Drug Safety
https://doi.org/10.1007/s40264-024-01493-7

ORIGINAL RESEARCH ARTICLE

Empowering African Expertise: Enhancing Safety Data Integration and Signal Detection for COVID-19 Vaccines Through the African Union Smart Safety Surveillance Joint Signal Management Group

Victoria Prudence Nambasa · Hannah May Gunter · Modupe Bamidele Adeyemo · Neetesh Yanish Bhawaneedin · Marc Blockman · George Tsey Sabblah, et al. ***[full author details at the end of the article]***

Accepted: 28 October 2024

Abstract

Introduction The COVID-19 pandemic accelerated new vaccine development. Limited safety data necessitated robust global safety surveillance to accurately identify and promptly communicate potential safety issues. The African Union Smart Safety Surveillance (AU-3S) program established the Joint Signal Management (JSM) group to support identification of potential vaccine safety concerns in five pilot countries (Ethiopia, Ghana, Kenya, Nigeria, South Africa), accounting for approximately 35% of the African population.

Objective Our objective was to provide an overview of the JSM group's role in supporting signal management activities for the AU-3S program during the COVID-19 pandemic.

Methods Spontaneous, electronically reported COVID-19 vaccine adverse events following immunization (AEFI) from each country's safety data were integrated into the interim Data Integration and Signal Detection system. Statistical disproportionality methods were used to identify and review vaccine–event combinations (VECs) for potential safety concerns. The JSM group—which comprised pharmacovigilance and subject matter experts from National Medicine Regulatory Authorities, Expanded Programs on Immunization, and vaccine safety committees—conducted signal detection activities on cross-country safety data and provided recommendations.

Results From April 2021 to December 2023, a total of 48,294 spontaneously reported AEFI were analyzed for six COVID-19 vaccines (NRVV Ad [ChAdOx1 nCoV-19]; Ad26.COV2.S; Elasomeran; Tozinameran; Covid-19 vaccine [Vero Cell], Inactivated; NRVV Ad26 [Gam-Covid-Vac]) administered in Ethiopia (34.6%), Nigeria (30.3%), South Africa (16.9%), Ghana (13.5%), and Kenya (4.7%). Overall, 2,742 VECs were validated. A causal association between the COVID-19 vaccines and the reported AEFI cannot be inferred, as data were reported spontaneously. JSM group recommendations included monitoring for further evidence, no immediate action required, engaging marketing authorization holder(s) for additional information, or sensitizing healthcare providers and/or the public about events. Although no new safety signals were identified, nine safety-related recommendations were issued, including patient and healthcare provider education.

Conclusions The JSM group established a scalable and replicable model for future signal management of other priority health products in low- and middle-income countries, fostering ongoing collaboration and capacity building. Knowledge and experience gained from this pilot initiative will guide stakeholders in future safety surveillance initiatives within the African continent.

Plain Language Summary

During the COVID-19 pandemic, the urgent need for vaccines led to the development of new vaccines. However, there were concerns about the limited amount of safety data on the vaccines when used in the real world by large populations. To address this, the African Union launched its Smart Safety Surveillance program in five countries in Africa. Each of these countries used mobile technology for spontaneous reporting of COVID-19 vaccine adverse events following immunization (AEFI), resulting in a huge amount of safety data combined in one database. This allowed experts in Africa from various fields (i.e., the Joint Signal Management [JSM] group) to use statistical methods to analyze the combined data and identify any safety concerns. Over 32 months, the JSM group analyzed 48,294 spontaneously reported AEFI for six COVID-19 vaccines and verified the safety of 2,742 events reported for specific vaccines. However, a causal association with the COVID-19 vaccines

cannot be assumed, because AEFI were reported spontaneously and were not investigated. This notwithstanding, the JSM group was able to make recommendations to the five countries, including education for patients and healthcare providers and engaging with vaccine manufacturers for more information on specific events. This initiative established a unified collaborative safety response model for low- and middle-income countries that is also applicable to other health products and diseases in Africa beyond COVID-19 vaccines. The JSM group seeks to provide reliable guidance for future safety surveillance initiatives in Africa.

Key Points

The Joint Signal Management Group of the African Union Smart Safety Surveillance program is the first continental effort to perform collaborative signal detection and risk management on all adverse events following immunization during the COVID-19 pandemic.

Considering the limitations of spontaneous reporting of adverse events, the efforts of the African Union Smart Safety Surveillance program aim to enhance patient confidence in African regulators to safeguard their health, even when products are developed through accelerated pathways. The approach will aid future vaccination efforts and provide a model for safety responses in low- and middle-income countries during pandemics.

Resources (and safety expertise) to support signal detection and risk assessment within the African continent are historically limited. The Joint Signal Management group provided an opportunity to strengthen pharmacovigilance expertise among country and continental stakeholders and enabled end-to-end close collaboration across historically siloed disease-specific programs and National Medicines Regulatory Authorities.

1 Introduction

Evaluating the safety of medical products is an important process that extends beyond pre-marketing studies [1]. Clinical trials provide vital efficacy and safety information, but they have limitations such as relatively small sample sizes, highly controlled environments, and limited study durations [2, 3]. The ongoing monitoring of medicine and vaccine safety through active and passive surveillance is essential once these products are available to the public [3].

Passive surveillance relies on spontaneous reporting by healthcare professionals, consumers, and marketing authorization holders (MAHs). This method is valuable for detecting rare events and identifying harmful effects of medicines and immunizations, hence widely used for post-marketing surveillance by countries' pharmacovigilance programs. However, spontaneous reporting has limitations; it relies on unprovoked reporting of adverse events, it is subject to reporting biases due to its retrospective nature, and the quality of reports varies [4]. Without further investigation and causality assessment, a causal link between a vaccine and an event cannot be established based solely on spontaneous reports. Additionally, the method does not allow for determining actual incidence rates, as true numerators and denominators are not known [4–6]. Despite these limitations, spontaneous reporting remains the preferred and most cost-effective approach for post-marketing surveillance in pharmacovigilance [7].

In recent years, considerable efforts have been made by governments and global health organizations to improve access to essential medicines and vaccines in low- and middle-income countries (LMICs), which often carry a higher burden of disease than high-income countries [8]. Higher demand for medicines and vaccines to prevent and treat diseases inevitably leads to an increase in the number of people in LMICs being at risk of adverse drug reactions (ADRs) and adverse events following immunization (AEFI) [9]. Maintaining a balanced benefit–risk profile, informing policy decisions, and proactive risk management strategies are essential for all medicines and vaccines used by the public [10]. This includes continuously providing accurate information and appropriate recommendations to key users, conducting targeted training, and executing regulatory actions such as product prescribing restrictions and targeted adverse event monitoring [10].

The unexpected outbreak of the severe acute respiratory syndrome (SARS) virus (coronavirus disease 2019 [COVID-19]), declared as a public health emergency and pandemic in March 2020, led to accelerated development of COVID-19 vaccines [8, 11]. Large-scale deployment of COVID-19 vaccines was necessary to protect against severe disease, hospitalization, and death [11]. Alongside accelerated vaccine development and deployment through regulatory pathways, robust safety surveillance systems became imperative to promptly identify safety signals, initiate rapid responses, and communicate effectively to address safety concerns and maintain public confidence in vaccines and health systems [12].

High-income countries such as those in the European Union and the United States of America (USA) have robust pharmacovigilance and risk management systems, but

resource-limited LMICs face challenges in implementing such systems [2, 12]. Challenges include inadequate human capacity, lack of financial resources and infrastructure, and the need for large electronic healthcare databases for administration and surveillance [13]. Despite recent improvements, implementing risk management strategies at all levels of the healthcare system remains a concern, with Africa being no exception [13–15]. Additionally, pharmacovigilance challenges in Africa include low reporting rates of adverse events, fragmented pharmacovigilance systems with limited data sharing, lack of African-specific background rates, and insufficient safety expertise for signal detection and risk assessment [13, 16].

Smart Safety Surveillance (3S), which is a pharmacovigilance risk prioritization strategy, has been tested as a strategy to navigate the challenges faced in the implementation of pharmacovigilance in Africa [14, 15]. The African Union Smart Safety Surveillance (AU-3S) program, launched in 2020 as one of the flagship programs of the African Union Development Agency-New Partnership for Africa's Development (AUDA-NEPAD) with funding provided by the Bill & Melinda Gates Foundation, was created to strengthen the safety surveillance of priority health products across the continent [16, 17]. The COVID-19 pandemic and the rollout of COVID-19 vaccines created an opportunity for the AU-3S program to shift its focus toward creating effective solutions that could address the need for a robust safety monitoring system of the vaccines that were arriving on an unprecedented scale, with limited safety data available for use in the African population.

