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AFRICAN UNION DEVELOPMENT AGENCY

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SMART
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SURVEILLANCE

An African Perspective on Implementing and Conducting Safety Surveillance of COVID-19 Vaccines

AFRICAN UNION SMART SAFETY SURVEILLANCE (AU-3S) PROGRAMME

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Authors and acknowledgements

List of Acronyms

AACVS	African Advisory Committee on Vaccine Safety
AEFI	Adverse Events Following Immunisation
AESI	Adverse Event of Special Interest
AMRH	African Medicines Regulatory Harmonisation
AUDA-NEPAD	African Union Development Agency
AU-3S	African Union Smart Safety Surveillance
AVAREF	African Vaccine Regulatory Forum
AVATT	African Vaccine Acquisition Task Team
BMGF	Bill and Melinda Gates Foundation
CDC	Centers for Disease Control and Prevention
CEM	Cohort Event Monitoring
CIOMS	Council for International Organizations of Medical Sciences
EPI	Expanded Programme on Immunization
EUA	Emergency Use Authorisation
FDA	Food and Drug Administration (United States)
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunizations
GBT	Global Benchmarking Tool
HCW	Health Care Worker
HICs	High-Income Countries
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

JSM	Joint Signal Management
LMICs	Low and Middle-Income Countries
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
ML	Maturity Level
MoH	Ministry of Health
MTaPS	Medicines, Technologies, and Pharmaceutical Services
NRA	National Regulatory Authority
RECs	Regional Economic Communities
RMP	Risk Management Plan
SF	Substandard / Falsified
UMC	Uppsala Monitoring Centre
USAID	The U.S. Agency for International Development
WHO	World Health Organisation
WHO-AFRO	World Health Organisation Regional Office for Africa

Objectives of this Publication

The COVID-19 pandemic and COVID-19 vaccines rollout, by their unprecedented nature and record timelines respectively, further strengthen the importance of safety surveillance. To support stakeholders in conducting safety surveillance, the World Health Organisation has published the "COVID-19 Vaccines: Safety Surveillance Manual". This manual is a comprehensive set of guidelines that all countries are encouraged to leverage as a core document in ensuring the successful safety surveillance of their populations during their COVID-19 vaccine(s) rollout. The World Health Organisation has also released a protocol for active vaccine safety surveillance titled "Cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines" – based on the principles outlined in the WHO COVID-19 Vaccines Safety Surveillance Manual – and has published interim guidance to aid "Evaluation of COVID-19 vaccine effectiveness".

This AUDA-NEPAD publication aims to provide a series of reflections to successfully implement the above-mentioned guidance, within the context of Africa. Additionally, this document presents relevant tools, materials, and initiatives to support African countries to effectively implement safety surveillance of COVID-19 vaccines and future medical products and provides learnings based on the experiences of the African Union Smart Safety Surveillance programme.

The document has two main sections. The first section focuses on outlining the importance of pharmacovigilance generally and specifically for COVID-19 vaccines, after which unique challenges and considerations in the context of Africa are discussed. The second section provides a series of recommen-dations to successfully implement safety surveillance in Africa in the light of all identified challenges and considerations. These recommendations are grouped into 6 key categories: passive surveillance, active sur-veillance, manufacturers' pharmacovigilance activities, training and capacity strengthening, collaboration and coordination, and safety communications.

1. Introduction:
Importance of strong African safety surveillance in preparation for COVID-19 vaccine rollouts

1.1 Importance of safety surveillance for COVID-19 vacciness

Generally, medical products and technologies are monitored to ensure their safety. The detection, assessment, understanding, and prevention of adverse effects or any other medicine-related effects is known as pharmacovigilance[1] (PV), and it is done to establish that medical products and other health technologies remain safe throughout the product life cycle. These are essential public health activities designed to ensure that medical interventions consistently retain a favourable benefit-risk profile. Clinical trials do not always fully capture the benefit-risk profile of products because they are undertaken in well-controlled environments, for short periods, and do not typically include special populations or participants with comorbidities. That is an important reason why post-market surveillance, which falls under the umbrella of PV, is done. It occurs after regulatory approval and

is designed to monitor products when they are in use by patients.

The COVID-19 pandemic and COVID-19 vaccines rollout, by their unprecedented nature and record timelines respectively, further point to the need for a more fulsome understanding of the safety of these products:

• Vaccines have been developed at record speed. Some COVID-19 vaccines were ready for rollout less than a year after the COVID-19 outbreak started around January 2020, even though it usually takes several years to develop a vaccine.

• In addition to established organisations with proven track records, many new developers and manufacturers have emerged, with little or limited experience in vaccine production at scale.

[1] Further information available from: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance. Accessed 20 April 2021

- Due to urgency, regulators are shortening the time and path to market, notably through emergency use authorisations (EUAs), to allow for COVID-19 products to be made available in a timely manner.

- The scale of exposure of patients to COVID vaccines is unprecedented, with an objective to vaccinate several billion people in a short timeframe.

To support stakeholders in conducting safety surveillance, the World Health Organisation (WHO) has published the "COVID-19 Vaccines: Safety Surveillance Manual"[2] (latest version released on the 22nd December 2020). This guide outlines critical information around the infrastructure, processes, and capacity for performing safety surveillance of COVID-19 vaccines for all stakeholders before, during, and after the commencement of the vaccine rollout. This manual is a comprehensive set of guidelines, and all countries are encouraged to leverage it as a core document in ensuring the successful safety surveillance of their populations during the COVID-19 vaccine rollout, as well as for strengthening safety surveillance for non COVID related products. The WHO

has also released a protocol for active vaccine safety surveillance titled "Cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines"[3] – based on the principles outlined in the WHO COVID-19 Vaccines Safety Surveillance Manual. Furthermore, the WHO has published interim guidance for evaluating COVID-19 vaccine effectiveness (titled "Evaluation of COVID-19 vaccine effectiveness"[4]). The guidance is "targeted mostly for evaluations undertaken in (Low and Middle-Income Countries) LMICs" and – with clear links to the safety profile – will aid to fill gaps from clinical trials such as "effectiveness in subgroups, effectiveness against variants of concern and duration of protection".

