriers between development and intervention, and developing and characterising prototype vaccines for known pathogens. The CEPI toolbox of evidence-generation techniques (e.g., clinical trials, early versus delayed vaccine trials, test negative designs) and priority pathogens could be of interest in preparing for different scenarios. Accumulating this knowledge beforehand would allow the prototype to be rapidly adapted and tested once a pathogen-specific vaccine is needed.

2.2. Real-world evidence in evaluations of PCVs and RSV vaccines

Bradford Gessner (Pfizer) provided insights from a high-income country perspective and based on experience gleaned from efforts of using RWE for regulatory purposes, with a focus on Pneumococcal Conjugate Vaccines (PCV) and Respiratory Syncytial Virus (RSV) vaccines.

Regulatory agencies increasingly recognise the value of RWE, as demonstrated by recent U.S. Food and Drug Administration (FDA) guidelines [12]. However, challenges persist in defining vaccination status, exposure definitions and outcomes. The vaccination status source is the primary limitation of RWE for VE evaluation. Few countries or jurisdictions have accurate vaccination registries. Where data are available, distinguishing between vaccines and manufacturers may not be possible. Potential solutions include a national registry, self-contained health systems, e.g., Kaiser Permanente [13], linking multiple data sources, and tokenisation.

Exposure definition remains problematic even with an accurate vaccination status. Several exposure permutations exist for adult PCV, e.g., PCV-naïve populations or those without prior PCV/PPSV within a specific timeframe. RSV has fewer permutations, as currently, it is a single dose unlikely to last more than two seasons at high efficacy or high effectiveness, thus limiting the data history needed. However, maternal vaccination and monoclonal antibodies will complement each other, further complicating the analysis.

Lastly, outcome definitions in real-world databases (in the U.S. and Europe) frequently rely on restrictive ICD coding, preventing symptom-based definitions, which regulators often prefer. Furthermore, few studies have validated ICD coding with chart reviews, adding uncertainty about observed outcomes aligning with the desired ones. Some examples of potential outcomes for post-licensure analyses of PCV VE include invasive pneumococcal disease (IPD), vaccine-type otitis media, vaccine-type pneumonia or LRTI, and all-cause pneumonia or LRTI. Several RWE/RWD studies on all-cause outcomes [14–19] have been accepted and used by vaccine technical committees across Europe and the U.S. Also, an observational post-marketing requirement study ("RECAP20 Study") using an administrative database allowed a pneumonia indication on the PCV20 label for the FDA [20]. Nevertheless, to what extent regulatory agencies will accept RWE/RWD studies for label enhancement or new indications remains unclear. As mentioned, various complexities exist, and using clinically-defined or all-cause outcomes would address some concerns and raise others.

3. Emergency use authorisation (EUA) of COVID-19 vaccines: regulatory and public health perspectives and actions

3.1. EUA of COVID-19 vaccines: role of RWE and the vaccine monitoring platform to evaluate safety and effectiveness

Hector S Izurieta (U.S. FDA) provided an overview of the U.S. FDA (FDA) regulatory framework for vaccine access, highlighting pathways such as "traditional" approval, accelerated approval, and EUA in response to public health emergencies. Evidentiary standards vary among these pathways, with traditional approval requiring the highest level of direct evidence of benefit. RWE has been used for accelerated approval and EUAs, shortening the time required to access needed vaccines and drugs.

During the COVID-19 public health emergency, the FDA issued guidance for EUA vaccines [21]. For EUA, FDA evaluates whether the known and potential benefits of the vaccine outweigh the known and potential risks, considering the totality of the evidence submitted. The initial EUAs for COVID-19 vaccines were granted after a thorough review of data from large-scale randomised placebo-controlled efficacy trials, enabling authorisation even when the duration of protection was uncertain (for the EUA, the duration of protection was evaluated through a median of 2 months). Post-EUA safety data, especially regarding myocarditis and pericarditis, were rigorously reviewed.

Booster doses received EUAs based on data submitted by the Applicants. Data presented at public open session expert advisory committee meetings included safety/immunogenicity data against the reference (Wuhan-like) strain from approximately 300 adults and RWE from several observational studies that suggested waning of protection during the Delta variant surge among 2-dose Original strain vaccinees [22]. Effectiveness was based on immunobridging analyses. On 21 September 2021, the FDA authorised the booster dose under EUA for individuals 65 years and older, individuals 18 through 64 years at high risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional/occupational exposure [22–24]. This decision, made within the context of the Department of Health and Human Services (HHS) emergency declaration, followed an advisory committee meeting and considered the totality of data available to support the effectiveness of the booster dose and the known and potential benefits and potential risks. Using RWE made it possible to respond promptly to the pandemic with credible, evidence-based regulatory decisions.

In summary, the FDA provides multiple pathways for vaccine access, including accelerated approval (licensure) and EUA (authorisation of investigational products during an emergency). EUAs provide an expeditious pathway for more extensive access to investigational products (other options include expanded access programs and investigational new drug applications) in the context of a declared public health emergency. During the pandemic, the FDA used RWD to inform decision-making for COVID-19 booster vaccines under EUA.

3.2. Real-world vaccine safety evidence and public health decision-making in the United States during the COVID-19 vaccination program

Tom Shimabukuro (U.S. Centers for Disease Control and Prevention (CDC)) presented two case examples highlighting the effectiveness of CDC's vaccine safety monitoring programs in generating actionable RWE. The CDC employs multiple public health surveillance systems to monitor vaccine safety through signal detection, assessment, and clinical consultation. Two of the main U.S. programs include the spontaneous reporting (passive surveillance) system, the Vaccine Adverse Event Reporting System (VAERS), and the active surveillance system, the Vaccine Safety Datalink (VSD).

In the first example of an association between COVID-19 vaccines and specific adverse events, an increase in reporting of myocarditis to

VAERS was observed when mRNA COVID-19 vaccine administration to younger individuals and children began. The risk of myocarditis after receiving Pfizer-BioNTech and Moderna mRNA-based COVID-19 vaccines was increased across multiple age and sex strata and was highest after the second dose in adolescent males and young men [25]. These data were subject to the limitations of passive surveillance but were confirmed by additional VSD data [26,27]. Careful assessment of this information led to FDA updating the regulatory language in EUA documents and package inserts [28]. A study looking at longer-term outcomes showed that most individuals who developed myocarditis after vaccination were judged as fully recovered by their healthcare providers at least 90 days out from their myocarditis event [29,30].

The second example was the unusual reporting of thrombosis with thrombocytopenia syndrome (TTS) after the introduction of the authorized Janssen adenoviral-vectored COVID-19 vaccine. These reports to VAERS were observed within weeks of the Janssen vaccine being introduced in the United States and rapidly recognised, prompting a pause in the use of the Janssen vaccine [31]. Subsequent public health assessments resulted in regulatory action and updated recommendations, thus demonstrating the dynamic nature of public health decision-making, and ultimately, at the manufacturer's request, the FDA revoked the EUA of the Janssen vaccine in June 2023 [32,33].