The AU-3S program was implemented as a pilot initiative with the aim to strengthen the capacity for detecting and assessing COVID-19 vaccine safety signals that may not be identified in data from a single country. The program is governed by a Steering Committee comprising the chief executive officers (CEOs) of National Medicines Regulatory Authorities (NMRAs) from participating countries, the chairperson of the Joint Signal Management (JSM) group, the World Health Organization (WHO)—represented by both African and Eastern Mediterranean regional offices—and, as technical partners, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA) [13]. The AU-3S initiative delivered on three integrated solutions: (i) at the country level, electronic safety data collection, spontaneously reported through the Med Safety App and other data collection tools; (ii) at the cross-country level, a system for data integration and signal detection (DISD); and (iii) a multi-country group of safety experts known as the JSM group [15].

In this article, we present an overview of the activities of the JSM group and its accomplishments in conducting cross-country signal management during the COVID-19 pandemic, based on electronic, spontaneously reported AEFI for COVID-19 vaccines. Our objectives were therefore to (i) describe the composition and responsibilities of the JSM group; (ii) describe the signal management process and activities of the JSM group for the COVID-19 vaccines; (iii) present the outcomes and practical application of signal assessment by the JSM group; and (iv) identify lessons learned and implications for the future.

2 Methods

2.1 Setting and Time Frame

In early 2021, AUDA-NEPAD implemented the AU-3S approach as a pilot project during the active COVID-19 vaccine rollout in four pilot countries, namely Ethiopia, Ghana, Nigeria, and South Africa, with Kenya phased in as a fifth pilot country in 2022, representing approximately 35% of the African population [16, 17]. The UK MHRA played an instrumental role, as a peer regulator and technical partner, in the implementation of an interim cross-country DISD system to enable the aggregation of spontaneously reported safety data across the pilot countries. This article covers the activities of the JSM group in signal management of AEFI, spontaneously reported for the following COVID-19 vaccines administered in the pilot countries from 21 April 2021 to 11 December 2023: NRVV Ad (ChAdOx1 nCoV-19); Ad26.COV2.S; Elasomeran; Tozinameran; Covid-19 vaccine (Vero Cell), Inactivated; NRVV Ad26 (Gam-Covid-Vac).

2.2 Data Sources and Tools

A quick and easy way of reporting adverse events was needed to support the rollout of the COVID-19 vaccines. The UK MHRA provided technical support to the pilot countries to expand and/or enhance their existing technology and systems to facilitate electronic collection of safety data. For this purpose, the program, with support from the UK MHRA, made the Med Safety App [18] available in the pilot countries. This was a mobile application developed for spontaneous reporting of suspected ADRs [19, 20] and subsequently updated with reporting capabilities to enable the electronic reporting of AEFI.

A crucial aspect of this initiative was the development of capabilities within the App to allow reporting of AEFI for all vaccines, and not only specifically for COVID-19 vaccines, including the 25 core variables recommended by the WHO for collecting AEFI data [21]. Using the Med Safety App for electronic reporting of AEFI was motivated by the advantage of electronic reporting being easier and faster than traditional paper-based reporting. An additional advantage of the Med Safety App is that it allows reporting of both AEFI and ADRs

for medicines and reporting by not only healthcare providers (HCPs) but also patients and consumers, enhancing overall reporting rates. The Med Safety App was rolled out in February 2021 after undergoing user acceptance testing by pilot country representatives to ensure its suitability and effectiveness for AEFI reporting. Financial support for communication plans to increase awareness of the use of the Med Safety App in the pilot countries was offered by the AU-3S program.

The back-end system of the Med Safety App is managed by the Vigilance Hub. The UK MHRA also provided support to pilot countries to launch the Vigilance Hub as a case management platform allowing the review of vaccine-related cases, editing of submitted case reports if necessary (e.g., when relevant information was obtained during case investigations), re-coding of a drug name if a term outside of the Medical Dictionary for Regulatory Activities had originally been captured, updating vaccine names if the reporter did not use the vaccine name from the dropdown list, and manual entering of data for paper-based submitted reports. All data in the Vigilance Hub, submitted through the Med Safety App and/or when updated, are automatically updated in the WHO Uppsala Monitoring Centre VigiFlow environment [18].

2.3 Data Integration Across Countries

At the cross-country level, the DISD was deployed as the data intergration and signal detection system for data entered via the Vigilance Hub. This system comprised a sentinel database and Empirica signal detection software, allowing automated cross-country signal detection to be conducted within the DISD system. The DISD generated a report summarizing data for each vaccine–event combination (VEC) through a data mining process, grouping reports into VECs across countries.

2.4 Preparation for Program Implementation

2.4.1 Establishment of the JSM Group

The JSM group was established by AUDA-NEPAD, with the group's overall aim to facilitate cross-country signal management to identify cross-country signals and strengthen each country's ability to respond effectively and timeously to COVID-19 vaccine signals in the interests of public health and safety. Specific objectives to fulfill this aim were to (i) assess signals from safety data on priority medical products combined across countries (priority medical products were initially limited to COVID-19 vaccines); (ii) promote collaboration on safety surveillance among African member countries; (iii) be a forum for technical support from reference regulatory authorities to African regulatory authorities; and (iv) strengthen the capabilities of JSM group members through working with the UK MHRA and learning from good practice across member countries. The JSM group's mode of operation was collaborative across countries and organizations, and consensus driven.

The process of establishing the JSM group commenced by assembling a dedicated working group to formulate a comprehensive model for signal management. This working group, comprising pharmacovigilance experts nominated by the CEOs of participating countries' NMRAs and AUDA-NEPAD staff, engaged in a series of collaborative meetings. They subsequently constructed a model that deliberated on critical factors, including the scope of the JSM group, its role, membership, and expertise; its integration with national safety committees; and its governance arrangements, comprising of the following:

- Secretariat, responsible for signal validation: AUDA-NEPAD staff (through AU-3S), with technical support from the UK MHRA and representatives from pilot countries for capability strengthening.
- AU-3S JSM group members, responsible for signal review: country representatives from NMRAs and Expanded Programs on Immunization (EPIs), national safety committee chairpersons, and other core expert members. National safety committees maintained their full scope of responsibilities and activities, with decisions regarding the AU-3S JSM group's recommendations being considered by countries' NMRAs.
- Ad-hoc co-opted experts providing support on signal review: additional experts co-opted on an ad-hoc basis when required, depending on the AEFI under discussion.

All members of the group were nominated by the CEOs of the NMRAs and heads of EPIs in the respective countries. The AU-3S Steering Committee subsequently endorsed the final JSM composition and operating model (see Fig. 1).

2.4.2 Terms of Reference, Operational Model, and Standard Operating Procedures

Terms of reference and an operational model for the JSM group were compiled by a working group comprising AU-3S staff and representatives from the participating countries' NMRAs to ensure the effective functioning of the JSM group in achieving its aim and objectives. In parallel, a standard operating procedure was developed to guide the signal management process that the JSM group would follow. This procedural framework outlined in detail the respective responsibilities for signal detection, validation, prioritization, assessment, and the formulation of recommendations for action. Notably, the working group responsible for devising the JSM group operational model also played a pivotal

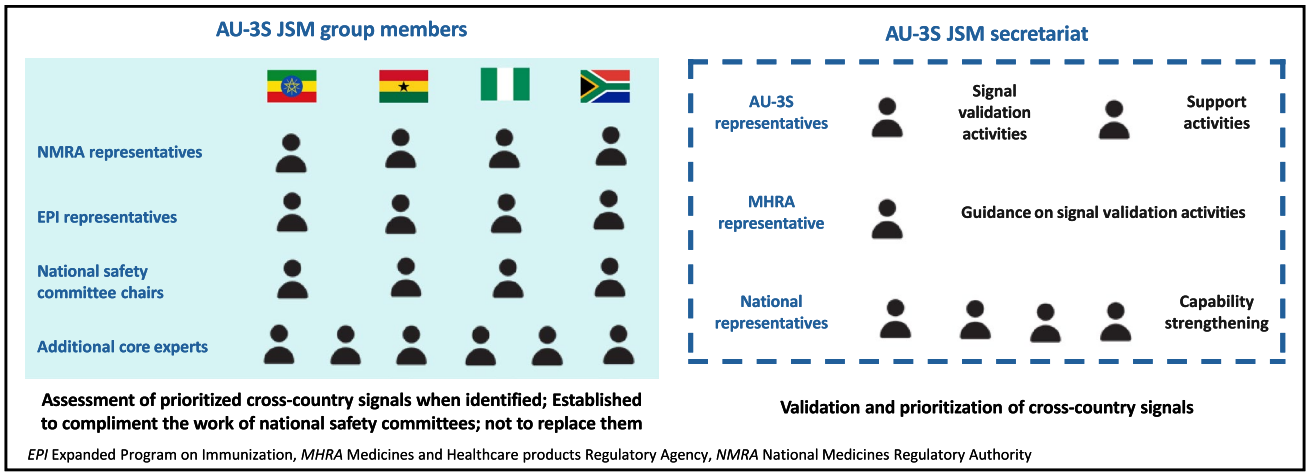


Fig. 1 Proposed model and composition of the Joint Signal Management (JSM) group as approved by the African Union Smart Safety Surveillance (AU-3S) Steering Committee

role in shaping this procedural guideline, which subsequently received formal approval from the AU-3S Steering Committee.