1.2 African context: Need for strengthened safety surveillance on the continent

The African continent faces a unique context and specific challenges related to safety surveillance. Many African countries have constrained resources including financial, human, and technical. Particularly for National Regulatory Authorities (NRAs), there is often a lack of sustainable funding and a shortage in qualified staff and operational resources[5]. This lack of resources prevents them from setting up dedicated national PV systems, deploying data collection and signal detection tools, building the required expertise to support signal detection and risk assessment, conducting thorough assessments of detected signals, and sharing the data between national and global stakeholders.

The result of resource constraints is that PV capacity is limited. Vaccine adverse event reporting has been historically low in Africa, and in fact, less than 1% of all Adverse Events Following Immunisation (AEFIs) contained in the global database VigiBase[6] were generated in African countries[7]. This is concerning as the African population accounts for ~17% of the world's population and many large immunisation campaigns have been conducted on the continent. Within this small portion of African reports, the majority

USER MANUAL

COVID-19 VACCINE

COVID-19

Coronavirus Vaccine

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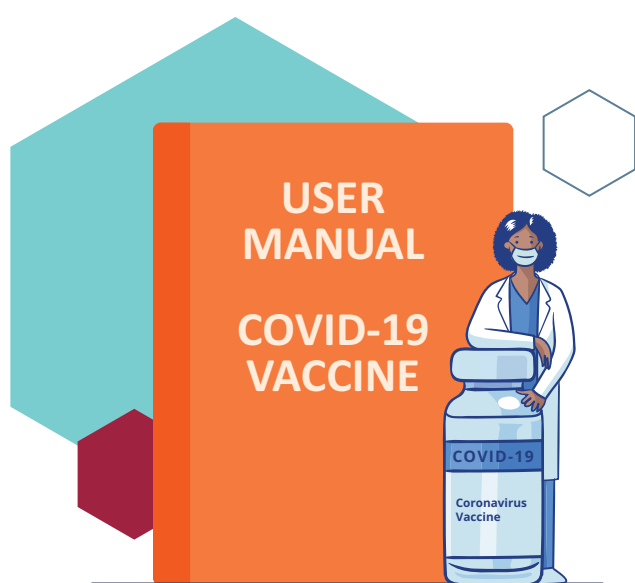
[2] Available from: https://www.who.int/publications/i/item/10665338400. Accessed 18 March 2021
[3] Available from: https://www.who.int/publications/m/item/protocol-template-CEM. Accessed 26 March 2021
[4] Available from: https://apps.who.int/iris/handle/10665/340301. Accessed 26 March 2021
[5] WHO. (2010). Assessment of medicines regulatory systems in sub-Saharan African countries: An overview of findings from 26 assessment reports.
Available from: https://www.who.int/medicines/publications/assesment_africa/en/. Accessed 08 April 2021
[6] Vigibase is managed by the Uppsala Monitoring Centre (UMC), which is the WHO's Collaborating Centre for International Drug Monitoring
[7] Yamoah, P., Bangalee, V., & Oosthuizen, F. (2019, Mar 8). Vaccines (Basel). Knowledge and Perceptions of Adverse Events Following Immunization among Healthcare Professionals in Africa: A Case Study from Ghana

(>95%) were generated by only 10 out of a total of 55 African countries[8].

When looking at results of the WHO's Global Benchmarking Tool (GBT), Tanzania and Ghana are the only WHO Regional Office for Africa (WHO-AFRO) countries that have received a maturity level 3 (ML3) rating for their PV systems for regulating health products[9]. As COVID-19 vaccine rollouts were imminent, African countries were not yet fully ready to conduct safety surveillance. This was seen when looking at the 44% average COVID-19 vaccines readiness score for WHO-AFRO countries in January 2021[10].

PV systems are also siloed in many African countries, preventing safety data from being made available to relevant stakeholders, fully analysed, and acted upon. While most countries have mechanisms in place to monitor the safety of marketed medicines, safety surveillance measures typically fall short during implementation and are not sufficiently integrated with other regulatory activities[11].

The limited capacity has a number of implications in the context of COVID-19 specifically. For example, African regulators typically have access to limited safety data

packages for COVID-19 vaccines. While it is not unusual that clinical trials are conducted in high-income countries (HICs), novel products are typically introduced first in HICs prior to introduction in LMICs, allowing them to rely on safety data from HICs. While this may be possible for select COVID-19 vaccines already approved in HICs, other vaccines with significantly less safety data are likely to first be rolled out in Africa or simultaneously with other countries across the globe. Furthermore, even when relying on safety data from HICs, there will be limitations in the volume of data available – particularly for select racial and ethnic populations, notably in the context of African populations.

PV systems also play a role in detecting sub-standard and falsified (SF) medical products. SF products are more likely to occur under certain conditions, including situations with constrained access, weak regulatory capacity, and poor governance[12,13]. Reports of sub-standard or falsified COVID-19 related vaccines have already been seen globally, including in Africa[14], and can undermine public confidence in vaccination efforts.

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[8] 10 countries are Egypt, Democratic Republic of Congo, Morocco, South Africa, Sierra Leone, Zimbabwe, Tunisia, Ghana, Nigeria, and Senegal. Full list of 55 African Union Member States available from: https://au.int/en/member_states/countryprofiles2#:~:text=Share%3A,countries%20on%20the%20African%20continent.&text=The%20 following%20list%20shows%20all,or%20its%20predecessor%20the%20OAU. Accessed 30 March 2021

[9] Four maturity level (ML) ratings exist, on a scale of ML1, existence of some elements of regulatory system, to ML4, operating at advanced level of performance and continuous improvement. Additional information available from: https://www.who.int/medicines/regulation/benchmarking_tool/en/. Accessed 03 March 2021

[10] Based on results from the Vaccine Introduction and Readiness Assessment Tool (VIRAT) developed by WHO and The World Bank

[11] WHO. (2010). Assessment of medicines regulatory systems in sub-Saharan African countries: An overview of findings from 26 assessment reports. Available from: https://www.who.int/medicines/publications/assesment_africa/en/. Accessed 08 April 2021

[12] The link between constrained access to quality, safe, efficacious, and affordable medical products and substandard and falsified medical products available from: https://apps.who.int/gb/sf/pdf_files/MSM9/A_MSM9_6-en.pdf. Accessed 20 April 2021

[13] Olsson, S., Pal, S. N., & Dodoo, A. (2015). Pharmacovigilance in resource-limited countries. Expert Review of Clinical Pharmacology, 449-460.