COVID-19 vaccines were administered under the most intensive vaccine safety monitoring effort in U.S. history. These two examples showed how rapid assessment and interpretation of COVID-19 vaccine safety data during the pandemic informed regulatory action, vaccination policy, and clinical considerations in near real-time. Regarding the safety signal for TTS after the Janssen vaccine, the RWE eventually led to a preferential recommendation for using mRNA COVID-19 vaccines over the Janssen adenoviral-vectored COVID-19 vaccine. This RWE was, therefore, essential in protecting and informing the public during the COVID-19 vaccination program.

4. Experiences with using RWE for regulatory and public health decision-making on COVID-19 vaccines

4.1. RWE use for COVID-19 public health decision-making in the United Kingdom (UK)

Nick Andrews (UK Health Security Agency, UKHSA) and **Katherine Donegan** (MHRA) presented perspectives from the UK, sharing experiences and lessons learned using RWE for COVID-19 public health decision-making.

Nick Andrews (UKHSA) shared that COVID-19 public health decisions in the U.K. encompassed various topics, including vaccination prioritisation, dosing intervals, age recommendations for specific vaccines, booster strategies, VE against new SARS-CoV-2 variants to inform on the need for non-pharmaceutical interventions (NPIs), and pregnancy and paediatric vaccination recommendations.

To guide these decisions, the UKHSA, other UK Public Health Institutes, the Medicines and Healthcare products Regulatory Agency (MHRA) and other groups, including academia, provided evidence to the Joint Committee on Vaccination and Immunisation (JCVI), which advised the UK government [34,35]. Recommendations were based on benefit-risk assessments of data from an array of sources, including RWE on VE (different endpoints, manufacturers, dosages, variants, and timeframes), mathematical models predicting future waves of SARS-CoV-2, data from general practitioner (GP) systems on COVID-19 incidence and severity, and information on vaccine adverse events. VE and safety were key drivers in the benefit-risk assessments.

One significant achievement was the establishment of a new register, the National Immunisation Management Service (NIMS), in late 2020. With this system, most of the effectiveness and safety studies were possible. NIMS rapidly collected detailed data on COVID-19 and flu vaccinations, including manufacturer and batch information. It allowed for quick analyses and provided a population denominator file with the unique National Health Service (NHS) numbers, meaning both vaccinated and unvaccinated individuals could be identified. NIMS also allowed data to flow back to GP records, making it an invaluable tool for public health decision-making. While NIMS proved to be a valuable resource for exposure information, there is a need for better access to detailed laboratory-type testing outcome data from hospital records, which would aid in assessing safety signals more effectively.

In terms of lessons learned, establishing a national vaccine registry with a population denominator and unique ID (NHS number) is crucial for informed public health decisions. Utilising multiple studies with diverse methods increases the robustness of the data. Furthermore, effective communication among stakeholders is vital to prevent duplication of efforts and misunderstandings.

Challenges for the future include maintaining data sources like NIMS as COVID-19 funding decreases, addressing bias in RWE generation, and exploring how manufacturers can utilise RWE generated by public health institutes for regulatory purposes. Collaborative efforts in data-sharing agreements with manufacturers could improve the overall effectiveness of RWE in decision-making.

Ultimately, using RWE in COVID-19 public health decision-making in the UK was successful. However, there is room for improvement in data access and communication to ensure the best possible outcomes.

Katherine Donegan (MHRA) presented experiences in practice from the UK's COVID-19 vaccine safety surveillance.

Despite the successful deployment of COVID-19 vaccines, various challenges emerged. One primary issue was the limited availability of long-term safety data, particularly for high-risk populations. Moreover, the concurrent impact of COVID-19 on the healthcare system, the rapidly evolving evidence base, and the public perception of an "accelerated" vaccine further added to the complexity. Consequently, it was more important than ever to have near-real-time and proactive vigilance, including mechanisms for surveillance, timely and consistent risk communication, and global networks to share knowledge, experience, and information.

To address some of these challenges, the MHRA, in collaboration with public health partners, developed a comprehensive vigilance strategy that proactively ensured robust data collection, sharing, and access while maintaining a continuous benefit-risk assessment process guided by expert working groups to inform vaccination policies. The strategy's key pillars included the "Yellow Card scheme" for active and passive reporting of adverse events, rapid cycle analyses in electronic healthcare record data for specific adverse events of special interests (AESIs), and formal epidemiological studies.

Evaluating some safety signals, particularly TTS, was challenging due to public and political pressure to act quickly, a lack of a case definition and relevant background data, and inadequate recording of events in electronic healthcare records. Case reports were a crucial primary data source for decision-making, and bespoke studies were required with active case collection as part of a holistic approach. This issue highlighted a pressing need for more immediate access to hospital admissions data to inform more rapid evaluation. For the myocarditis and pericarditis safety signals [36–38], rapid cycle and observed-to-expected (O/E) analyses were helpful. However, there were challenges in interpreting case reporting and establishing the relevance of background rates. In response, RWE studies were quickly conducted to provide more insights. Effective risk communication benefited greatly from placing the risk in the specific disease context [39]. Additionally, conducting country-specific analyses was valuable in accounting for schedule variations and other factors.

In summary, key lessons and challenges included the importance of case reports and the need for enhanced data infrastructures to identify adverse events rapidly. Understanding background rates for signal detection refinement and risk communication was necessary; however, applying these rates in O/E analyses should not be a one-size-fits-all approach and requires careful consideration. Furthermore, multiple studies with alternative designs and data sources are essential for a

comprehensive understanding of vaccine safety, and effective collaboration between researchers and regulatory agencies is crucial to ensure data quality and reduce duplication. Quicker and more comprehensive evidence on vaccine safety during pregnancy was also identified as an urgent need, as well as the necessity to remain alert for novel data around specific signals such as menstrual disorders.

4.2. Vaccine monitoring collaboration for Europe (VAC4EU) association: experiences, lessons learned, remaining challenges

Miriam Sturkenboom (University Medical Center Utrecht) shared the experiences and lessons learned by the VAC4EU association during the COVID-19 pandemic.

VAC4EU implements the Innovative Medicines Initiative (IMI)-ADVANCE project blueprint and aims to collaboratively generate the best RWE on vaccine coverage, benefits, and risks in Europe [40,41]. The consortium conducts studies using electronic health records and employs a common protocol, transforming data into a common data model and distributed analytics to generate conclusive evidence. Extensive quality checks are also performed at multiple levels to ensure that the data are fit for purpose [42]. VAC4EU has been involved in various COVID-19 studies [40,42–47], where the entire network collaborates, contributing data and expertise. The lesson learned is that while rotating roles allow for rapid scale-up, the heterogeneity in approaches presents a challenge, and it is now necessary to harmonise how work is being done.

From the completed studies, results such as background rates [47] were made rapidly available to stakeholders for analysis. Having a list of AESIs was positive, but some countries faced difficulties accessing data, resulting in delays. Results from the near real-time monitoring of the AESI study showed significant increases in post-vaccination rates [46]. The challenge, however, was making the appropriate adjustments to avoid false positive signals due to the highly channelled initial vaccine rollout. In a third study, cohort event monitoring was done across 13 countries using different systems but a common protocol and data model, collecting data from 650,000 vaccinees [45]. The lessons learned were that it is essential to have infrastructure and approvals ready before vaccine rollout and that cohort event monitoring is a very resource-intensive system. Evaluation studies indicated associations between certain vaccines and safety outcomes (e.g., myocarditis) [48]. However, the challenges were that age and gender are important effect modifiers for some safety outcomes. Even with ample data, the power to look at brand and dose-specific estimates is limited.