2.4.3 Training and Capability Strengthening

To ensure capacity building within the countries and transition of expertise from peer regulators, the UK MHRA provided technical support to strengthen the safety monitoring capabilities in each country across all levels and activities, including use of the Vigilance Hub. These efforts involved providing training materials and delivering live virtual training sessions for core participants from countries' NMRAs and EPIs, to ensure that the group was fully equipped to carry out safety monitoring activities.

2.5 Data Management and Analysis

All AEFI data submitted by the pilot countries through the Med Safety App were integrated within the DISD system. Through technical support from the UK MHRA, Empirica signal detection software was designed for the AU-3S program and used by the DISD system for the storage and signal detection of cross-country AEFI data and subsequent signal management by the JSM group.

3 Results

3.1 Composition and Responsibilities of the JSM Group

The inaugural meeting of the AU-3S JSM group took place on 21 April 2021, with 18 members in attendance. The main responsibilities of the JSM group were discussed. These were: (i) to perform cross-country signal management from the combined safety data provided by the participating countries; (ii) to better understand product safety profiles within the African context; and (iii) to provide scientific recommendations on the safety of COVID-19 vaccines. Emphasis was placed on the importance of fostering collaboration and cooperation between the JSM group and key stakeholders, such as national safety committees within participating countries, who play a crucial role in managing safety signals. The operational model of the JSM group, guided by its terms of reference, was discussed in detail (see Table 1), followed by the nomination of a chairperson and deputy chairperson.

3.2 Signal Management Process and Activities of the JSM Group for the COVID-19 Vaccines

3.2.1 Capability-Strengthening Training

At the outset of the AU-3S program, between January 2021 and May 2021, the UK MHRA provided the JSM group and all dedicated safety surveillance personnel from the NMRAs, EPIs, and members of national safety committees in the pilot countries with capability-strengthening training. This initiative supported the AU-3S program in building capacity within the pilot countries and enhancing skills in signal validation and assessment. Comprehensive end-to-end safety monitoring training across five e-learning modules covered the crucial aspects of safety monitoring activities, including data collection, signal detection and management, benefit–risk assessment, safety communication, and functions of the pharmacovigilance expert advisory committee. Members of the JSM group also received additional capacity building during meetings where experts were invited to

Table 1 Operational model of the Joint Signal Management (JSM) group as guided by its terms of reference

Principles	• Decisions and recommendations should be based on science and evidence • Decisions should be based on consensus among JSM group members and, if relevant, invited experts • Safety data remain owned by the member countries • The JSM group is designed to complement the work of national safety committees, not to replace it • Open and timely communication among countries' national safety committees, the JSM group and other relevant stakeholders • Work of the JSM group should be collaborative, with member countries working together to improve safety surveillance in Africa
Scope	• The initial scope of the JSM group is COVID-19 vaccines, with the potential to extend to other priority medical products at a later stage • Any scope extension should be agreed upon by JSM group members in consultation with the AU-3S Steering Committee • Decisions and actions taken based on recommendations from the JSM group remain the responsibility of member countries' national safety committees, NMRAs and EPIs
Key roles	• Validating and assessing signals from member countries' combined data • Sharing findings on signals and recommendations with member countries' national safety committees and key continental and global stakeholders through African Union channels • Supporting national safety committees, if asked, in providing a forum for discussion of signals found in-country • Enabling knowledge and experience sharing on signals and other safety surveillance topics from reference regulatory authorities • Providing input into requirements for relevant cross-country data analysis
Membership	• Expert representation from member countries, including the following: o NMRAs o EPIs o National vaccine safety committees, represented through their chairperson, deputy chairperson, or an assigned representative o Independent experts, including biostatistics, clinical pharmacology, epidemiology, geriatrics, immunology, microbiology, pathology, pharmacy, public health, toxicology, and vaccinology • If expertise is required for the assessment of a specific signal but is not covered among members of the JSM group, additional experts can be sourced to attend a specific meeting • If required, further clinical assessment of specific signals can be conducted by continental safety assessment committees, in consultation with national safety committees if additional information is required
Governance	• Nomination of a chairperson and deputy chairperson • Confidentiality agreement and conflict of interest declaration • Reporting responsibilities to the AU-3S Steering Committee • Review of membership • Terms of reference
Scientific secretariat	• The JSM group's secretariat is led by AUDA-NEPAD • Membership: o AU-3S staff o Representatives from member countries' NMRAs and/or EPIs o Representation from the UK MHRA as reference regulatory authority from outside the African continent to provide technical support as required • Main functions: o Detect signals using the interim DISD system and other relevant data sources o Validating signals from member countries' data and prioritizing them in preparation for JSM group meetings, where prioritized signals will be assessed o Arrangement of JSM group meetings, taking minutes at JSM group meetings, and distributing minutes for review o Communicating relevant information to key stakeholders o Regular reporting to the AU-3S Steering Committee

AUDA-NEPAD African Union Development Agency - New Partnership for Africa's Development, *AU-3S* African Union Smart Safety Surveillance, *DISD* data integration and signal detection, *EPIs* Expanded Programs on Immunization, *MHRA* Medicines and Healthcare products Regulatory Agency, *NMRAs* National Medicines Regulatory Authorities.

the JSM group meeting to share their knowledge and expertise on specific safety issues of interest, and some JSM group members were accorded an opportunity to observe an advisory meeting of the UK MHRA. All these efforts ensured that the group was fully equipped to carry out safety monitoring activities effectively and efficiently.