[14] See an example from South Africa available from: https://www.reuters.com/article/us-health-coronavirus-safrica-crime/hundreds-of-fake-covid-19-vaccines-seized-in-south-africa-interpol-says-idUSKBN2AW27Q. Accessed 20 April 2021

2. Recommendations for successful implementation of safety surveillance in the African context

The second section of this paper aims to complement the WHO's COVID-19 Vaccines Safety Surveillance Manual and active surveillance protocol by contextualising these guidelines to the African context and providing additional safety surveillance information and recommendations considering the continental safety challenges. The discussed activities are not comprehensive, albeit do aim to cover the broad range of safety surveillance topics.

Relevant AUDA-NEPAD experience and key insights will also be outlined. These experiences and learnings are mainly from the African Union Smart Safety Surveillance (AU-3S) programme which is a 10-year programme that aims to strengthen PV capability in Africa, using the introduction of needed public health products that may have unknown or understudied safety profiles as a driver[15]. It is being funded by The Bill and Melinda Gates Foundation (BMGF) with the UK's Medicines and Healthcare products Regulatory Agency (MHRA) as a technical partner.

Although the AU-3S programme commenced in February 2020 before the COVID-19 pandemic began, it pivoted strategic focus to address COVID-19 PV needs in the short-term. It is being piloted in 4 African countries: Ethiopia, Ghana, Nigeria, and South Africa. Together, these countries comprise ~30% of Africa's population. For these countries, AU-3S is in the process of rolling out data collection tools for AEFIs to expand electronic vaccine data collection through a smart phone based app called The Med Safety App (see further information in Section 2.1.1), and is developing a cross-country data integration and signal detection system. The programme is also setting up a continental medical products safety committee called the Joint Signal Management (JSM) Group which aims to strengthen regional capacity for detecting and assessing signals based on combined cross-country data. In the medium-term, the AU-3S approach for COVID-19 vaccines will be scaled-up to other African countries. In the longer-term, it will expand to other priority products.

[15] See 'priming resource-limited countries for pharmacovigilance' publication available from: https://www.who.int/medicines/publications/druginformation/issues/WHO_DI_31-4_Safety-Medicines.pdf?ua=1. Accessed 22 April 2021

AU-3S policy assessment against WHO's COVID-19 Vaccines Safety Surveillance Manual

AU-3S engaged with each of the 4 pilot countries to complete a detailed landscape assessment to understand key challenges of the safety surveillance landscape and tailor future recommendations appropriately. This work involved a series of meetings with NRAs and other key stakeholders from each country as well as a detailed review of all relevant safety monitoring-related policies, laws, guidelines, and forms.

After reviewing the contents of key safety-related documents for the pilot countries, an analysis was performed to assess their documents against the guidelines / provisions of the WHO's COVID-19 Vaccines Safety Surveillance Manual. The figure below provides an overview, showing that in general, many international best practices related to reporting, safety strategies, decisioning and communication are partially in place, but that there is still more work required to get to full implementation.

Extent to which existing in-country documents cover provisions

General view for AU-3S pilot countries

Category	Provisions from WHO COVID-19 Vaccines Safety Surveillance Manual	Coverage	Comment(s)
General	Mandate for safety surveillance		Provisions fully exist in all countries
	Mutual reliance and reciprocity for assessments, emergency mobilization provisions (EUA). Includes involvement in preparations for EUA/EUL		Ranges from no provisions exist to fully existing provisions – country dependent
Reporting	Mandatory AEFI reporting requirements for MAHs, HCPs, public, importers, distributors, and NGOs[1]		Provisions mostly partially in place, but only mandatory for MAHs
Safety strategies	Mandatory safety monitoring system for MAHs, manufacturers, importers, and distributors		Provisions exist in all countries, but not always for entire distribution chain
	Mandatory QPPV for MAH/manufacturers		Exists in 3 of the 4 AU-3S pilot countries
	PV activities outlined within operational documents of PHPs (incl. EPIs)		Activities outlined in all countries
	Submission and review of RMPs and PSURs from MAHs		Provisions exist in all countries, but sometimes they do not cover older products
	Specific studies – as required by the NRA based on RMPs – on post-licensure safety surveillance for MAHs, manufacturers, and importers		Provisions exists in 3 of the 4 AU-3S pilot countries
	Provision to conduct surveys and monitoring related to post-licensure safety surveillance[2]	N/A	Pending inputs from select countries
	Provision to conduct appropriate forms of active surveillance, where recommended/suggested		Exists only in 1 of the 4 AU-3S pilot countries
Decisioning	Signal investigation and causality assessment (independence)		Provisions exist in all countries, but not always clear who coordinates the committee
	Provision for conduct of review and investigation of AEFIs		Provisions exist in all countries, but sometimes they are only implied (e.g. via SOPs)
	Provision for issuing directives on appropriate regulatory actions		Provisions fully exist in all countries
Comms.	Communication and information sharing with immunisation programmes, manufacturers, MAHs, importers, distributors, and other national / regional / international stakeholders[1]		Provisions exist in all countries, but sometimes they are only implied (e.g. via SOPs)

[1] If country-level policy only covers select stakeholders, partially meets provisions is reflected with missing stakeholders listed   [2] Including on social media
Note: AESI = Adverse Event of Special Interest; EUA = Emergency Use Authorisation; EUL = Emergency Use Listing; HCI = Health Care Institution; MAH = Marketing Authorisation Holder; PHP = Public Health Programmes; PSUR = Periodic Safety Update Reports; QPPV = Qualified Person Responsible for PV; RMP = Risk Management Plan; SOP = Standard Operating Procedure

2.1 Passive surveillance

The WHO's COVID-19 Vaccines Safety Surveillance Manual states that "routine passive surveillance, whether via electronic- or paper-based systems, is the fundamental, basic type of surveillance for all immunization strategies". Considering PV maturity and resource constraints, this is also an important recommendation for the African context.