In conclusion, ADVANCE had created, prior to the pandemic, an ecosystem for data, people, and method readiness, and it was beneficial that VAC4EU existed to provide RWE during the pandemic. Sharing tools within the community allowed for successful and timely responses to questions from regulators and manufacturers. However, there were challenges in meeting the speed, response times and the six-monthly reports required by regulators. These constraints left limited time for profound discussions about results and methodologies.

4.3. COVIDRIVE: experiences, lessons learned, remaining challenges

Kaat Bollaerts (P95 Epidemiology & Pharmacovigilance) shared the experiences and lessons learned from the epidemiological studies performed by COVIDRIVE, which is a public-private partnership initiated to evaluate brand-specific COVID-19 VE in Europe [49]. These studies are regulatory commitments endorsed by the European Medicines Agency (EMA).

COVIDRIVE collaborates with a network of hospitals, GP networks, and population registers. The partnership's guiding principles include open collaboration between public and private stakeholders, long-term perspective, knowledge sharing, and cooperation. COVIDRIVE allows all partners to join its data collection efforts, reducing study costs and facilitating more extensive studies, but enabling data access for secondary use is still on the agenda. COVIDRIVE is well-prepared to deliver high-quality epidemiological studies.

The first study implemented focuses on brand-specific COVID-19 VE against COVID-19 hospitalisations. Data collection began in September 2021 across several European countries, and the evidence generated has been used for regulatory submissions by multiple vaccine companies. Results from AstraZeneca's first interim analysis were published in 2023 [50].

The lessons learned from the collaborative efforts in conducting regulatory-required studies reveal that different vaccine manufacturers, public partners, and study contributors can work together effectively. This success is attributed to the willingness to share experiences, regulatory feedback, scientific expertise, and resources, such as a network of study contributors. The key to this success is adaptability, allowing adjustments to be made in response to changing COVID-19 epidemiology and robustness in the face of evolving vaccine products on the market. However, the effort has faced challenges, as it does not neatly fit within established company templates and standard operating procedures. Agreeing on an acceptable quality assurance framework for all parties has also been problematic. Issues around roles and responsibilities, shared study budgets, and changes to the budget due to companies leaving or joining the study have led to prolonged discussions. Additionally, relying solely on private funding has caused disruptions in the continuity of resources for data collection. Nevertheless, COVIDRIVE aims to sustain its platform in preparedness for new vaccines (e.g., RSV) and potential future pandemics.

4.4. Example of use of RWE to support decision-making

Sylvia Taylor (AstraZeneca) presented an example of how RWE supported global decision-making for the use of the Oxford AstraZeneca COVID-19 vaccine.

AstraZeneca and the University of Oxford launched a public-private partnership to develop a COVID-19 vaccine using Oxford's adenoviral vaccine platform early in the pandemic. Key to approvals for EUA and authorisations by the EU and WHO was the Oxford-led Phase III trial showing 70% VE against symptomatic COVID-19 [51]. From that point on, there was a linked interplay between clinical trial data and RWD to increase understanding of various aspects, including protection from severe disease, the overall VE, VE in older age groups, booster doses, and against different variants of concern. The phase III trial enrolled younger adults first and had, therefore, limited efficacy data for older and elderly individuals, leading regulatory agencies to consider these results to be inconclusive in those age sub-groups. In February 2021, the first RWE was released, showing that the vaccine was highly effective in older individuals [52], raising external confidence. Clinical trial results from the US would later confirm these RWE results [53]. RWE also played a key role in showing continued high effectiveness against the different variants as they arose.

Understanding the benefit-risk profile was also critical, especially concerning reported cases of TTS. Although EMA considered there was a positive benefit-risk ratio across age groups, differences by age group led most European countries' NITAGs to limit vaccination recommendations for this vaccine to older adults. The WHO continued recommending the vaccine as part of booster dose vaccination programs and heterologous dosing recommendations. The continued global use allowed the effectiveness of booster doses to be assessed and was shown to be at a similar and high level as mRNA vaccines in relation to severe COVID-19 [54]. As the vaccine became less used globally, the VE of second boosters could only be assessed on data from two countries: Thailand and Brazil [55,56].

It is crucial to be aware that much COVID-19 VE data were driven by data from HICs: the US, UK, Israel and Canada [57]. Therefore, if a vaccine was not approved in one of these HICs, the same level of evidence could not be generated, impacting the ability to monitor the vaccine's effectiveness and benefit continuously. Another important

consideration relates to the healthcare infrastructure and limitations in LMICs, where vaccine campaigns are rolled out later and potentially slower than in HICs, delaying the availability of effectiveness data.

Lessons learned that are critical for the next pandemic include the importance of harmonisation and collaboration with health authorities, the need for advanced planning, and international cooperation on data infrastructures, including the possible set up of cohorts ahead of time for RWE generation. It is also essential to ensure equitable data generation from both HICs and LMICs and acknowledge that lower-income countries need data that applies to their situation to make timely global decisions.

4.5. Global Vaccine Data Network (GVDN): genesis, experience, lessons learned, remaining challenges

Steve Black (GVDN) presented the lessons learned and challenges encountered in the GVDN COVID-19 vaccine safety studies. The GVDN is a growing network of sites which agree to conduct globally coordinated active surveillance and epidemiologic vaccine studies that are multinational and investigator-led [58]. In 2021, activities commenced on the safety of COVID-19 vaccines. The projects vary from background rates to outcome or association studies for myocarditis, vaccine-mediated enhanced disease (VMED), and genomic and maternal immunisation studies.

Regarding the current status, background rates of COVID-19-associated AESI have been published [59], a background rate dashboard is available [60], and an observed vs expected dashboard will be made public shortly. Significant progress is being made in association studies related to TTS, Guillain-Barré syndrome (GBS), and myo-/peri-carditis. Additionally, cohort studies for VMED and maternal immunisation are currently underway. Genomic studies are actively collecting specimens for myocarditis, pericarditis, GBS, and VITT, with the results set to be shared within the network at a meeting planned in Annecy in April 2024. Genomic studies could help improve understanding of the pathophysiology of adverse events and potentially facilitate personalised vaccine selection for at-risk individuals.

Concerning lessons learned, the GVDN COVID-19 vaccine safety studies were launched a year into the pandemic, lacking pre-existing infrastructure. This led to a slow start due to the necessity of relationship-building, trust establishment, contract arrangements, protocols, and ethics framework development. Involving parties lacking the capability to perform studies was suboptimal. Hands-on medical record reviews, a key component of many protocols, proved challenging to implement promptly at various sites. Moreover, including low-income countries has required the development of a different data collection system.

For the future, GVDN is developing a rapid-response protocol to address new safety concerns. There is also a need for decentralised infrastructure and sustainable funding. Further challenges are that some study sites have no or limited electronic healthcare data. Some sites have inpatient data only, while others have outpatient, inpatient, laboratory, and radiology data. Data access times vary among sites, but this variability is embraced as a strength for capacity-building and tailored involvement in studies according to site capabilities.