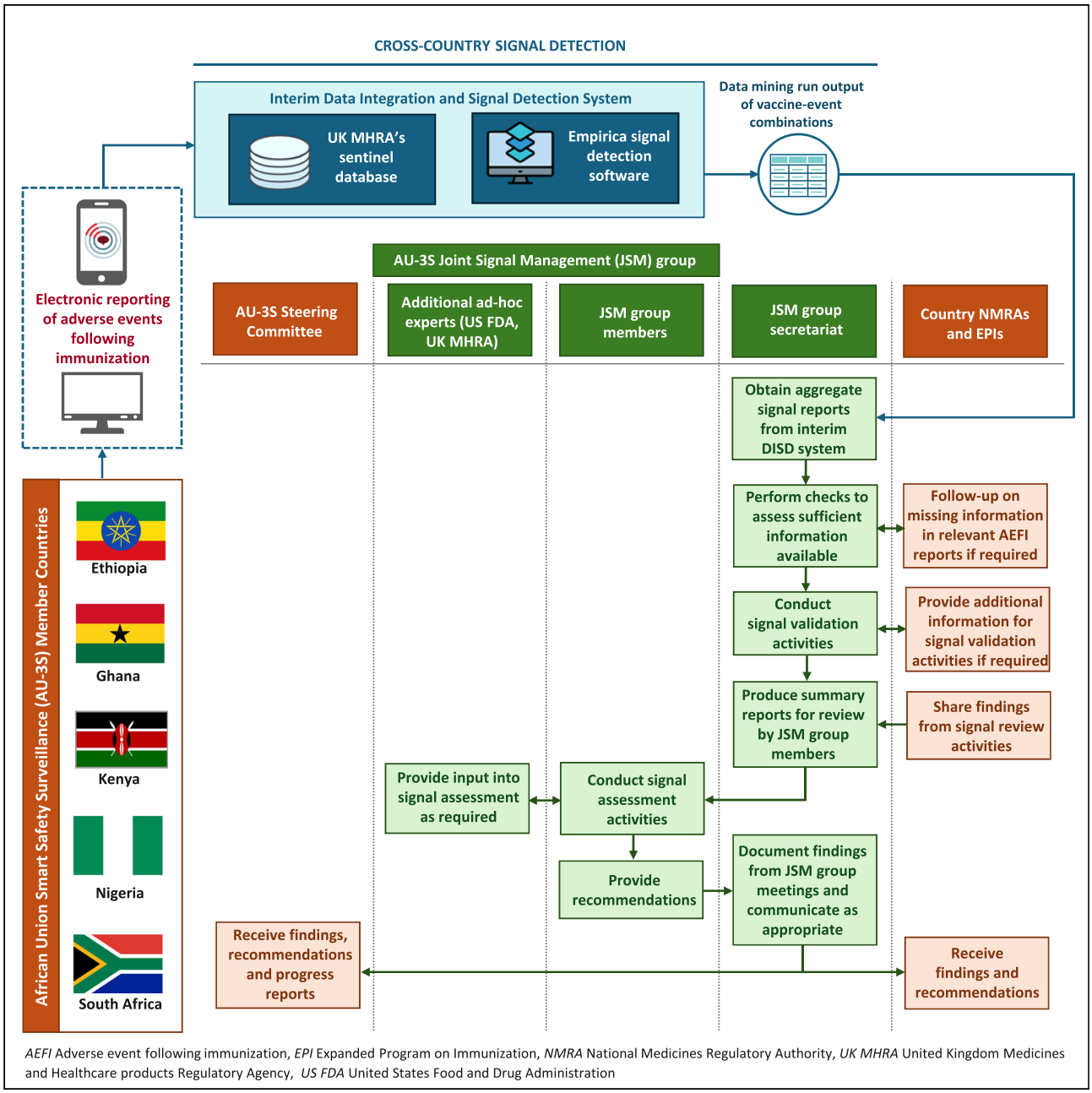
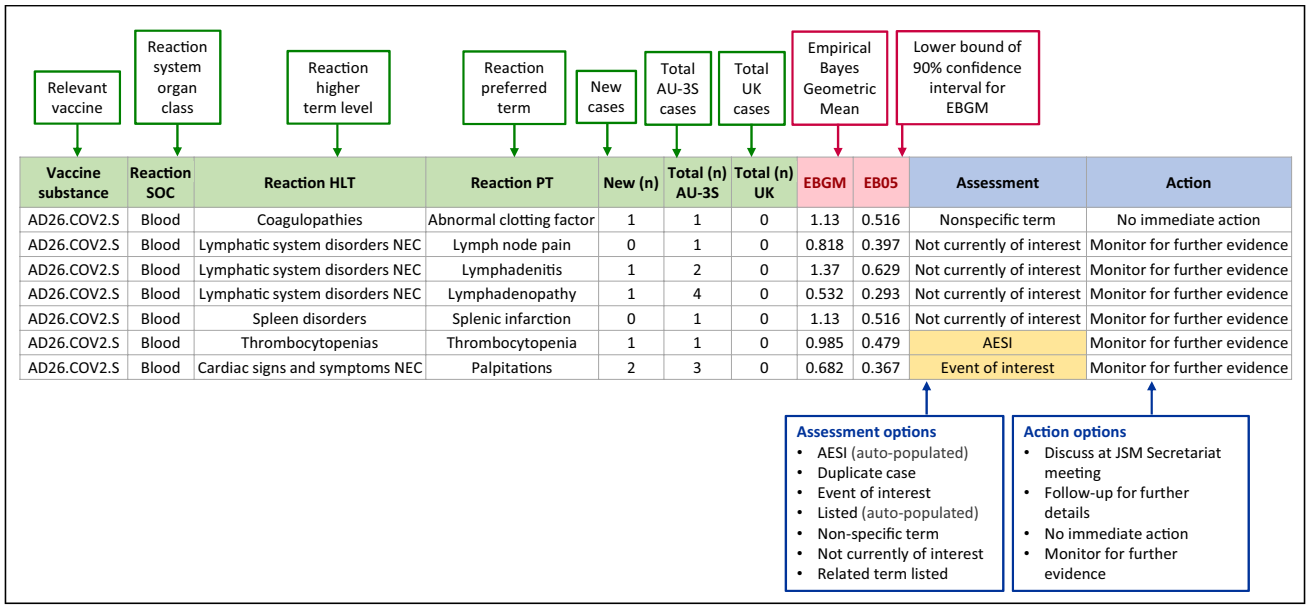


Fig. 2 Data flow linkage from participating countries to the data integration and signal detection (DISD) system and signal management process within the African Union Smart Safety Surveillance (AU-3S) program

3.2.2 Data Flow and Signal Detection

Figure 2 illustrates the data flow linkage from participating countries to the DISD system and the signal management process within the AU-3S program. AEFI data submitted by the countries through the Med Safety App were integrated within the DISD system, with the Vigilance Hub functioning as a case management platform. The DISD system used Empirica signal detection software, which was designed for the analysis of cross-country AEFI data within the AU-3S program.

The UK MHRA supported biweekly data mining runs on the combined country data in the DISD system. This entailed applying statistical methods to this large database with the objective of discovering new information [22]. The disproportionality approach, where the observed number of reports of a suspected VEC is greater than the expected number from the background data, was used to identify possible signals. With support from the UK MHRA, the disproportionality empirical Bayes geometric mean (EBGM) score and the EB05 (lower bound of the



Vaccine substance	Reaction SOC	Reaction HLT	Reaction PT	New (n)	Total (n) AU-3S	Total (n) UK	EBGM	EB05	Assessment	Action
AD26.COV2.S	Blood	Coagulopathies	Abnormal clotting factor	1	1	0	1.13	0.516	Nonspecific term	No immediate action
AD26.COV2.S	Blood	Lymphatic system disorders NEC	Lymph node pain	0	1	0	0.818	0.397	Not currently of interest	Monitor for further evidence
AD26.COV2.S	Blood	Lymphatic system disorders NEC	Lymphadenitis	1	2	0	1.37	0.629	Not currently of interest	Monitor for further evidence
AD26.COV2.S	Blood	Lymphatic system disorders NEC	Lymphadenopathy	1	4	0	0.532	0.293	Not currently of interest	Monitor for further evidence
AD26.COV2.S	Blood	Spleen disorders	Splenic infarction	0	1	0	1.13	0.516	Not currently of interest	Monitor for further evidence
AD26.COV2.S	Blood	Thrombocytopenias	Thrombocytopenia	1	1	0	0.985	0.479	AESI	Monitor for further evidence
AD26.COV2.S	Blood	Cardiac signs and symptoms NEC	Palpitations	2	3	0	0.682	0.367	Event of interest	Monitor for further evidence

Fig. 3 Sample output from the data integration and signal detection (DISD) and reviews routinely done by the Joint Signal Management (JSM) secretariat. *AESI* adverse events of special interest, *AU-3S* African Union Smart Safety Surveillance, EBGM empirical Bayes geometric mean

90% confidence interval for the EBGM) were calculated for each VEC.

From the data mining, an aggregated dataset was produced as an output, summarizing the number of reports per VEC. An EBGM score greater than one indicated significance for a VEC. This was followed by review of individual case reports and case series where necessary by the JSM secretariat. Figure 3 shows an example of the spreadsheet produced from the data mining run for the selection of assessment options and possible actions to assign to each VEC during signal validation.

3.2.3 Signal Validation and Prioritization

The UK MHRA conducted a thorough biweekly data mining run on the combined country data in the DISD system to create a comprehensive report summarizing the number of reports for each VEC. A designated signal validation lead, representing the participating country in the JSM secretariat, led the validation process with support from the AU-3S staff. The lead then presented the validation outcome to the JSM secretariat team for in-depth discussion and necessary action. Additionally, the UK MHRA focal person provided support to the secretariat by sharing expertise in validation and prioritization based on their experience with UK processes, aiming to transfer skills to NMRA staff from the participating countries.

The JSM secretariat, in collaboration with the UK MHRA, meticulously investigated the aggregated dataset for specific signals or VECs that may require urgent attention. They used statistical disproportionality methods to pinpoint any VECs with reporting rates that were higher than expected. This analysis was based on UK background data for vaccines, pending the collection of sufficient African data by the AU-3S program to calculate background rates specifically for the African population.

During the validation process, special attention was given to unlisted events in the approved vaccine product information, adverse events of special interest (AESI), serious events (whether listed in the product information or unknown), and events that may have a significant impact on public health. The review of available information in the line listing included the time to onset, relevant medical and drug history, reporter demographics, relevant risk factors, and available causality assessment outcomes.

The JSM secretariat followed-up with member countries to obtain relevant additional information and preliminary assessments of cases conducted at the country level. In the case of a reviewed AEFI/AESI or a potential signal being validated and considered a priority for further evaluation, it was escalated to the JSM group for further assessment, discussion, and subsequent recommendation to the NMRA and/or national safety committees in the relevant countries.

3.3 Outcomes and Practical Application of Signal Assessment by the JSM Group

3.3.1 Adverse Event Reports Submitted to the DISD

Between 21 April 2021 and 11 December 2023, the DISD system accumulated 48,294 AEFI reports, all spontaneously

reported for six COVID-19 vaccines (NRVV Ad [ChAdOx1 nCoV-19]; Ad26.COV2.S; Elasomeran; Tozinameran; Covid-19 vaccine [Vero Cell], Inactivated; NRVV Ad26 [Gam-Covid-Vac]) administered in the five pilot countries (see Table 2). The proportion of events reported by the different countries ranged between 34.6% from Nigeria and 4.7% from Kenya, bearing in mind that Kenya joined the program only towards the end of 2022. During the specified period, the JSM group convened a total of 15 meetings, three of which were conducted in person. Additionally, the JSM secretariat held 65 meetings of which two were in-person meetings.