2.1.1 Safety data collection and reporting

Although the responsibility of safety surveillance should lie with the NRA, it is the Expanded Programme on Immunization (EPI) that takes responsibility for collecting vaccine AEFIs in many countries. Therefore, countries should ensure that there is good communication and coordination between the two – with clear and well-defined expectations.

In terms of the medium for collecting AEFIs, the WHO's COVID-19 Vaccines Safety Surveillance Manual states that "each country must adapt the generic data sharing model to their local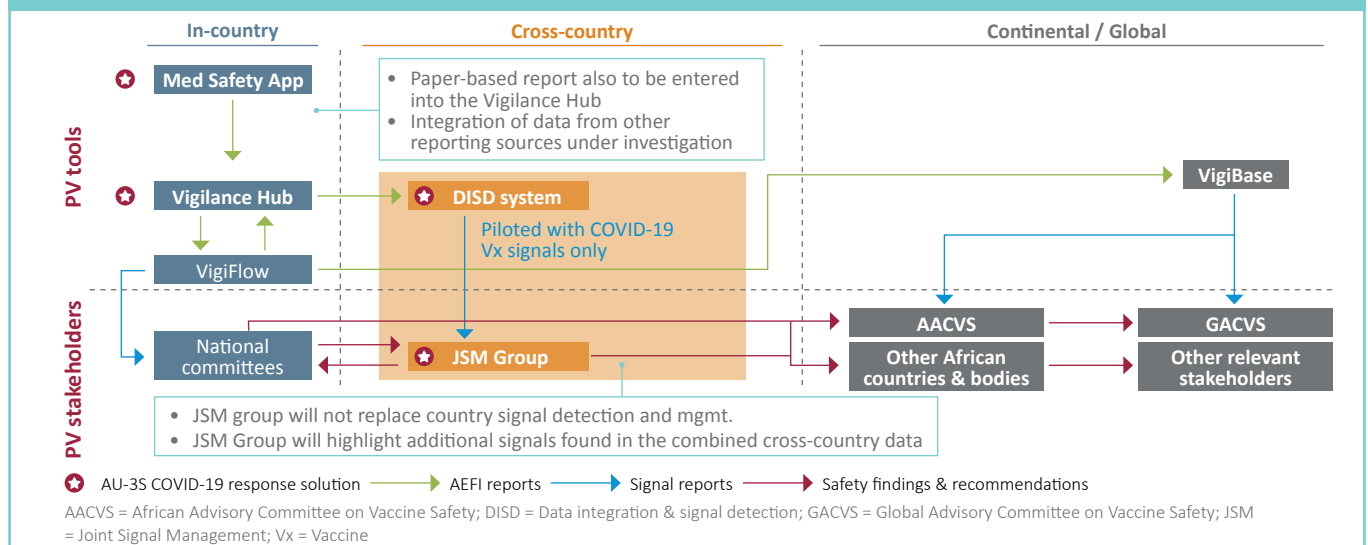 context". Many African countries still rely on paper-based systems for AEFI reporting and data sharing despite the availability of tools to assist countries to set-up electronic AEFI reporting. Notable examples of such tools are[16]:

- The Med Safety App[17] allows for reporting from a smartphone, using a simple reporting interface. A COVID-19 Vaccine AEFI reporting form has been developed by the MHRA for use in the app.

- DHIS2[18] is an open-source health information management system coordinated by the Health Information Systems Programme at the University of Oslo. A 'DHIS2 COVID-19 Vaccine Delivery Toolkit' (particularly the 'AEFI Tracker' data model for vaccine safety monitoring) has been developed for use.

- WHO offers the VigiFlow[19] program, run by the Uppsala Monitoring Centre (UMC), which gives countries the ability to report electronically to WHO's VigiBase, and use accompanying software to perform analyses on aggregated data.

AU-3S reporting and data collection flow

The figure below outlines the AU-3S programme reporting and data collection elements and how they relate to other programs that are being used for COVID-19 vaccines.

After AEFIs are reported through the Med Safety App, data are stored in the back-end of the app which is called the Vigilance Hub. Data are then linked to the Data Integration and Signal Detection (DISD) system, where cross-country signals are detected leveraging the UK MHRA's data mining and signal detection capabilities. Cross-country signals are then investigated by the Joint Signal Management (JSM) Group.

AACVS = African Advisory Committee on Vaccine Safety; DISD = Data integration & signal detection; GACVS = Global Advisory Committee on Vaccine Safety; JSM = Joint Signal Management; Vx = Vaccine

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[16] Other tools do exist, such as Open Data Kit which focuses on offline data collection. More information available from: https://getodk.org/. Accessed 23 March 2021
[17] Further information available from: https://web-radr.eu/mobile-apps/med-safety/. Accessed 09 March 2021
[18] Further information available from: https://dhis2.org/. Accessed 23 March 2021
[19] Further information available from: https://www.who-umc.org/global-pharmacovigilance/vigiflow/about-vigiflow/#:~:text=VigiFlow%20is%20a%20 web%2Dbased,to%20facilitate%20effective%20data%20analysis. Accessed 23 March 2021

African countries should explore which of these systems, or combinations, will best suit their needs. It is worth noting that the Med Safety App and DHIS2 are complementary to the VigiFlow program and should be able to communicate with each other, including via importing and exporting data.

In addition to tools for electronic reporting, other suitable and convenient reporting channels such as telephone hotlines should be considered. Despite all of these options, however, it is likely that many African countries will still rely on paper-based reporting for COVID-19 PV – even if only for select parts of their current reporting procedures. Whether using electronic and/or paper-based tools, African countries should adapt their data model to their existing PV structure and stakeholders. This will require a particular focus on mapping and implementing data flows between and from the district and/or provincial levels, as well as making necessary adjustments based on how much of a role the private sector plays in the surveillance space. Due to the need for timely signal management, detection, and subsequent analysis, the frequency of data sharing should be considered at all points in the data sharing model. One of the largest drawbacks of paper-based reporting is that it takes significant time to have the data electronically captured for further distribution and analysis. Where it is not possible to replace paper-based systems with electronic ones, it is recommended that paper-based data be converted to electronic records as soon as possible. This way, data can be sorted and analysed more efficiently, and there is not a need for physical storage space.