4.6. African Leadership in Vaccinology Expertise (ALIVE) network: experience, lessons learned, remaining challenges

Clare Cutland (Wits-Alive) presented background information on two active COVID-19 vaccine safety studies in Africa: The African COVID-19 Vaccine Safety Surveillance (ACVaSS) and the South African (SA) studies. ACVaSS is a collaboration funded by Gavi, the Vaccine Alliance, set up to establish active COVID-19 vaccine safety surveillance across 48 study sites in eight countries. The CDC funded the second study through a grant to the GVDN, and it was conducted at five study sites across South Africa [58].

Both studies aimed to set up a system of hospital case-based surveillance of a predetermined list of AESIs following COVID-19 vaccine vaccination. The primary objective was to estimate the risk of these predefined AESIs with acute onset in a set period following vaccination using a self-controlled risk interval study design. The secondary objective was to contribute data to the GVDN association studies.

The studies included patients admitted with a possible AESI and followed until hospitalisation outcome. The first patients were enrolled in the SA study in October 2021 and the ACVaSS study in April 2022. Enrolment was completed on 31 March 2023. The ACVaSS and SA teams captured data in a database developed in REDCap [61]. In total, 12,700 patients were enrolled in the two studies, 6795 in the ACVaSS study and 5961 in South Africa; more data will be available through publications in the coming months.

Several key lessons were learned from the studies. Funding and contracting were challenging and time-consuming; reimbursive grants are particularly problematic in LMICs and must be avoided where possible. Ethics approval took 7–120 days, depending on the study site, and significantly impacted the start of the studies. Two databases were developed, which posed challenges with merging and analysing data, but REDCap functioned well overall. A significant issue was access to vaccination source data, which was available only for a minority of patients. Vaccination data access and validation were difficult, mainly because an electronic data system was only available in South Africa, with limited accessibility. Paper-based records were also hard to access and often incomplete. Synchronisation issues and duplicate patient entries occurred at upload of data from tablets. Data specificities (e.g., Gregorian calendar in Ethiopia), language barriers, varying staff levels, and facility disparities across different countries posed additional challenges. REDCap introduced a translation feature within the database to address some of these issues.

5. Improving the use of RWE for regulatory and public health decision-making

5.1. The BeCOME project and its RWE roadmap

Philip Bryan (GSK), speaking on behalf of the Beyond COVID Monitoring Excellence (BeCOME) initiative Steering Committee, gave insights into how the COVID-19 pandemic posed significant challenges for vaccine manufacturers, with multiple and expedited regulatory requirements for pharmacovigilance (PV) and RWE generation. The COVID Vaccine R&D Sharing Group (Nov 2020–March 2022) was established in response to these challenges, facilitating unprecedented cooperation among typically competitive pharmaceutical companies. The primary focus was to share best practices and to seek solutions to enable the delivery of high-quality, real-world safety and effectiveness evaluations, implement safety reporting and signal detection requirements, and engage with global health authorities on critical topics.

This collaboration yielded a paper published in early 2023, leading to the inception of the BeCOME initiative [62,63]. BeCOME aims to sustain the cooperative and innovative momentum from the pandemic and apply these lessons and challenges to routine immunisations and therapeutics. The initiative acknowledges the importance of aligning regulatory requirements, rather than harmonising, as country requirements differ, and optimising resource utilisation for future pandemics, especially when the pool of expertise is limited.

BeCOME currently operates under the International Federation of Pharmaceutical Manufacturers and Associations and has identified priority topics for collaboration. These include signal detection, safety study conduct, pregnancy surveillance, vaccine benefit studies, enhancing vaccine PV in LMICs, and digital innovation to streamline PV processes. In June 2023, BeCOME organised a multi-stakeholder conference where delegates openly discussed the challenges and priorities in the field. The objective was to achieve broad alignment on which priority areas needed to be addressed and develop a five-year plan for

collaborative solutions. The conference recognised the importance of RWE in benefit-risk decision-making, encompassing both active and passive surveillance and published data. Key priorities identified included improving global data source awareness and leveraging, aligning health authorities in guidance and acceptability of RWE, understanding the value of background incidence data for signal detection, and enhancing surveillance infrastructure and data sources in LMICs. The conference also recognised the need to engage with patient groups in this roadmap.

In conclusion, the BeCOME initiative stemmed from a successful non-competitive collaboration that addressed common vaccine development and deployment challenges. This initiative should evolve into a global, multistakeholder collaboration with appropriate and transparent governance to foster trust and tackle the shared priorities in enhancing vaccine benefit-risk monitoring to benefit public health. A BeCOME publication, including the conference proceedings and options for a public-private partnership/cooperation, is in development.

5.2. Brighton Collaboration's role in establishing an RWE infrastructure for vaccine safety during early deployment

Robert Chen (Brighton Collaboration) presented an overview of the Safety Platform for Emergency vACcines (SPEAC) project.

Since 2000, the Brighton Collaboration has been instrumental in enhancing vaccine research by standardising methods for monitoring vaccine safety [64]. As vaccine safety is generally assessed indirectly, the absence of multiple adverse events following immunisation (AEFIs) is an essential indicator. The challenge lies in standardising case definitions, as rare AEFIs might be overlooked without established criteria. With sponsors employing their approaches, safety signals may be missed in individual clinical trials.

The Brighton Collaboration has developed over 70 standard case definitions and, in collaboration with CEPI, initiated the SPEAC project to help mitigate the risk posed by missed signals through harmonising vaccine safety assessments across its portfolio [65]. In 2022, SPEAC was renewed by CEPI to help support its "100 Day Mission" [11]. Historically, safety assessments in pre-approval trials were frequently distinct from post-approval RWE, creating a barrier to a comprehensive lifecycle approach. Additionally, large administrative datasets, standard in HICs, were often absent in LMICs.

SPEAC's work packages address several critical aspects. Key initiatives include expanding the local expertise pool through training in Data Safety Monitoring Boards (DSMBs) and establishing meta-DSMB liaisons with CEPI-funded developers. Standards and tools for AESI identification have also been developed utilising standardised case definitions and creating companion guides. Vaccine Safety Templates have also been designed to facilitate standardised benefit-risk assessments. SPEAC is digitalising Brighton case definitions and other guidelines to facilitate timely evaluation and use in existing processes and infrastructures for vaccine safety surveillance. Attention has been given to special populations (pregnancy, paediatric, and immunocompromised), with tools developed for their inclusion in vaccine development, evaluation, and implementation for emergency pathogens. Lastly, SPEAC plans to leverage mobile phone applications and pregnancy registry protocols for RWE active vaccine safety surveillance; this will be especially relevant in LMIC settings.

In summary, the SPEAC initiative aims to develop tools for vaccine safety assessment in the pre-introduction phase that links with post-introduction. To do so, an RWE infrastructure for vaccine safety during early deployment is being established. This model applies to AEFIs for vaccines targeted at other pathogens, including CEPI-pathogens.