3.3.2 Vaccine–Event Combinations Validated

Based on the 48,294 AEFI reports in the DISD, the JSM group validated 2742 VECs across six different COVID-19 vaccines (see Fig. 4). It must be noted that AEFI reports were collected within the pilot countries via spontaneous reporting systems, hence a causal association between the COVID-19 vaccines and the reported AEFI cannot be inferred.

Figure 5 illustrates the 20 most common VECs reported spontaneously for each of the COVID-19 vaccines used in the pilot countries during the pandemic. As mentioned previously, a causal association between the COVID-19 vaccines and the reported AEFI cannot be inferred because of the spontaneous reporting and in the absence of available background rates. However, most of the reported AEFI/AESI had already been observed during the COVID-19 vaccine clinical trials and were listed in the respective summary of product characteristics, but there were a few exceptions. The most frequently reported AEFI were neurological symptoms such as headache; general symptoms such as pyrexia, malaise, and asthenia; events linked to vaccine administration or to the vaccine injection site; musculoskeletal symptoms such as myalgia, arthralgia, and back pain; and gastrointestinal symptoms such as nausea, abdominal pain, and diarrhea. Anaphylaxis, followed by palpitations were the most frequently reported AESI.

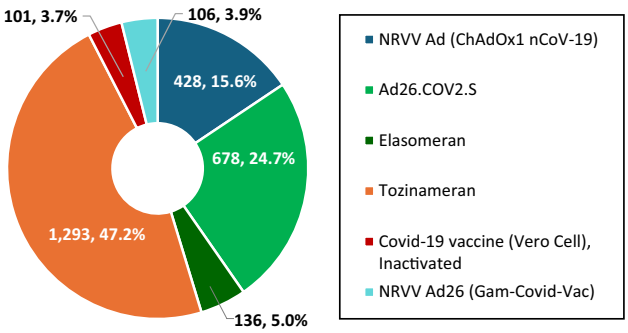


Fig. 4 Distribution of vaccine–event combinations validated for the COVID-19 vaccines monitored between 21 April 2021 and 11 December 2023. Disclaimer: COVID-19 vaccines are identified by generic names. Data on AEFI were collected via spontaneous reporting systems, hence a causal association between the COVID-19 vaccines and the reported AEFI cannot be inferred

Table 2 Adverse events following immunization (AEFI) reported in the data integration and signal detection (DISD) system for the COVID-19 vaccines per the number of doses administered, distributed by the five pilot countries for the period 21 April 2021 to 11 December 2023 ($n=48{,}294$)

COVID-19 vaccine	Number of AEFI (number of doses administered) per country					Total number (%) of AEs
	Ethiopia	Ghana	Kenya	Nigeria	South Africa	
NRVV Ad (ChAdOx1 nCoV-19)	4977 (6,552,847)	3405 (10,545,038)	629 (8,990,800)	9231 (19,365,944)	7[a] NA	18,249 (37.8)
Ad26.COV2.S	4557 (43,768,507)	1170 (8,983,153)	881 (5,590,480)	131 (75,372,515)	2178 (735,908)	8917 (18.5)
Elasomeran	NA	66 (1,065,357)	133 (2,325,240)	4693 (15,492,167)	2[a] NA	4894 (10.1)
Tozinameran	5251 (8,660,564)	6 (7,903,938)	621 (8,636,813)	587 (24,130,454)	5986 (2,9419,294)	12,452 (25.8)
Covid-19 vaccine (Vero Cell), inactivated	1903 (12,776,714)	NA	0 (39,711)	NA	1[a] NA	1904 (3.9)
NRVV Ad26 (Gam-Covid-Vac)	NA	1878 (18,368)	0 (3866)	NA	NA	1878 (3.9)
Total number (%) of AEFI	16,688 (34.6)	6525 (13.5)	2264 (4.7)	14,642 (30.3)	8174 (16.9)	48,294

Disclaimer: COVID-19 vaccines have been identified by generic names. Data on AEFI were collected via spontaneous reporting systems, hence a causal association between the COVID-19 vaccines and the reported AEFI cannot be inferred

NA not applicable because not administered in the country

[a]Suspected vaccine selected erroneously by reporter

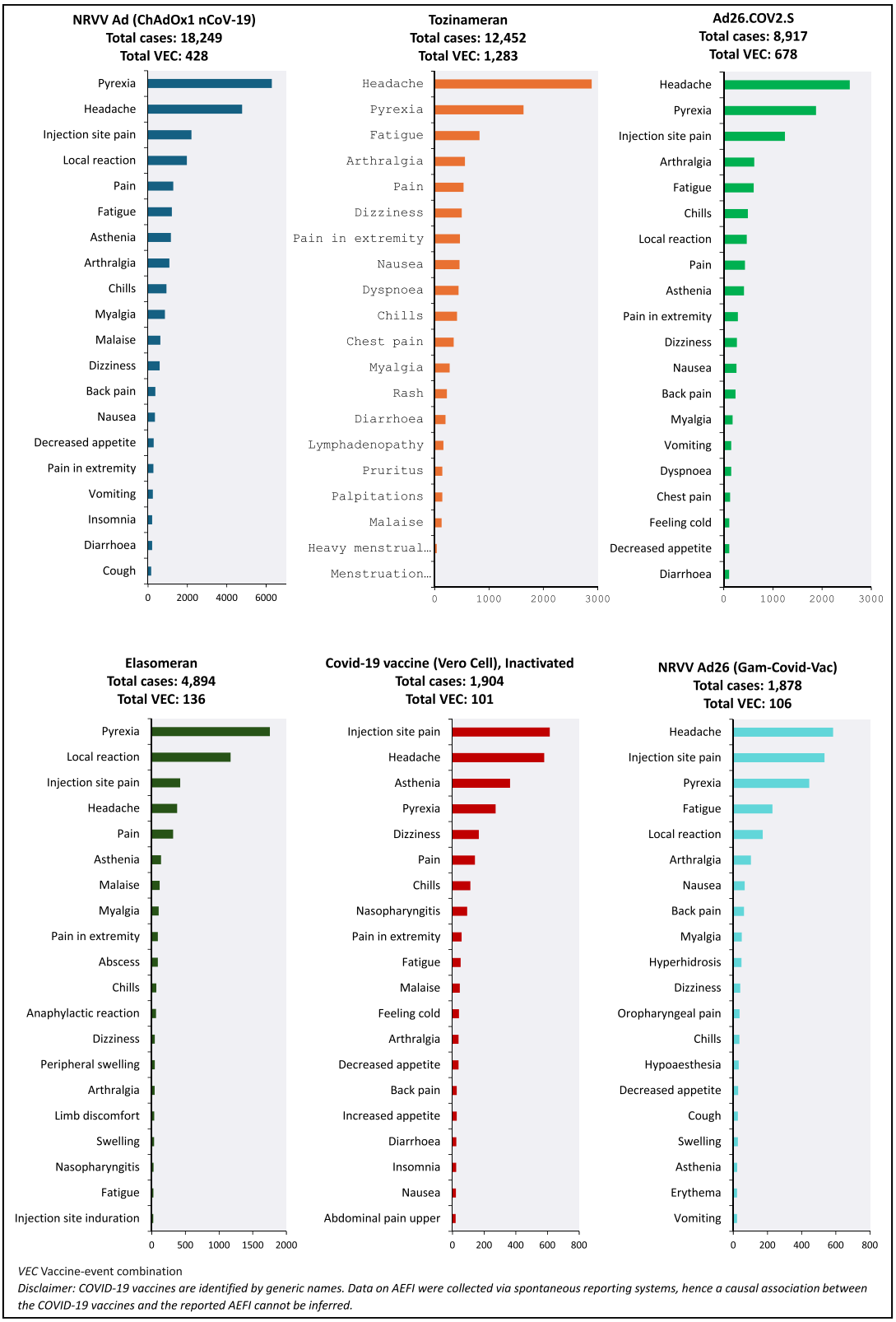


Fig. 5 The 20 most common spontaneously reported vaccine–event combinations (VECs) distributed by COVID-19 vaccine administered in the pilot countries for the period 21 April 2021 to 11 December 2023

3.3.3 Events of Interest and Signal Assessment

The main objective of signal assessment was to further investigate possible safety signals and AESI, to evaluate and determine whether any regulatory action or risk minimization measures would be warranted. Upon identifying a possible signal or AESI, the JSM secretariat performed a thorough evaluation to verify and ensure sufficient evidence was available to substantiate recommendations of appropriate action(s). Information from case listings associated with the signal or event were investigated, considering scientific evidence such as biological plausibility, temporality, clinical information, demographics, relevant risk factors, the quality of reported cases, and any outcomes of the causality assessment from national safety committees. During this process, the relevant countries were contacted to obtain additional information as appropriate. Delayed case investigations and subsequent causality assessment by national safety committees was a significant challenge faced by the countries.