It is also important that countries convert paper-based data to electronic records to enable submission of the data to VigiFlow / VigiBase for global visibility. There is typically under-reporting of African countries in this regard, which can result in countries being wrongfully perceived as not adequately monitoring the safety of medical products used in their populations.

Recognising the significant time and effort needed to adapt existing PV systems, it is recommended that new processes and tools be carefully designed with scalability in mind. New solutions can be developed, tested, and refined over the course of the COVID-19 vaccination campaign. Work done to improve processes and tools for data collection should be applicable to future vaccine and/or other medication rollouts.

2.1.2 Safety data assessment

The WHO's COVID-19 Vaccines Safety Surveillance Manual stresses the need to "strengthen routine passive surveillance reporting systems to enable them to cope with the expected increase in frequency or severity of AEFI". As seen in ongoing surveillance by the MHRA and US Food and Drug Administration (FDA), reporting rates can be expected to surge more than 10 times the typical rate. Early data from the pilot countries involved in the AU-3S programme suggest that this surge will also be the case in LMICs. This expected increase in reporting rates will put the safety data assessment structure of African countries under pressure. Countries will need sufficient capacity to manage, detect, review, and respond to AEFI safety signals.

While many African countries have already established AEFI committees, it will be important for them to mobilise as many resources as possible to assist in safety data assessment. A key lever for this could be the simplification of signal management activities. AUDA-NEPAD's technical partner, the MHRA, has seen that significant resource savings are possible during AEFI reporting by using drop-down lists and data validation criteria when capturing information (instead of capturing non-standardised free text) in electronic data collection tools.

Another important point is that it will be crucial for African countries with limited resources to have clear guidance around the types of safety signals that need further evaluation to ensure that available capacity is not overwhelmed. Benign adverse events are expected with COVID-19 vaccines such as headaches, body aches, mild fevers, and swelling at the administration site. While it is important that such adverse events are reported, limited signal assessment resources should focus on serious and/or unexpected AEFIs. Likewise, tools and processes for follow-ups need to be carefully defined to avoid spending resources that are unlikely to be of high value.

AU-3S Joint Signal Management (JSM) Group

WHO's COVID-19 Vaccines Safety Surveillance Manual also encourages countries with more capacity to "act as resources for neighbouring countries with less capacity". The AU-3S programme, through the JSM Group, aims to foster collaboration among African countries, by work-sharing and strengthening capabilities for signal detection and assessment activities through regular meetings of experts. A focus of the AU-3S programme is to combine safety data across countries to strengthen signals identified, and to identify signals that potentially would not be picked up in a single country's data. The goal of the JSM Group is to validate, prioritise, and assess these cross-country signals. Other goals include promoting the collaboration on safety surveillance between African member countries, acting as a forum for technical support from reference regulatory authorities such as the MHRA and FDA, and strengthening the capabilities of JSM Group members who can then transfer knowledge to their organisation(s) and other relevant national stakeholders. Members of the JSM Group include representatives from member countries' NRAs, EPIs, and national committees. The secretariat is led by AUDA-NEPAD, with representatives from countries for capability strengthening, and from the MHRA for technical support.

2.2 Active surveillance

Although there are clear benefits for implementing active surveillance to supplement passive surveillance data, it requires significantly more capacity and resourcing. Therefore, the WHO's COVID-19 Vaccines Safety Surveillance Manual outlines the need for countries "to determine if they have the capacity to implement active surveillance of adverse events of special interest (AESIs)" and also refers to a 6-step algorithm – developed by the Council for International Organizations of Medical Sciences (CIOMS) – to help countries identify when to implement active surveillance systems[20]. This assumes that the key objectives for national passive surveillance systems have been met.

Based on early discussions with the NRA's from the pilot countries of the AU-3S programme, most African countries do not have significant experience in active surveillance. For African countries that do decide to pursue active surveillance, it will be essential to carefully consider whether to use it for the monitoring of COVID-19 vaccines. An active surveillance strategy needs to be developed before looking into more tactical aspects such as active surveillance tools, processes, or logistics.

Key considerations for the development of an active surveillance strategy in Africa

- At a national level, the questions that active surveillance efforts should aim to answer need to be clear. Limiting the scope of active surveillance can help most efficiently utilise whatever resources are available. Duplication of efforts can be avoided if neighbouring or other similar countries are answering the same questions for the same vaccine(s). Cross-country or regional collaboration for active surveillance initiatives is therefore encouraged.

- Countries should focus AESI reporting and subsequent signal management and analysis on the most important events if very limited capacity is available for all signal assessment activities. The Brighton Collaboration[21] has published a list of AESIs for COVID-19 (which has also been approved by WHO) that countries should leverage as a starting point[22].

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[20] Guide to Active Vaccine Safety Surveillance available from: https://cioms.ch/publications/product/cioms-guideto-active-vaccine-safety-surveillance/. Accessed 10 March 2021
[21] Further information available from: https://brightoncollaboration.us/. Accessed 30 March 2021
[22] See first document in Brighton's COVID-19 resources and tools list available from: https://brightoncollaboration.us/covid-19/. Accessed 23 March 2021

- Active surveillance plans need to consider the prevalence of all local diseases (e.g. TB, HIV/AIDS, malaria) that may not be present or as dominant in other regions when identifying which AESIs to monitor.

- There are likely to be limitations on the availability of historical safety surveillance data to assist in the estimation of background rates for AESIs that have been selected for monitoring. In trying to overcome such data limitations, countries should leverage all relevant national and regional sources. This should include sources such as national surveys / censuses, main hospitals' databases, academic publications, and models.

- For active surveillance in rural areas, community-based surveillance may be a suitable and effective approach. The use of simplified reporting forms (paper-based if necessary due to lack of technological resources in the area) and case definitions will ensure that what is being seen by key community focal points on the ground is captured and investigated. More information on this can be found in WHO-AFRO's "Integrated Disease Surveillance and Response in the African Region: A Guide for Establishing Community Based Surveillance"[23].