6. Experiences using RWE for health economics and public health decision-making on non-COVID-19 vaccination in Belgium

6.1. Exploring the cost-effectiveness of RSV preventive interventions in children with RWE (IMI-RESCEU project)

Xiao Li (University of Antwerp) presented a cost-effectiveness analysis on RSV preventive measures. This analysis, funded by the Innovative Medicines Initiative (IMI) projects RESCEU (Respiratory Syncytial Virus Consortium in Europe) and PROMISE (Preparing for RSV Immunization and Surveillance in Europe), examined the efficacy of a single dose long-acting monoclonal antibody (mAb) and maternal immunisation against RSV.

RSV imposes a considerable disease burden in Belgium, especially in children, and a dedicated dashboard from Sciensano illustrated a clear seasonal pattern [66]. The RSV immunisation landscape features multiple manufacturers with candidates progressing from Phase I trials to market approval [67]. Advice on RSV programmes has been issued by bodies such as JCVI and ACIP [68,69]. In both cases, multi-country cost-effectiveness analysis has been used to generate robust and up-to-date RWE to inform decision-making. RESCEU, specifically, focuses on the economic impact of the RSV disease burden across Europe and has published several health economic studies using RWE, including economic burden, health-related quality of life, model comparison studies and multi-country cost-effectiveness analysis [70–73].

The presented cost-effectiveness analyses used a static model to compare different RSV programmes, namely the year-round maternal vaccine and year-round and seasonal mAb programmes [71,73,74]. RWE was pivotal in estimating the RSV disease burden. National registry retrospective studies, quality-of-life studies, and time-series analyses were employed to understand the baseline RSV disease burden [70,75]. The highest disease burden and associated healthcare costs are observed in infants aged zero to two months. However, the greatest number of RSV cases, encompassing primary care visits, occurs in the slightly older cohort of three to five months, resulting in a significant loss in quality of life.

The analysis had limitations, such as difficulties accessing data on accident and emergency visits across Europe. Additionally, the seasonal programmes for maternal RSV immunisation faced challenges in implementation due to timing constraints. Non-medically attended cases and herd immunity were not included in the analysis.

In summary, the analysis considered country-specific disease burdens, intervention types, their costs, and the optimal timing for administration, aiming to identify the most cost-effective interventions. The use of RWE in decision-making about vaccination programs depends on factors such as the country setting and the country-specific disease burden (RSV hospitalisation and quality-adjusted life years associated with RSV disease). The choice between no programme, a year-round maternal immunisation programme, a seasonal mAb programme, or a catch-up mAb programme varies based on intervention costs and a country's willingness to pay, which often vary between countries. The perspective taken, whether from the payer or societal, is also significant.

6.2. Public health impact and return on investment of Belgium's Paediatric Immunization Program (PIP)

Olivier Ethgen (Université de Namur) shared the outcomes of a modelling study evaluating the public health impact and return on investment of Belgium's paediatric immunisation program (PIP) [76].

Vaccines are among the most cost-effective public health interventions available. However, vaccination programs remain highly vulnerable to budget cuts. Their benefits are not necessarily directly observable and, as such, may not be perceived immediately. Effects such as reductions in disease complications, productivity gains, and improvements in quality of life may not fully be reflected in the economic

evidence. In the model, two perspectives have been taken. First, a healthcare perspective that considers the cost of vaccinations and the direct medical costs of managing the diseases when they occur. Second, is a societal perspective that takes, in addition to the healthcare perspective, all the productivity loss resulting from the diseases, the premature mortality and the time needed to travel to get vaccinated, including patients and caregivers.

The public health impact and the return on investment of the PIP were assessed in a Belgian birth cohort with a decision tree model. At the time of the analysis, the PIP consisted of six vaccines protecting against eleven pathogens. A comparison of two counterfactual scenarios (with or without the PIP) showed that the PIP provides large-scale prevention of disease-related morbidity and premature mortality. Indeed, across 11 pathogens and over the lifetime of a birth cohort of 117,800 children, the PIP would prevent 226,324 infections and 214 deaths. This was associated with significant savings for the healthcare system and society, with 1.4 euros saved for the healthcare system and up to 3.2 euros for society, for every 1 euro invested in the PIP. Limitations of the study included disease underreporting, which was conservatively not applied in pre-vaccine or post-vaccine incidence estimates; vaccine public prices that did not necessarily reflect tender prices and were potentially overestimated; diseases were all modelled separately without allowing for possible interactions between them; certain diseases were only modelled for younger ages based on available data; the model only included paediatric vaccines; data were limited for some diseases; and all model inputs were assumed to be constant over the modelled time horizon. Nevertheless, the results support the continued investment in the PIP to sustain its positive public health and financial impact.

6.3. PERCH (PartnERship to Contrast HPV) project

Hélène De Pauw (Sciensano) introduced the PartnERship to Contrast HPV (PERCH) project, conducted in 18 European countries and with 34 partner organisations [77]. The project aligns with the WHO's goal of achieving at least 90% HPV vaccine coverage among girls by the age of 15 years.

The project is divided into seven work packages (WP), detailed on the project website, with the last four being almost mandatory for participating countries. WPs 4 and 5, led by the Belgian health institute Sciensano, focus on integrating HPV vaccination into national policies, sustainability, and monitoring. To achieve the goals of WP4, Sciensano conducted a survey, collecting data from 17 countries on how HPV vaccination and screening are implemented and assessing the barriers and facilitators for vaccination, vaccine supply and vaccination, and the process of collecting and compiling HPV vaccination data. The results will be published and publicly available on the website by the end of 2023. WP5 includes monitoring vaccination coverage, investigating the possibility of linking individual patient data from mainly vaccination and cancer registries and investigating the impact of COVID-19 on HPV vaccination campaigns. Regarding the impact of COVID-19, a systematic review of publications is planned to collect all information to identify barriers and processes to avoid disruptions in the future.

Achievements of WP 4 and 5 include the establishment of a governmental advisory board, a list of countries that should integrate HPV vaccination, a report on updated evidence on HPV vaccine safety and efficacy, including the effectiveness of one-dose vaccination, status reports on implementation of HPV vaccination services, and a comprehensive table to collect HPV vaccination data.

For Belgium, the project intends to address the need for precise estimation of HPV vaccination coverage, which is essential because different regions have separate registers. The goal is to ensure the accurate recording of HPV vaccine administration in existing platforms, combine these databases into a single register, and link them with other health-related data sources like cancer and mortality registers. The plan is also to examine the early impact of HPV vaccination on HPV prevalence and cervical lesions through data linkage between vaccination and screening. The dream is to convince decision-makers to support and fund these operations, which could facilitate research and studies like Sweden's successful model [78], linking various registers to assess HPV vaccination's impact on cervical cancer and other related diseases to benefit public health.

6.4. Health information for policy decision-making on vaccination

Laura Cornelissen (Sciensano) presented Belgium as a case study for RWE use in a small European country and the existing hurdles.

RWE has been used in Belgium to inform vaccination strategies, procurement, and reimbursements and contribute to European collaborations. One representative example is related to invasive pneumococcal disease (IPD), with national RWE guiding PCV strategies [79]. PCV vaccination is part of the country's routine PIP. Every four years, a new tender is launched to determine which PCV vaccine to include, with price being a significant factor. After a switch from PCV 13-valent to PCV10, genomic surveillance data revealed a sharp rise in IPD cases caused by Serotype 19A. In response to this case surge, authorities reverted to the higher-valency vaccine [79].