Following thorough evaluation by the JSM secretariat, all possible signals or events of interest were again reviewed and discussed by experts within the larger JSM group at dedicated meetings. Subsequently, the JSM group suggested appropriate actions to the JSM secretariat and/or the NMRAs in the relevant pilot countries. These actions included ongoing monitoring for additional evidence, refraining from immediate action/intervention, engaging with the relevant MAH for supplementary information, or facilitating the dissemination of pertinent information about the event to HCPs or the public to ensure optimal use of the vaccines.

Over the period 21 April 2021 to 11 December 2022, the JSM group advised on nine noteworthy events based on the VECs evaluated and escalated from the JSM secretariat to the larger JSM group. The use of recommendations issued by the JSM group varied across NMRAs. For example, Ghana used the recommendation from the JSM group on appetite disorders with COVID-19 vaccines to request the MAH of the Ad26.COV2.S COVID-19 vaccine to review their safety data and share information about the event. This recommendation was aimed at providing a worldwide review on appetite disorders following administration of the vaccine, although some of the participating countries did not provide feedback on how they implemented this recommendation. Similarly, general recommendations such as capacity building for HCPs to identify and monitor specific events were actioned by countries; however, the AU-3S program did not obtain evidence to that effect. A summary of the notable events and the corresponding recommendations suggested by the JSM group is summarized in Table 3.

3.3.4 Knowledge and Experience Sharing

The accumulated data in the DISD served as a reference database for the pilot countries to compare what was observed in individual countries with cross-country trends. This was a significant advantage that has greatly empowered pilot countries to enhance discussions regarding potential signals identified within their borders. For example, upon request, the JSM group provided expert opinion on the safety of the Ad26.COV2.S COVID-19 vaccine to Ethiopia's Ministry of Health, which requested an opinion on the safety of the vaccine to assist in its decision-making process on providing emergency use authorization for the Ad26.COV2.S COVID-19 vaccine to be administered in the country. The JSM opinion was based on a review and collation of available published literature on the safety of the vaccine and a review of safety data from the DISD system. Additionally, the group sought the experience of participating countries using the vaccine and consulted information from the WHO global database of individual case safety reports in VigiBase®.

Following the reporting of suspected GBS cases post-COVID-19 vaccination in South Africa, the AU-3S JSM group facilitated cross-country signal assessment and reviewed all suspected GBS cases in the DISD system. Based on the cross-country data collected by the AU-3S program, GBS appeared to be a very rare event, limited to three fatal cases causally linked to the Ad26.COV2.S COVID-19 vaccine and reported from South Africa. South Africa's National Immunization Safety Expert Committee conducted causality assessment for these cases, using the WHO causality assessment methodology, to determine the likelihood of the event being linked to vaccination. In addition, the South African Health Products Regulatory Authority issued a media briefing about each of the events to assure the public that the safety monitoring systems which are in place enabled the identification of very rare adverse events such as GBS, building confidence in the vaccination program [23–25]. These cases were shared and discussed with the JSM group during one of the JSM meetings. Through the JSM review processes, Ethiopia also highlighted suspected GBS case reports and subsequently further investigated these cases and conducted causality assessment, mirroring the approach taken by South Africa. The JSM group recommended raising awareness and building HCPs' capacity to diagnose and manage cases of GBS.

3.3.5 Sharing of Recommendations and Information with the Wider Stakeholders

Safety-related communication with the media and the public was the responsibility of the participating countries. Country

Table 3 Summary of events of interest, motivation for signal assessment, and corresponding recommendations from the Joint Signal Management (JSM) group

Event of interest	Motivation for signal assessment	JSM group recommendations	Date discussed
Erectile dysfunction	Event not listed in the PI, and item of interest prioritized due to concerns among the public about erectile dysfunction being a potential side effect of COVID-19 vaccines. This gained media attention in pilot countries and may contribute to vaccine hesitancy.	More evidence is required to take any regulatory action. Recommendation to monitor for further evidence from additional reported cases.	19 May 2021
Malaria-like symptoms	Identified by one of the member countries during routine signal validation of cross-country data.	Initial review recommended monitoring for additional cases and further evidence	15 June 2021
	Additional cases continued to be reported and triggered a second review of the event since there was a potential for morbidity and mortality due to failure to diagnose malaria in patients receiving COVID-19 vaccines. Assessment of cases revealed that these were likely to be malaria-like illness erroneously reported as malaria. Malaria is a parasitic infection, not a vaccine side effect. A concern was raised regarding the possibility of assuming actual malaria illness being a vaccine side effect, resulting in delayed malaria diagnosis with subsequent severe illness.	Crucial for pilot countries to raise public awareness about seeking medical assistance if malaria-like symptoms are experienced. This would enable timeous identification and management of possible subclinical malaria.	28 March 2023
Menstrual disorders	The event was not listed in the PI and was prioritized due to media attention in pilot countries, which may contribute to vaccine hesitancy	Monitor for further evidence from additional reported cases, as there was insufficient evidence of a link between COVID-19 vaccines and menstrual disorders at the time the event was identified.	22 September 2021
Tinnitus	A review of cases of dizziness and tinnitus reported in the DISD system was triggered by a peer NMRA's communication and confirmation of dizziness and tinnitus as an adverse effect linked to the JAd26.COV2.S COVID-19 vaccine, and the recommendation to amend the PI for inclusion of tinnitus as a side effect.	Based on insufficient information available about the cases in the DISD system, the recommendation was to monitor for further evidence and additional cases being reported. The benefit–risk balance of the vaccine remained unchanged.	22 September 2021
Facial nerve disorder	Raised by one of the member countries.	The initial recommendation was to monitor for additional cases and further evidence.	15 June 2021
	Additional cases reported in the DISD triggered the need for another assessment of reported cases.	NMRAs of pilot countries to request the MAHs for review of their available safety data and provide information on the event.	13 September 2023
Appetite disorders (decreased appetite and increased appetite)	One of the member countries reported a decrease in appetite for the attention of the JSM group as a potential signal for the Ad26.COV2.S COVID-19 vaccine.	The initial recommendation after the first assessment was to monitor for further evidence and additional cases reported.	6 July 2022
	Additional cases reported in the DISD triggered a thorough review of cases reported in the system for all vaccines, including reports of increased appetite. The evidence for a class effect on decreased appetite was strong.	No action was recommended, due to insufficient evidence of a link between increased appetite and the Ad26.COV2.S COVID-19 vaccine. Continuous monitoring for any further evidence was recommended, and participating countries were advised to request the MAH to review available safety data and share information about the event.	1 November 2022
Alopecia	Identified during routine signal detection with the potential to affect the quality of life of an individual.	Recommendation to categorize alopecia as an event of interest and closely monitor for further evidence and additional cases reported.	28 March 2023
GBS	Reports from one of the pilot countries following the announcement of three deaths from GBS, which were causally linked to the Ad26.COV2.S COVID-19 vaccine by the national safety committee, and subsequent continuous media engagement. Request from the country to conduct a case–series analysis.	With GBS listed in the PI, continue to raise awareness of this very rare adverse event and enhance the capacity of HCPs in the clinical identification and management of GBS.	1 November 2022

Table 3 (continued)

Event of interest	Motivation for signal assessment	JSM group recommendations	Date discussed
Ocular (eye) disorders	Adverse event reports of blurred vision post-vaccination with the NRVV Ad (ChAdOx1 nCoV-19) and Ad26.COV2.S COVID-19 vaccines were brought to the attention of the JSM group due to a potential association of this event with blood clots/thrombocytopenia (a rare but identified adverse event for the NRVV Ad [ChAdOx1 nCoV-19] and Ad26.COV2.S vaccines).	Based on no evidence that these cases were causally linked to the vaccines, targeted follow-up of blurred vision cases with specific questions around blood clotting and thrombocytopenia was recommended.	22 September 2021
	Additional cases reported in the DISD triggered a routine case–series analysis.	Countries to monitor reported cases and follow-up with patients who may be complaining or presenting with ocular symptoms and take appropriate action.	31 October 2022

Disclaimer: COVID-19 vaccines have been identified by generic names. Data on AEFI have been collected by spontaneous reporting systems, hence a causal association between the COVID-19 vaccines and the reported AEFI cannot be inferred

AEFI adverse events following immunization, *AESI* adverse events of special interest; *DISD* data integration and signal detection, *GBS* Guillain-Barré syndrome, *HCPs* healthcare providers, *MAH* market authorization holders, *NMRAs* National Medicines Regulatory Authorities, *PI* product information

representatives in the JSM group therefore escalated all JSM group recommendations to their countries for use as appropriate. At the same time, a quarterly report describing the JSM group discussions and recommendations was shared with the African Advisory Committee on Vaccine Safety and other relevant stakeholders.

3.4 Lessons Learned from JSM Group Activities and Future Implications

3.4.1 Use of Joint Signal Management Enables Optimization of Resources and Building of Expertise

Signal management activities, such as those performed by the JSM group during the COVID-19 pandemic, should ideally lead to a stronger and more direct impact on countries' regulatory decisions. Joint signal management enabled participating countries to rely on coordinated activities to monitor the safety of vaccines during the pandemic. For this to have a more significant impact in future, mechanisms for follow-up on the recommendations of the JSM group and their impact on individual member countries' decision-making and implementation, will be critical for meaningful signal management.