The WHO active surveillance protocol "Cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines" can be used to assist LMICs to monitor "previously unrecognised and unsuspected adverse reactions" to the COVID-19 vaccine. Furthermore, WHO-AFRO is aiming to set-up resource mechanisms to support countries – both technically and financially – to conduct active surveillance activities. If possible, AU Member States are encouraged to implement this protocol.

2.3 Manufacturers' PV activities

A risk management plan (RMP) aims to outline the existing knowledge (benefits, risks, additional considerations, etc.) of a medical product's safety profile. The WHO's COVID-19 Vaccines Safety Surveillance Manual states that the pharmaceutical industry has "an essential role in verifying the safety of COVID-19 vaccines through vaccine safety surveillance activities described in RMPs for licensed vaccines particularly via periodic safety update reports". It is therefore important that countries ensure that national provisions[24] exist for marketing authorisation holders (typically the manufacturers) to prepare and submit such a plan for review during the NRA's application process, as well as to subsequently enforce the agreed upon plan.

Another important manufacturer responsibly is adverse event reporting. In many countries, it is a requirement that manufacturers report these occurrences within a short period of time to the regulator, particularly when the events are serious. Based on AU-3S programme experience, only some African countries have these provisions in place, but interviews and discussions with stakeholders suggest that compliance and enforcement of such activities is lacking.

Particularly when looking to the longer term, it is recommended that African countries perform a detailed gap-analysis to determine where legislation, policies, guidelines, etc. need to be produced or adapted. Where possible, these should be implemented in the context of COVID-19, but many of these activities (e.g. processes to prepare, enact and gazette new laws) will take significant time and effort to complete. WHO's GBT can be used as a reference for the particular policies and or legal mechanisms that should be put in place[25].

In relation to COVID-19 vaccine manufacturers, it is worth noting that initiatives to ensure equitable access to COVID vaccines, such as COVAX and the African Vaccine Acquisition Task Team (AVATT), may complicate the implementation of PV provisions for manufacturers. This is due to countries typically having to agree to central indemnification for vaccines procured via such initiatives, which is where a manufacturer is not legally liable for product liability claims. This is as a result of the urgency to rollout COVID-19 vaccines globally, and that "normal" liability insurance will not immediately be available to manufacturers themselves[26]. Therefore, for national vaccine approval, AUDA-NEPAD have seen Ministries of Health (MoHs) agreeing to approve a vaccine for use by agreeing to void manufacturers of legal responsibility in the case of severe adverse events. The WHO and Chubb Limited – a global insurance and reinsurance company – have signed an agreement

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[23] Available from: https://www.afro.who.int/sites/default/files/2017-06/community-based-surveillance_idsr_training-manual.pdf. Accessed 10 March 2021

[24] As stated in the COVID-19 Vaccines Safety Surveillance Manual, such provisions are already covered by existing guidelines "in countries where the regulatory authority is a member or an observer of the ICH"

[25] Available from : https://www.who.int/medicines/regulation/benchmarking_tool/en/. Accessed 20 April 2021

[26] For further information see COVAX's 'Additional Information On Indemnification For COVAX AMC Participants' available from: https://www.who.int/docs/default-source/coronaviruse/act-accelerator/briefing-note-indemnification-and-compensation-covax-amc-countries.pdf?sfvrsn=b4f8aeda_1&download=true. Accessed 23 March 2021

on behalf of COVAX for a no-fault compensation programme for all LMICs receiving doses via the COVAX facility. This programme will provide a no-fault lump-sum compensation for serious adverse events associated with COVAX vaccines until 30 June 2022[27].

2.4 Training and capacity strengthening

The WHO's COVID-19 Vaccines Safety Surveillance Manual outlines the need for the planning and implementation of "preparedness and basic training of staff to follow national guidelines or protocols for AEFI surveillance and, therefore, strengthen local capacity". Recognising the significant effort required to perform this at a national level, training priorities and timelines need to be continuously planned to ensure that the correct trainings are given to the right people at an appropriate time. These timelines should be centered around the milestones of vaccine rollout plans – e.g. dates of vaccine deliveries, vaccination kick-offs, launch dates of AEFI tooling or new processes being put in place, and phasing of population groups.

As safety surveillance in Africa is typically more limited, more intensive training is likely to be required. This is particularly important for health care workers (HCWs) who play a crucial role in reporting in passive surveillance systems. A challenge is that, for many LMICs, HCWs might perceive PV as an additional responsibility to their overburdened role[28]. This factor has been further exacerbated due to the unprecedented strain on national healthcare systems by the high number of COVID-19 infections. Even if individuals such as HCWs are willing to report AEFIs, comprehensive trainings are key to ensure that timely and high-quality data are captured.

Countries should monitor the performance and engagement of their safety surveillance trainings to ensure that the content is reaching the correct individuals, that it is relevant to them, and that they understand the material and what is required of them. Where possible, countries should outline the impact of training programmes (e.g. 2x increase in AEFI reports for X district after a specific training initiative is completed). This will help advocate for resources such as further funding, since many African countries will have to conduct these trainings with limited resources at the outset.

To accommodate these resource limitations and to accelerate training rollouts, African countries should leverage existing training material. However, training videos and/or key documents outlining guidelines, protocols, standard operating procedures, etc. – especially for the COVID-19 vaccine rollout – may be scarce. As a first priority, countries should look to leverage the available material from reputable organisations involved in safety surveillance.

AU-3S capacity strengthening trainings

The AU-3S programme is facilitating a series of capacity strengthening sessions that are being given by AU-3S's technical partner, the MHRA. The training package is grouped into 5 key modules covering the following broad range of topics: data collection, signal detection and management, benefit risk assessment, safety communication, and PV expert advisory committees. For a detailed view of the contents within each module, see Appendix A. The capacity strengthening trainings are being given in a recorded webinar format. These recordings, and all associated presentations and/or resources, will be made available via the AU-3S programme for in-country distribution and use.