As repeatedly emphasised, collaboration is essential. Even though having local data and being able to tailor decisions to local epidemiology is preferred, it is still crucial to contribute to European collaboration. Timeliness is a challenge, with administrative databases in Belgium having a two-to three-year delay, e.g. due to reimbursement system particularities. Digitalisation and reimbursement system changes are underway to address this barrier, but much remains to be done. Harmonisation of case definitions and coding language is another challenge, particularly with diverse laboratory data. Data linkage is potentially powerful but hindered by data privacy issues and a lack of a legal framework for pooling data.

Moreover, much health information, e.g., on infant vaccination in Belgium, must be in digital format. Much data exists, but even in Belgium, it is not well accessible. The federated organisation is a barrier, as data exist in different regional databases. There is a willingness to collaborate, but too often, it depends on personal networks and awareness of the existence of these datasets.

COVID-19 funding led to progress, but it required significant human resources. Sustainable practices are needed, as funders' expectations need to align with their willingness to pay. Belgium has excellent linkage potential due to national identifier numbers, and automated data extraction efforts have been initiated. However, a clear legal framework and European support may be necessary. Sciensano's vague mandate and differing GDPR interpretations between national and international stakeholders hinder progress.

Regarding data sharing related to vaccination certificates, people's consent is often lacking; thus, implementing an opt-out system might be more efficient than an opt-in. Efforts are being made within the European health data space in this direction and will hopefully lead to progress in the field. Also, a Belgian health data authority should reduce fragmentation and create data catalogues. Public-private collaboration is possible, but the perceived conflicts of interest must be addressed, particularly in post-marketing data collection and distribution. Public health institutes should also ensure independence to maintain public trust.

6.5. Improving the quality of evidence for decision-making through innovative design and collaborative studies leveraging RWE platforms

Laurence Torcel-Pagnon (Sanofi) shared experiences on improving the quality of evidence for decision-making with two proof-of-concept projects on influenza vaccine effectiveness evaluation.

While the use of RWE for informed decision-making is not new, it has been primarily used for safety signal evaluation, and the digital expansion in healthcare offers the possibility to generate evidence on vaccine usage and its performance in real-world settings. However, the potential

for bias and confounding in observational studies poses additional challenges for VE evaluation. The influenza vaccine's performance varies across seasons, populations, settings, and outcomes. RCTs may not represent the general population with various medical conditions and limit the assessment of broader clinical outcomes and the number of seasons. Assessing influenza VE in countries or regions with scattered vaccine type utilisation, heterogeneous policies, and uptakes further underscores the need for innovative, fit-for-purpose RWE platforms to produce robust vaccine performance estimates.

Two such fit-for-purpose approaches to improve the quality of RWE for VE evaluation are DANFLU-1 [80] and DRIVE [81,82]. The concepts have the same goal but were approached from very different angles.

DANFLU-1 aimed to assess the relative VE of a high-dose versus standard-dose influenza vaccination against broader clinically meaningful endpoints. The idea was to confirm findings from previous observational research through a hybrid randomised-real-world study. DANFLU-1 sought to evaluate the feasibility of integrating individual randomisation into routine seasonal influenza vaccination practice and using administrative health registries to collect baseline, outcome, and safety data. The results established that conducting such a pragmatic randomised study, utilising existing infrastructure and relying solely on registry-based data collection was feasible. This innovative RWE study design paves the way for a future, fully powered study (DANFLU-2), which will build upon the DANFLU-1 learnings and successes. Recruitment is underway, and the aim is to evaluate the relative VE of high-dose quadrivalent influenza vaccine vs. standard-dose quadrivalent influenza vaccine against influenza or pneumonia and cardio-respiratory hospitalisations in older adults using Danish nationwide administrative health registries for data collection, clinical outcomes follow-up, and safety monitoring [83].

The DRIVE approach aimed to fulfil regulatory obligations by assessing the brand-specific absolute VE for influenza vaccines used against laboratory-confirmed influenza and across seasons in the EU. DRIVE had a test-negative and cohort real-world study design done through a collaborative RWE platform between several public health institutes and vaccine companies. The feasibility results showed that it was possible to set up an efficient and cost-effective study platform operating through a transparent public-private partnership model. The platform provided brand-specific vaccine effectiveness estimates for 8 of the 12 vaccines used in the EU, and an annual joint report was submitted to EMA. However, several limitations were encountered. Despite focusing on populations with the highest disease burden of influenza and relatively high vaccine coverage, getting precise estimates on several brands for informed decision-making remains challenging. The EMA deemed the data insufficient for decision-making, and public-private partnership hesitancy and a parallel public-only initiative remain an obstacle to the scale-up of RWE collaborative platforms, which should be tackled more broadly by EU and national institutions. Nevertheless, the DRIVE platform was unique in offering consistently brand-specific results for each season in the EU and a successful proof-of-concept that deserves clarity in stakeholders' roles and responsibilities on vaccine monitoring at the EU level for further action.

These two concepts offer promising solutions to change the use and perception of RWE to support influenza vaccination programs and vaccine coverage. Implementation and acceptance warrant further steps and multi-stakeholder discussions to move to actionable decision-making.

7. RWE decision-making in pandemic situations-participants' Viewpoint

With the help of breakout sessions, participants engaged in focused discussions and shared experiences and insights on successful and not-so-successful decisions based on RWE in pandemic situations.

7.1. Successful decisions based on RWE during the COVID-19 pandemic

Participants identified several successful decisions that were crucial in shaping public health strategies during the COVID-19 pandemic. Dosing regimens were optimised by determining the right timing for booster doses and fine-tuning dosage intervals. RWE also informed guidance on the interchangeability of vaccines, particularly the effectiveness of heterologous vaccine regimens. Target population guidance was also enhanced, allowing the vaccination of special populations such as immunocompromised individuals or those with renal impairment.

RWE informed the decision-making process regarding relaxing non-pharmaceutical interventions, ensuring a timely and practical approach while maintaining confidence in vaccine effectiveness amidst emerging virus variants. Health authorities successfully assessed the performance of vaccines against new variants, guiding vaccination strategies accordingly. Access to vaccine effectiveness data through platforms like the International Vaccine Access Centre (IVAC) website proved beneficial. The importance of sustaining data infrastructure and linkage beyond the pandemic was also emphasised to accelerate non-emergency vaccine deployment.

Participants felt that RWD were successfully integrated into lifecycle management, including boosters and safety considerations. However, challenges in the initial authorisation process were acknowledged, with a proposed solution being the exchange of data between countries where the vaccine already has EUA to countries where it is under evaluation. RWE from Israel informed many of the booster campaigns, but the VE data was for a particular vaccine brand; the need for a broader exchange platform was recognised.

The concept of rolling reviews was appreciated for its efficiency. Regulatory transparency, or the openness of regulatory bodies in sharing their processes and decisions, was enhanced by online meetings accessible globally, significantly advancing public trust in the regulatory process. The infrastructure for RWE generation also saw notable improvements compared to previous pandemics, attributed to data collection and technology advancements.