3.4.2 Need to Strengthen Countries' Capacity to Investigate Serious Cases

Considerable effort was made to ensure the quality of recorded and reported information through electronic systems designed to ensure that case reports were complete before being submitted to the DISD system; however, an opportunity remains to enhance the quality of case reports submitted by countries. Sufficient information about reported events is needed, and timely investigation of severe cases need to be conducted at the country level, which would optimize signal assessment of cross-country data. Investigating serious cases involved challenges at the country level because safety reports were reported during a pandemic. Differences in the procedures for reporting serious cases and non-serious cases affected the comparison of reporting among the different countries when evaluating and making conclusions on the data. For example, some countries' procedures required serious events to be investigated before they were reported, whereas others required all events to be reported, even before investigations and causality assessments were conducted. Standardization of these procedures may be considered in future signal management activities across countries.

4 Discussion

In this article, we showcased the activities of the JSM group and its impact on ensuring vaccine safety across five participating countries during the COVID-19 pandemic. This is the first effort at safety signal management across multiple countries within the African continent with the collaboration of cross-country experts.

The safety data review conducted by the JSM group revealed no new safety concerns beyond those already documented in the product information. Recommendations from the JSM group have confirmed the safety of the COVID-19 vaccines administered in the participating countries, aligning with global observations. Although several studies have identified a deficiency in expertise to effectively use and act upon collected data as being a notable gap in Africa [9], the approach adopted by the JSM group aimed to facilitate collaborative assessment of safety by regulators, fostering improved expertise and confidence in decision-making processes. National regulatory authorities used the data collected across countries and the assessment outcomes to address safety inquiries regarding the vaccines administered to their populations.

The JSM group establishment enabled close collaboration across historically siloed disease-specific programs (e.g., EPIs) and the NMRAs in all countries. Having the two stakeholders assess the safety data allows trust and easy sharing of safety reports instead of running parallel systems for coordinated risk assessment of products. For the AU-3S COVID-19 vaccine pilot, the JSM group comprised all essential vaccine-related safety experts from the NMRAs, EPIs, national vaccine safety committees, and independent subject matter experts. With this strategic collaboration, the JSM group founded a scalable and adjustable framework for a future continental safety monitoring platform with an increased number of member states and products. The joint activities enabled the EPI and the NMRA to work together, which is an excellent example of a successful collaborative initiative that can be adapted to all future multi-product surveillance activities.

In addition, although GBS is documented in the product information, the assessment of GBS cases in the DISD system was conducted by the JSM group as South Africa reported three GBS deaths causally linked to the Ad26.COV2.S COVID-19 vaccine. The exact cause of GBS is unknown, but certain common risk factors such as infections by other viruses or bacteria, as well as vaccination, are reported in the literature [26]. The available cross-country data and the joint assessment of the data in the DISD enabled a conclusion that GBS was a very rare event and death as an outcome had not occurred in any of the other countries.

The JSM group provided a valuable opportunity for learning, information sharing, and capacity strengthening among experts from the pilot countries. As a result, all countries benefited from valuable safety information, which positively impacted the deployment of the vaccines and subsequent safety monitoring. For example, South Africa and Ghana shared their experiences in signal management activities, including investigation, causality assessment and its associated challenges, and the role in guiding regulatory decisions of AESI related to COVID-19 vaccines. In addition, all results from signal management activities were discussed during larger JSM group meetings, which provided opportunities for knowledge exchange with relevant experts from all participating countries and served as a peer-review mechanism for the functionality and performance of pharmacovigilance systems in participating countries.

The JSM group has also been strongly supported by the UK MHRA as a technical partner for the AU-3S program. Their participation, along with that of regulators from the member countries, in routine signal identification and validation on cross-country safety data has been pivotal in strengthening in-country safety expertise, backed by solid evidence-based decision-making through tailored collaboration with a peer regulator such as the UK MHRA. Furthermore, the UK MHRA provided safety monitoring training at various levels that continue to be used by country NMRAs for other capacity development areas to improve data quality management and in-country signal management activities.

In the long-term, AfriVigilance, a continental database based on African safety data and background rates, will replace the DISD to support signal management and analysis for the continent. These efforts will ensure that NMRAs, public health programs, and the pharmaceutical industry can make informed decisions about health product safety and efficacy for public health.

The aim of the AU-3S program is for the JSM group to continue to serve as a platform for technical support for both established NMRAs and their African counterparts as well as relevant African public health programs. The capabilities of the AU-3S JSM group members will be enhanced by interaction with experts from reference regulators and the fostering of exchange of experiences and best practices among participating countries [27].

5 Limitations

We acknowledge that this research project has some limitations. Our data on suspected AEFI were collected via passive surveillance and spontaneous reporting systems. Information from the spontaneous reports was often insufficient, and this complicated the ability to perform objective assessments of

AESI. It is possible for adverse events to be reported several times by the same reporter. The number of reports in our dataset therefore does not reflect the number of AEFI cases. Furthermore, spontaneous reporting of AEFI is voluntary and does not undergo formal causality assessment. A causal association between each COVID-19 vaccine and the reported AEFI documented in our research cannot be inferred, and further investigation is required.

6 Conclusions

The JSM group laid a foundation for effective collaboration across borders in Africa with the shared purpose of safety monitoring of medicines, including vaccines for the African population amidst the COVID-19 pandemic. The JSM group showed successfully how LMICs can collaborate to create cross-country safety signal management processes. Although no new safety signals were detected, safety-related recommendations issued by the JSM group provided opportunities for countries to review their vaccine programs, ensured HCPs remained vigilant regarding vaccine safety, and educated the public to maintain confidence in the vaccines and the health system. The group's approach to continuous capacity building and signal management is scalable and replicable for other priority products and diseases in Africa and provides a model for future safety responses in LMICs. The group will continue to leverage the knowledge acquired during the COVID-19 vaccine pilot to enable Africa to provide robust guidance for future safety surveillance measures.

Acknowledgements The authors thank the Bill and Melinda Gates Foundation for funding the entire project through AUDA-NEPAD, and the project lead, Raj Long, for her vision of safety monitoring and adverse event reporting of health products used in Africa via an African AfriVigilance database. We thank all individuals and agencies for the support rendered during the development and implementation of the AU-3S Program: (1) Members of the JSM secretariat for their dedication to signal management activities: Habtamu Gashaw and Mehiret Maru, Ethiopian Food and Drug Authority (EFDA); Abena Asamoa-Amoakohene and Adela Ashie, Ghana Food and Drugs Authority (FDA); Tanko Naziru, Expanded Program on Immunization, Ghana; Martha Mandale, Pharmacy and Poisons Board, Kenya; Angela Faniyi, National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria; Victoria Sekiti and Robert Ndzovela, South African Health Products Regulatory Authority (SAHPRA); Ndimuhulu Dowelani, National Department of Health, South Africa; (2) Technical partners for support provided in the implementation of signal management activities: June Raine and Mick Foy from the Medicines and Healthcare products Regulatory Agency, UK; Steve Anderson, Narayan Nair, and Gopa Raychaudhuri from the US FDA; (3) Strategic vision, technical partnership, and review of the manuscript: Raj Long, Shyam Bhaskaran, Charles Preston, Rebecca Drinkwater, Deirdre McCarthy, and June Cha from the Bill & Melinda Gates Foundation, USA.

Declarations

Funding Open access funding provided by Sefako Makgatho Health Sciences University. The implementation of the AU-3S program in the pilot countries, which resulted in the work presented in this paper, were funded by the Bill & Melinda Gates Foundation, Seattle, WA, USA (grant number: INV-045215 [OPP1213055]). Open access for this paper was enabled through an agreement between Sefako Makgatho Health Sciences University and Springer Nature.

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and material N/A.

Ethics approval N/A.

Consent to participate N/A.

Consent for publication All authors have read the manuscript and consent to its publication.

Code availability N/A.

Author contributions JSM group involved in the implementation of the work presented in this paper: VPD, HMG, MBA, NYB, MB, GTS, JOG, EMG, TA, WA, HJL, MCL, AM, KAA, MM, UGE, HM, AKN, MS, MK, KM, YIT, AA, KMY, OE, LS, KD, KO, MCA, DMD, HG, BS, FS, AA, and JCM. Data acquisition and analysis: VPN, MBA, NYB, and HM. First draft of the manuscript: VPN and JCM. Revision for important intellectual content: VPD, HMG, MBA, NYB, MB, GTS, JOG, EMG, TA, WA, HJL, MCL, AM, KAA, MM, UGE, HM, AKN, MS, MK, KM, YIT, AA, KMY, OE, LS, KD, KO, MCA, DMD, HG, BS, FS, AA, and JCM. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. World Health Organization. The importance of pharmacovigilance. Safety Monitoring of medicinal products. 2002 [cited 2002 1 January 2002]. https://www.who.int/publications/i/item/10665-42493.
2. Sharrar RG, Dieck GS. Monitoring product safety in the postmarketing environment. Ther Adv Drug Saf. 2013;4(5):211–9.
3. Singh S, Loke YK. Drug safety assessment in clinical trials: methodological challenges and opportunities. Trials. 2012;20(13):138.