Other relevant training or supporting material includes:

- Alongside the WHO's COVID-19 Vaccines Safety Surveillance Manual, training presentations for each module in the manual have been prepared and published by the WHO to facilitate the implementation of guidelines outlined in the manual itself. See the training materials section of the "COVID-19 vaccines: safety surveillance manual" webpage[29]. There has also been socialisation of the guidelines through mechanisms such as the WHO-AFRO Regional Safety Surveillance Workshop (which took place between the 9-10 February 2021) as well as select country level initiatives.

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[27] Further information is available from: https://www.who.int/news/item/22-02-2021-no-fault-compensation-programme-for-covid-19-vaccines-is-a-world-first#:~:text=The%20World%20Health%20Organization%20(WHO,eligible%20for%20support%20via%20the. Accessed 23 March 2021
[28] Ogar, C., Mathenge, W., Khaemba, C. et al. The challenging times and opportunities for pharmacovigilance in Africa during the COVID-19 pandemic. Available from: https://link.springer.com/article/10.1007/s40267-020-00748-4. Accessed 27 Feb 2021
[29] Available from: https://www.who.int/publications/i/item/10665338400. Accessed 18 March 2021

- UMC has educational materials, including online videos and articles, that give guidance on signal detection and analysis of reported adverse events. Furthermore, UMC runs a two-week PV training course on a yearly basis and can provide ad-hoc supporting courses on request[30].

- The Global Alliance for Vaccines and Immunizations (GAVI) has provided guidance on strengthening health systems data quality which includes suggested analyses for AEFIs (not specific to COVID-19)[31].

- US Centers for Disease Control and Prevention (CDC) has released practical guidance on all aspects of vaccine deployment. Although the context focuses on the United States, there are some general best practices to bear in mind (including those related to safety surveillance)[32].

- The Brighton Collaboration has released a standardised template – called the Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) tool[33] – which has been developed for manufacturers to explain key characteristics of vaccines in a standardised way.

As per the above, there are many stakeholders providing a broad variety of training material. It is important that countries ensure alignment to global best practices and that any self-produced trainings align to core standards. AUDA-NEPAD has also seen that trainings between similar organisations (e.g. NRA trainings provided by peer regulators or one EPI programme to another) is an effective way to ensure that they are most relevant to participants. This is also very beneficial when it comes to experience sharing and discussions around questions and answers, as all trainers and invitees then have a similar context and baseline understanding of the content and job requirements.

A final challenge in Africa relates to ensuring training accessibility. Contrary to the situation in HICs, LMICs may not be able to sufficiently leverage digital trainings (online recordings, quizzes, etc.). Often this will be due to limitations in access to suitable technological devices and internet connectivity, which is expected to be the case in rural, hard-to-reach areas. It is therefore important that countries centrally plan and prepare materials and corresponding implementation plans in order to successfully perform in-person training campaigns for HCWs and other safety surveillance related staff members operating in remote areas.

AU-3S digital training key learnings

The AU-3S programme has noted key learnings for managing a series of digital trainings. Registration forms are an important means of access control[34]. After the training, a poll or survey is recommended to track satisfaction with participants. Internet connectivity is often a challenge for participants to engage in live training webinars[35], but the extent of internet connectivity is ultimately country specific. Where applicable, countries may look to electronically record any live trainings for further national distribution.

2.5 Collaboration and coordination

The WHO's COVID-19 Vaccines Safety Surveillance Manual highlights that keeping an up-to-date mapping of "national, regional, and global stakeholders and their responsibilities is key for ensuring appropriate vaccine safety monitoring". AUDA-NEPAD has noted that, due to the COVID-19 pandemic and given the importance of safety surveillance in this context, many global and continental stakeholders have adapted from their 'usual' scope of activities, while some new national bodies

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[30] See more information available from: https://www.who-umc.org/education-training/education-training/. Accessed 23 March 2021
[31] Available from: https://www.gavi.org/sites/default/files/document/guidelines/Analysis-Guidance-2020.pdf. Accessed 23 March 2021
[32] Available from: https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf. Accessed 23 March 2021
[33] Available from: https://brightoncollaboration.us/bravato/. Accessed 29 March 2021
[34] Here helpful to capture data fields such as full name, email address, country, organisation, and position / role
[35] Across the 4 AU-3S programme pilot countries, data showed that on average ~40% of individuals had to join / reconnect to the webinar more than once (i.e. experience a full loss of or temporary break in connection). To date, we have observed the average number of join / reconnection attempts per attendee to be ~2

have been established to respond to the needs caused by the COVID-19 pandemic. Staying aware of such developments is critical for countries to make sure that they are collaborating with the correct and complete set of stakeholders.

At a national level, many African countries have put in place some form of 'COVID-19 taskforce'. Often this taskforce includes members from the NRA, EPI, and MoH – as well as select national and/or supranational experts where applicable. Similarly, already existing national AEFI review committees for signal review (analysis, response, etc.) are likely to have been refocused to closely monitor the safety of COVID-19 vaccines being used in the local context.

At a regional level, there are stakeholders working on the topics of either safety surveillance and/or regulatory topics. For safety surveillance, key regional stakeholders include:

WHO-AFRO has established the African Advisory Committee on Vaccine Safety (AACVS) which looks to provide broad technical support to African countries on PV and COVID-19 vaccine safety. This forum has the responsibility to provide "high quality, well considered, advice and recommendations on matters described in their terms of reference that will guide Member States in the WHO African Region to attain regional and global targets for the reduction in morbidity, mortality and disability caused by vaccine preventable diseases"[36].

AUDA-NEPAD, via the AU-3S programme, is establishing the JSM Group which aims to strengthen the regional capacity for detecting and assessing safety signals based on integrated cross-country data. AUDA-NEPAD works to keep track of ongoing safety challenges in Africa, and have published an article providing an overview of challenges related to safety surveillance for COVID-19 in Africa which largely focuses on the AU-3S programme's role in providing support to the continent[37].

For regulatory aspects more generally, key regional stakeholders include:

WHO-AFRO's African Vaccine Regulatory Forum (AVAREF) platform brings together NRAs and national Ethics Committees on the African continent, to ensure timely regulatory evaluation and decision-making on clinical trials. In 2020, AVAREF has notably established emergency joint-review timelines for clinical trial applications.