Positive political influence was highlighted as crucial in encouraging studies and RWE gathering, emphasising the importance of collaboration with governments in facilitating data collection and research efforts. Swift reactions to safety signals, as demonstrated by the US response to TTS signals from the Janssen vaccine, underscored the value of real-time data monitoring in ensuring vaccine safety. Lastly, efforts toward data standardisation, such as CEPI-sponsored projects with clear data rules, were appreciated for improving data quality and usability.

7.2. Challenges and less-successful decisions based on RWE

Regarding the challenges and less successful decisions based on RWE analysis related to vaccines, predominant concerns related to data issues were most frequently highlighted. The limited availability of vaccine data using non-mRNA platforms hindered comprehensive analysis and comparison. Indeed, smaller companies struggled to generate robust RWE with limited patient data in the presence of dominant market players. For example, the RWE from Israel informed many booster campaigns, but the VE data was exclusively on one mRNA vaccine brand. Additionally, poor quality data from some settings, characterised by unclear definitions of case fatality rates and infections, made analysis challenging. The scarcity of RWD on virus transmission and VE in preventing transmission also restricted comprehensive analysis. There was also insufficient robust pregnancy data, which affected vaccine uptake among pregnant women, emphasising the need for better safety and efficacy data for this high-risk population.

Furthermore, some countries relied on others for data due to infrastructure and resource limitations, which led to delays. Some potentially valuable data sources remained underutilised, e.g., population surveys to better identify risk groups or adjust for potential confounders. The timing of data collection posed an additional challenge, as vaccination

programs prioritised vulnerable populations but collected effectiveness data for this group last, creating a data lag.

Suboptimal safety assessment methods, like observed/expected ratios, limited evaluation of certain adverse events. There were challenges in defining 'Immunosuppressed' as the term covered a broad spectrum of individuals, presenting difficulties for studies with varying definitions. Discordance in decision procedures relating to safety concerns, like TTS and their implications for vaccination campaigns, existed among different countries. While the EMA provided initial guidance, different countries issued varying public health advice based on the same data, creating public confusion. Better integration of RWE for children was highlighted as a pressing need as many safety issues have an age-specific risk, and the burden of disease has an inverse age-specific risk.

Resource constraints and the high workload on public health staff during the pandemic raised questions about resource allocation and sustainability. Trust in RWE and communication challenges were pervasive issues; building population trust and effectively communicating results were difficult, highlighting the need for skilled communication.

Lack of coordination in research and overviews of ongoing studies, especially on safety, resulted in inefficiencies and potential duplication of research efforts. Lastly, national decision-making processes lacked global contextualisation, as decisions were made quickly but influenced by local or international data without adequate global contextualisation.

8. Overcoming barriers and meeting requirements for effective RWE utilisation for regulatory and public health decision-making

RWE holds immense potential in informing regulatory and public health decisions. However, its successful implementation faces significant challenges. Conference participants engaged in several breakout sessions addressing the essential requirements for and difficulties in harnessing RWE effectively.

Data quality and standardisation are crucial for both regulators and public health authorities. It is imperative to ensure that data is high quality, consistent and complete and that robust data validation processes are in place to establish trust in the data sources. The availability of precise data on exposure, vaccination, and outcomes is critical. Trusting data quality and analyses can be a concern, primarily when manufacturers or countries rely on external partners. Clear guidance from authoritative bodies on case definitions and methodologies is pivotal. Expertise in conducting and interpreting RWE studies is crucial for sound decision-making.

The availability of precise data on exposure, vaccination, and outcomes is essential, as incomplete data can introduce bias, adding complexity to RWE analyses. Access to data on potential confounding factors is equally important, as is denominator data, but is often challenging to obtain, especially in low-resource settings. Lengthy time lags for hospital data in certain countries also create obstacles.

Uniform diagnostic standards are needed. These are currently lacking and are particularly challenging in resource-constrained environments. Standardised definitions and methodologies are essential for meaningful comparison across different clinical trials and evidence sources. Inconsistent information capture and limited accessibility due to fragmented health systems pose barriers, particularly in the U.S.

Data Privacy concerns, especially under the GDPR in Europe, limit data sharing and access and ambiguities in GDPR interpretation may hinder data utilisation. Legal constraints, especially in public-private partnerships, raise issues of conflict of interest and necessitate clear data use agreements.

Regulatory requirements can be complex. Clear commitments from regulators to accept RWD are crucial, with defined requirements. RWE may play a valuable role before licensure, potentially expediting approval decisions. Also, rare disease treatments may necessitate alternative study approaches beyond standard RCTs. Regulatory authorities sometimes seek direct access to all data, potentially complicating matters for manufacturers who may be reluctant to present "second-hand data". Functional and robust regulatory and public health systems also require expertise to make evidence-based decisions.

Adopting Technologies, such as barcoding for vaccine vials, can improve the efficiency of data capture, but there is a reluctance to embrace such technologies. Indeed, unclear labelling poses a challenge when collecting RWE to demonstrate vaccine benefits, as seen in cases like Flu and DTaP vaccines in the U.S.

Public Acceptance and Cultural Barriers, such as a lack of acceptance for RWE compared to clinical trial data, pose challenges, particularly in special populations like pregnant individuals. Fostering public acceptance is a fundamental prerequisite. Developing a global "Good RWE Practices" Framework for RWE utilisation, akin to GCP or GMP, may facilitate broader acceptance.

Global commitments and multi-country networks are necessary to access diverse populations, including exposed populations and cases, enabling comprehensive decision-making. Establishing reliable data linkage mechanisms is also crucial in certain regions. Additionally, for successful RWE implementation, there is a pressing need for strong collaboration with regulators, public health partners, and sustainable funding mechanisms. Maintaining high levels of global political funding for RWE is essential to avoid post-pandemic funding declines. Building trust between collaborators, particularly in low-resource settings, is also essential for effective partnerships. Resource inequalities hinder access to valuable data sources, e.g., vaccination registries in low-resource settings. It is crucial to ensure the continuity of local-level infrastructure, including systems like NIMS and vaccine registries, particularly in LMICs.

8.1. Conditions/scenarios in which real-world vaccine effectiveness data can replace phase III vaccine efficacy data for regulatory licensure

Under current vaccine licensing guidelines, the requirement for Phase III efficacy data can be waived in certain circumstances, such as an established Correlate of Protection (CoP), which may serve as a surrogate endpoint for efficacy. In cases where a CoP has not been firmly established, regulatory authorities may consider immune bridging if it is demonstrated that the new vaccine induces a similar or superior immune response to a licensed product with proven efficacy. Alternatively, approaches include animal challenge studies, typically involving two studies with at least one conducted on non-human primates (NHP) or human challenge studies.

In the context of these established alternatives to Phase III efficacy data, the proposal to use RWE to extend current provisions was discussed. The conference participant groups felt that although it remains challenging to forego the necessity of Phase III RCTs entirely and rely solely on RWE, there are potential scenarios where the use of RWE could be considered, such as in emergency or crisis situations, to leverage evidence from existing vaccine platforms for their use against emerging pathogens (within or even beyond the same virus family), to extend vaccine indication or to add another population to the approved indication.