4. Alomar M, Tawfiq AM, Hassan N, Palaian S. Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future. Ther Adv Drug Saf. 2020;11:2042098620938595.
5. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ. 2004;329(7456):44–7.
6. Varallo FR, Planeta CS, Herdeiro MT, Mastroianni PC. Imputation of adverse drug reactions: causality assessment in hospitals. PLoS ONE. 2017;12(2): e0171470.
7. van der Boor SC, Schmitz-de Vries ETJ, Smits D, Scholl JHG, Rolfes L, van Hunsel F. Spontaneously reported adverse events following COVID-19 basic and booster immunizations in the Netherlands. Vaccine. 2023;41(29):4319–26.
8. Sentes K, Kipp W. Global burden of disease: huge inequities in the health status in developing and developed countries. Healthc Manage Forum. 2003;16(3):27–9.
9. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. Expert Rev Clin Pharmacol. 2015;8(4):449–60.
10. Council for International Organizations of Medical Sciences. Practical approaches to risk minimisation for medicinal products: report of CIOMS working group IX. Geneva; 2014.
11. Kashte S, Gulbake A, El-Amin Iii SF, Gupta A. COVID-19 vaccines: rapid development, implications, challenges and future prospects. Hum Cell. 2021;34(3):711–33.
12. World Health Organization. COVID-19 vaccines: safety surveillance manual. 2021.
13. Chandler RE. Optimizing safety surveillance for COVID-19 vaccines. Nat Rev Immunol. 2020;20(8):451–2.
14. Iessa N, Macolic Sarinic V, Ghazaryan L, Romanova N, Alemu A, Rungapiromnan W, et al. Smart Safety Surveillance (3S): multi-country experience of implementing the 3S concepts and principles. Drug Saf. 2021;44(10):1085–98.
15. Bhaskaran S PC, Long R. Smart safety surveillance (3S): proven approach to building functional LMIC pharmacovigilance systems. US: Bill & Melinda Gates Foundation; 2021.
16. African Union Development Agency–NEPAD: AU-3S. An African Perspective on Implementing and Conducting Safety Surveillance of COVID-19 Vaccines. 2021 [cited May 2021]. https://www.nepad.org/publication/african-perspective-implementing-and-conducting-safety-surveillance-of-covid-19.
17. African Union Development Agency–NEPAD: AU-3S. An african perspective on implementing and conducting safety surveillance of COVID-19 Vaccines. Midrand: AUDA-NEPAD; 2021.
18. AUDA-NEPAD. Electronic Reporting using the Med Safety App. 2021 [cited 2021 February 2021]. https://www.nepad.org/microsite/electronic-reporting-using-med-safety-app.
19. AUDA-NEPAD. Overview of AfriVigilance. 2021.
20. Kiguba R, Olsson S, Waitt C. Pharmacovigilance in low- and middle-income countries: a review with particular focus on Africa. Br J Clin Pharmacol. 2023;89(2):491–509.
21. World Health Organization. Reporting form for AEFI. Standard reporting form for adverse events following immunization (AEFI). 2021 [cited 2021 13 April 2021]. https://www.who.int/publications/m/item/reporting-form-aefi.
22. Levin MC, Krichavsky M, Berk J, Foley S, Rosenfeld M, Dalmau J, et al. Neuronal molecular mimicry in immune-mediated neurologic disease. Ann Neurol. 1998;44(1):87–98.
23. SAHPRA. Update On COVID-19 Vaccine Janssen—Guillain-Barré Syndrome. 2022 [cited 2022 04 August 2022]. https://www.sahpra.org.za/news-and-updates/update-on-covid-19-vaccine-janssen-guillain-barre-syndrome/.
24. SAHPRA. COVID-19 Vaccine Janssen Update—Second Fatal Case of Guillain-Barré Syndrome. 2022 [cited 2022 12 September 2022]. https://www.sahpra.org.za/news-and-updates/covid-19-vaccine-janssen-update-second-fatal-case-of-guillain-barre-syndrome/.
25. SAHPRA. COVID-19 Vaccine Janssen Update—Third Fatal Case of Guillain-Barré Syndrome. 2023 [cited 2023 21 April 2023]. https://www.sahpra.org.za/news-and-updates/covid-19-vaccine-janssen-update-third-fatal-case-of-guillain-barre-syndrome/#:~:text=SAHPRA%20has%20been%20informed%20of,Health%20Organization's%20(WHO)%20methodology.
26. Ogunjimi OB, Tsalamandris G, Paladini A, Varrassi G, Zis P. Guillain-Barré syndrome induced by vaccination against COVID-19: a systematic review and meta-analysis. Cureus. 2023;15(4): e37578.
27. Shyam Bhaskaran, Charles Preston, Long R. Smart safety surveillance (3S): proven approach to building functional LMIC pharmacovigilance systems. 2021 [cited 2023]. https://globalforum.diaglobal.org/issue/december-2021/#smartsafety.

Authors and Affiliations

Victoria Prudence Nambasa[1] · Hannah May Gunter[2] · Modupe Bamidele Adeyemo[1] · Neetesh Yanish Bhawaneedin[3] · Marc Blockman[2] · George Tsey Sabblah[4] · John Owusu Gyapong[5] · Eric Muriithi Guantai[6] · Tamrat Abebe[7] · Workeabeba Abebe[8] · Henry Jeremy Lawson[9] · Mercedes Chawada Leburu[1] · Abdullahi Mohammed[10] · Kwame Amponsa-Achiano[11] · Mafora Florah Matlala[12] · Uchenna Geraldine Elemuwa[13] · Hudu Mogtari[1] · Alexander Kwadwo Nyarko[14] · Marione Schönfeldt[15] · Mercy Kamupira[16] · Kerrigan McCarthy[17,18] · Yohannes Lakew Tefera[19] · Asnakech Alemu[20] · Kabir Mawashi Yusuf[21] · Obi Emelife[21] · Ladji Sidibe[1] · Kudakwashe Dandajena[1] · Kenneth Onu[1] · Mojisola Christianah Adeyeye[13] · Delese Mimi Darko[4] · Heran Gerba[20] · Boitumelo Semete[12] · Fred Siyoi[22] · Aggrey Ambali[1] · Johanna Catharina Meyer[23,24]

✉ Victoria Prudence Nambasa
victorian@nepad.org; vpnambasa@gmail.com

✉ Johanna Catharina Meyer
hannelie.meyer@smu.ac.za

[1] African Union Development Agency-NEPAD, Johannesburg, South Africa

[2] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

[3] Patient Safety Monitoring, Safety and Surveillance Group, Medicines and Healthcare products Regulatory Agency, London, UK

[4] Food and Drugs Authority (FDA), Accra, Ghana

[5] University of Health and Allied Sciences, Ho, Ghana

[6] Department of Pharmacology, Clinical Pharmacy and Pharmacy Practice, Faculty of Health Sciences, University of Nairobi, Nairobi, Kenya

[7] Department of Microbiology, Immunology, and Parasitology, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia

[8] Department of Paediatrics and Child Health, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia

[9] Department of Community Health, University of Ghana Medical School, Accra, Ghana

[10] Department of Pathology, Ahmadu Bello University Teaching Hospital SHIKA, Zaria, Kaduna State, Nigeria

[11] Expanded Program on Immunization, Ghana Health Service, Accra, Ghana

[12] South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa

[13] National Agency for Food and Drug Administration and Control (NAFDAC), Abuja, Nigeria

[14] College of Health Sciences, University of Ghana School of Pharmacy, University of Ghana, Accra, Ghana

[15] National Department of Health, Directorate: Child, Youth and School Health, Pretoria, South Africa

[16] Population Council, Johannesburg, South Africa

[17] Division of Public Health, Surveillance and Response, National Institute for Communicable Diseases, Johannesburg, South Africa

[18] Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg, South Africa

[19] Expanded Programme on Immunization, Ministry of Health, Addis Ababa, Ethiopia

[20] Ethiopian Food and Drug Authority, Addis Ababa, Ethiopia

[21] National Primary Health Care Development Agency, Abuja, Nigeria

[22] Pharmacy and Poisons Board, Nairobi, Kenya

[23] Department of Public Health Pharmacy and Management, Sefako Makgatho Health Sciences University, Pretoria, South Africa

[24] South African Vaccination and Immunisation Centre, Sefako Makgatho Health Sciences University, Pretoria, South Africa