AUDA-NEPAD, through the African Medicines Regulatory Harmonisation (AMRH) pro-gramme, supports regional regulatory harmonisation initiatives. The AMRH provides ad-hoc support to African countries as required.

Africa CDC focuses its activities on strengthening the capacity and capability of Africa's public health institutions as well as supporting quick detection and effective response to disease threats and outbreaks.

[36] AACVS terms of reference available from: https://www.who.int/immunization/ToRs_Regional_Committee_on_Vaccine_Safety_Final.pdf. Accessed 19 March 2021
[37] Available from: https://www.nepad.org/publication/auda-nepad-covid-19-series-volume-1-au-smart-safety-surveillance-au-3s-and. Accessed 25 February 2021

The Africa CDC, AVAREF, and AMRH have jointly formed the Africa Regulatory Taskforce and have published guidelines to expedite regulatory authorisation processes for COVID-19 vaccines in Africa[38].

At a global level, the WHO's COVID-19 Vaccines Safety Surveillance Manual contains a comprehensive list of stakeholders – including The Global Advisory Committee on Vaccine Safety (GACVS). There is also a GACVS COVID-19 subcommittee, meeting bi-weekly with additional ad-hoc meetings when required, that provides recommendations for country level use[39].

Other global stakeholders working on initiatives to support select African countries in strengthening their safety surveillance capacity include:

The Brighton Collaboration will support select African countries to implement app-based adverse event reporting solutions and will financially support some African countries to implement active surveillance[40]. It has also published a list of AESIs for COVID-19 vaccines that can be leveraged by African countries.

The US CDC are providing technical support to African countries to conduct causality assessments, support safety data collection and management, identify and address barriers to reporting AEFIs, and support EPIs to prioritise safety initiatives and allocate funding to ad-hoc initiatives.

The U.S. Agency for International Development (USAID) funds the Medicines, Technologies, and Pharmaceutical Services (MTaPS) program which aims to support select Regional Economic Communities (RECs) and African countries[41] developing safety surveillance processes and systems – amongst other topics. This support will extend to COVID-19 vaccines.

2.6   Safety communications

The WHO's COVID-19 Vaccines Safety Surveillance Manual explains that "various COVID-19 vaccine-related events could occur that may negatively influence perceptions of vaccine safety. These could include publication of new data on COVID-19 vaccines, and information about events such as a temporary vaccine suspension or recall, adverse events, negative messaging in the media, and community attitudes and beliefs".

It is therefore important for countries and regulatory authorities to communicate timeously and frequently to their populations regarding the safety profiles of medical products and technologies including COVID-19 vaccines. Such transparency will improve public confidence in marketed products and also have the beneficial effect of reducing vaccine hesitancy.

Communication from the JSM Group

The JSM Group will share safety signals of concern from the cross-country data with the national committees of the pilot countries as well as global committees such as the AACVS and GACVS – as necessary. The JSM Group will also communicate directly to a wider AU audience through the AUDA network. Once available, Member States are encouraged to leverage such information in their safety communications to their populations.

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[38] See Africa Regulatory Taskforce 'Guidance on Emergency Expedited Regulatory Authorisation and Access to COVID-19 Vaccines in Africa' available from: https://africacdc.org/download/guidance-on-emergency-expedited-regulatory-authorisation-and-access-to-covid-19-vaccines-in-africa/. Accessed 23 March 2021

[39] Latest materials from the GACVS COVID-19 subcommittee are typically published on the WHO's News page, available from: https://www.who.int/news. Recent examples of this include a statement of safety signals related to the AstraZeneca COVID-19 vaccine and a review of reports on influenza-like illness in individuals vaccinated with COVID-19 vaccines – available from: https://www.who.int/news/item/19-03-2021-statement-of-the-who-global-advisory-committee-on-vaccine-safety-(gacvs)-covid-19-subcommittee-on-safety-signals-related-to-the-astrazeneca-covid-19-vaccine and https://www.who.int/news/item/08-03-2021-gacvs-covid-19-review-influenza-like-illness/. Accessed 26 March 2021

[40] Done through the Safety Platform for Emergency Vaccines (SPEAC) which is funded by CEPI through the Task Force for Global Health. US CDC has also provided funding which is currently available for Ethiopia, Nigeria, Ghana, Malawi, and Kenya

[41] Supported RECs are the Economic Community of West African States (ECOWAS) and the Intergovernmental Authority on Development (IGAD). Countries are Mozambique, Rwanda, and Burkina Faso. Further information available from: https://www.mtapsprogram.org/. Accessed 30 March 2021

3. Conclusion

Safety surveillance in the context of COVID-19 is of utmost importance due to the unprecedented nature of the pandemic and record timelines associated with vaccine rollouts. The WHO's COVID-19 Vaccines Safety Surveillance Manual outlines important information around the infrastructure, processes, and capacity for performing safety surveillance of COVID-19 vaccines. African countries face a wide array of unique challenges to effectively implement safety surveillance of medical products, with the most common themes being that of both technical and financial resource limitations and the downstream effects. In this paper, AUDA-NEPAD have provided insights into the African context as well as implementation recommendations to assist Member States. AUDA-NEPAD, primarily through the AU-3S programme, will continue to work on developing improved safety surveillance across the continent.

Appendix A: AU-3S Capacity Strengthening overview

The below table provides a breakdown into the contents of each module in the AU-3S programme's capacity strengthening series that have been and are being given by AU-3S's technical partner, the UK's MHRA.

Module	Title	Contents	Timing
1	Data collection	• Introduction to pharmacovigilance • Overview of spontaneous reporting schemes and promotion • ADR data and vaccine specific considerations • Tools and resources for data collection and management • Good practice coding	January 2021
2	Signal detection and management	• Causality assessment • Signal detection, management, validation, and assessment	February 2021
3	Benefit risk assessment	• Risk assessment • Risk management plans • Periodic Safety Update Reports • Role of pharmacoepidemiology in pharmacovigilance • Regulatory decision making	March 2021
4	Safety communication	• Risk communication – routine communication, crisis management, media handling, special considerations for vaccines • Decision making in communications	April 2021
5	Pharmacovigilance expert advisory committee	• National Safety Committees – experience from the UK • Joint committees	May 2021