To use RWE in place of Phase III trial data, and in the absence of an accepted CoP and where approval based on animal or human challenge studies is not feasible, there must be ample consideration of several epidemiological, scientific, regulatory, and data-sharing aspects.

The epidemiological and public health perspective: RWE is deemed appropriate when addressing a significant public health concern, emphasising urgency and the existence of a critical timeframe for intervention. Furthermore, there must be an evident lack of viable alternatives to address the situation, establishing an unmet need. The willingness to take the risk of mass immunisation for emergency vaccines was also highlighted.

Scientific and clinical considerations: robust Phase II data, encompassing safety and immunogenicity, including identifying

effective surrogates, is essential, with support from animal or primate model investigations where feasible. RWE studies should define clear stopping rules for safety and effectiveness, incorporating randomisation methodologies such as wedge designs, hybrid trials, and randomised pragmatic trials, especially in early phases, should be considered to generate data. A better understanding of the roles CHIM studies and CoPs can play within RWE was also proposed. Improving harmonisation and standardisation of guidance on endpoints, approaches, and trial designs was recommended for better comparability. Public engagement, education, and fostering confidence in vaccination are also crucial components.

Data collection and regulatory aspects: It is essential to ensure high-quality RWD, address potential confounders, and commit to the indirect assessment of CoPs, e.g., via antibody levels and effectiveness differences across time or age groups, to support licensure. Collaboration across regulatory agencies and emergency preparedness, particularly in LMICs, is crucial and should include prior discussions with regulators, scenario planning, and clear outcome definitions. A paradigm shift in relationships is advocated, with increased reliance on public-private partnerships, transparency, and collaboration. Developing an ICH-like framework to instil regulator confidence and standardisation, like the ENCEPP seal of approval, and performing benefit-risk evaluations with finer stratification of emergency declarations and scenario planning are also suggested.

RWD collection and sharing: it is vital to recognise that most major safety issues impacting benefit-risk assessments are too rare to be detected in Phase III trials and must be identified in the real world. Thus, there is a need to address data collection responsibility, balance industry and health authorities' roles, and establish a framework for data access and sharing. An overarching supranational organisation to authorise and oversee emergency responses was proposed to enhance coordination and response effectiveness.

8.2. Requirements for generating real-world vaccine effectiveness data, particularly in LMICs

To overcome barriers in generating RWE in LMICs, conference participants shared various strategies encompassing infrastructure development, public engagement, data and research, quality and trust, and proactive scenario planning.

Infrastructure: There is a need to establish a level of infrastructure and evidence hubs in LMICs as a preparedness measure. This can be achieved through a multilateral mapping process that strategically identifies infrastructure needs and suitable locations. Expanding global hospital networks for reporting cases and genomic virus sequencing is crucial to identifying desired endpoints. Infrastructure sustainability is of utmost importance, and mapping and utilising local expertise and laboratory capacities can aid in achieving this goal. In addition, leveraging existing infrastructure from CEPI pathogen trials for RWD collection and building up sentinel study sites to expand the study network could be beneficial. It is also essential to sustain functioning structures from previous pandemics and focus on the sustainability of funding for research. Exploring federated platforms like 'Odyssey' can also be helpful. Creating a global "Pandemic Money Fund (PMF International)" and leveraging existing funders and partnerships for research in LMICs are equally beneficial.

Public engagement: Engaging communities and governments is key to improving support for RWE studies in LMICs, and ensuring study success means involving the right stakeholders and addressing public health capacity building for sustainability. Empowering local LMIC regulatory agencies (e.g., African CDC) to take on greater responsibilities and transition away from reliance on HIC regulatory support is also crucial. Early engagement with target countries at the political level can help build trust and support. Finally, fostering international networking and mentoring programs can facilitate knowledge exchange and capacity building, improving public engagement and generating high-quality RWE in LMICs.

Scenario planning: Improving scenario planning for RWE studies is crucial for better preparedness and response during outbreaks. This involves proactively preparing for different outbreak scenarios and empowering local health authorities to make timely decisions with WHO/CEPI support. Another approach is enabling regional-level decision-making by local public health authorities before a global declaration.

Improving data and research quality: Guaranteeing access to data and establishing surveillance programs that provide valid data are essential. Additionally, harmonisation and coordination of data management are crucial. Obtaining ethical approvals and addressing privacy concerns are equally important. Embracing digital transformation and mobile technology for data collection, addressing data specification harmonisation and laboratory assay standardisation, training and educating individuals conducting studies in LMICs to build capacity, and developing data-sharing guidelines are other critical considerations. Additionally, vaccination status validation and confirmation are vital to improving data and research quality in RWE. Pilot cohort event monitoring for active safety surveillance and sustaining and extending platforms from previous pandemics, such as COVID-19 vaccine registers and linkages, can also be effective strategies. Finally, leveraging WHO's role and experience in African clinical trials can help build RWE generation capacity.

9. Meeting conclusions and next steps

In conclusion, this meeting was instrumental in shedding light on critical aspects of pandemic responses and the future of public health decision-making. The insights gained from the breakout sessions have underscored the profound impact that successful decisions made throughout the pandemic have had on vaccination strategies and public health. These decisions encompassed a wide array of factors, from dosing regimens to regulatory transparency, and they have not only shaped the course of the pandemic but have also highlighted the importance of data-driven decision-making and global collaboration in safeguarding public health.

While replacing Phase III clinical trials with RWE remains challenging, the discussions revealed specific scenarios where using RWE is both viable and beneficial. These scenarios included emergency situations, robust data supporting vaccine platform adaptability, and expanding vaccine indications. The essential conditions and considerations identified during the meeting, from epidemiological to regulatory aspects, emphasise the need for public health urgency, robust scientific support, regulatory collaboration, and a paradigm shift towards public-private partnerships.

While RWE remains a gold mine of information on safety and efficacy, the organisers acknowledged many challenges ahead. The discussion about the role of Phase III trials and the deployment of vaccinations based on surrogates or good immunogenic responses deserves further exploration. The harmonisation of capacity issues, particularly in LMICs, is paramount, and stakeholders must recognise the existing capacity within these countries. For LMICs, the requirements for generating RWE are multifaceted and call for a comprehensive approach that includes infrastructure development, public involvement, data harmonisation, quality assurance, and proactive scenario planning. These efforts would contribute to the overall preparedness of LMICs in the face of future crises.

Additionally, the meeting yielded valuable suggestions for future endeavours, including the exploration of pragmatic trials as a hybrid approach, the creation of a database of experiences and pathways from different countries in accelerated approval, not limited to COVID-19 but encompassing other contexts such as Meningitis C, HIV, or monoclonal antibodies, among others, and the publication of a concept paper summarising these experiences.

Many open questions remain, and clearly, the journey is just

beginning. It is crucial to look at these challenges globally and continue to work together to address them. To this end, it was proposed that stakeholders convene, possibly in a year, to further the collective understanding and progress in public health decision-making and the use of RWE.

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Declaration of competing interest

All authors declare no competing interests.

Disclaimer

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