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Lessons learnt during establishment of COVID-19 active vaccine safety surveillance in nine African countries

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ABSTRACT

Background: Globally, several gaps in vaccine safety surveillance exist, particularly in low- and middle- income countries (LMICs). Establishing and maintaining vaccine surveillance platforms in resource-constrained settings poses significant challenges. These countries often rely on paper-based medical records and immunization cards,

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lack unique patient identifiers across the healthcare systems, have limited electronic data capture capabilities, and face a shortage of clinical reviewers for case assessments.
This report highlights the establishment of two active vaccine safety surveillance studies across nine African countries: (i) **A**ctive **C**OVID-19 **va**ccine **s**afety **s**urveillance (ACVaSS) in eight COVAX 92 Advanced Market Commitment (AMC-92) eligible African countries including Ethiopia, Ghana, Kenya, Mali, Malawi, Mozambique, Nigeria and Eswatini and (ii) the **S**outh **A**frican **C**OVID-19 **v**accine **s**afety **s**urveillance study (SA-CVSS).
Methods: Both ACVaSS and SA-CVSS were hospital-based sentinel active surveillance studies designed to monitor the safety of COVID-19 vaccines in the aforementioned COVAX AMC-92 countries and South Africa, a middle-income African country. Patients presenting to healthcare facilities with illnesses resembling pre-selected adverse events of special interest (AESIs), were enrolled, with informed consent, into the studies. The Brighton Collaboration Case Definitions were applied to classify AESIs.
Findings: Over 60,000 admitted patients were screened and over 12,700 eligible patients were enrolled in 18 months. Despite challenges in accessing and abstracting data from predominantly paper-based medical and vaccination records, the identification of specific AESIs and estimating association with vaccination status was feasible in LMIC healthcare facilities.
Conclusions: The establishment of active vaccine safety surveillance sentinel sites is achievable in LMICs, though the lack of digital medical records hindered data accessibility and availability. Regulatory authorities, health departments and organizations supporting immunization programs must prioritize the development, maintenance and funding of active vaccine safety surveillance systems. Such surveillance is crucial to ensuring that new vaccines are properly monitored and assessed for safety following their introduction and use in these populations.
Funding: The SA-CVSS study was funded by a US CDC Grant to the GVDN (grant reference: CDC Funder Award Number: 1 NU38CK000485–01-00), the South African Medical Research Council (SAMRC) and the Task Force for Global Health (RVD_CDC-COV). Gavi, The Vaccine Alliance, funded the ACVaSS study (Agreement reference: MEL10500921).

1. Introduction

Various methods are utilized for safety surveillance of vaccines, including monitoring and reporting of potential adverse events through active and passive surveillance systems and monitoring of specific cohorts or population groups. Each reporting modality and method has advantages and disadvantages [1]. Pharmacovigilance (PV) systems in low and middle-income countries (LMICs) are limited and disparate compared with high-income countries as highlighted during the recent COVID-19 pandemic [2,3]. Pharmacovigilance systems in LMICs have previously monitored vaccines and other medicines, only after completion of extensive safety surveillance in high-income countries (HICs) has proven an acceptable safety profile. Nevertheless, several vaccines which have been developed recently to prevent diseases particularly relevant to LMICs, including vaccines against Ebola virus [4], malaria [5] and Lassa fever [6], will not undergo safety surveillance in HICs. Large clinical trials and implementation studies in LMIC settings for these vaccines have limited sample size and statistical power to detect rare adverse events following immunization (AEFI). Additionally, there may be genetic factors influencing safety profiles, which compels conduct of surveillance in diverse population groups.

Adequate vaccine safety surveillance after introduction of vaccines into healthcare programs is essential to promptly identify and report rare health events associated with vaccination. This ensures the safety of vaccine recipients, and helps to maintain public confidence in vaccines and vaccine programs. Vaccine surveillance platforms are challenging to establish and maintain in resource-constrained countries, which usually rely on paper-based medical records and immunization cards, have limited access to computers and internet, and have a paucity of reviewers for cases. [2,3]

This report highlights the challenges and successes in the establishment of two active vaccine safety surveillance studies across nine African countries. Additionally, patient demographics of screened and enrolled patients are described and the utility and generalizability of this approach is explored.

2. Methods

2.1. Study design & setting

The '**A**ctive **C**OVID-19 **va**ccine **s**afety **s**urveillance' (ACVaSS) study included eight COVAX 92 Advanced Market Commitment (AMC-92) eligible African countries: Ethiopia, Ghana, Kenya, Mali, Malawi, Mozambique, Nigeria and Eswatini. The '**S**outh **A**frican **C**OVID-19 **v**accine **s**afety **s**urveillance study (SA-CVSS) was conducted in South Africa. The ACVaSS and SA-CVSS studies were hospital-based sentinel active surveillance studies that aimed to monitor the safety of COVID-19 vaccines in Africa. Both studies utilized similar protocols, initially developed by investigators and working group experts affiliated with the Global Vaccine Data Network (GVDN), and later amended to align with the World Health Organization's (WHO) protocol template for 'Sentinel Surveillance of Adverse Events of Special interest (AESIs) after vaccination with COVID-19 vaccines' [7].

In addition to demonstrating the feasibility of conducting active hospital surveillance in LMIC, the primary objective of these demonstration studies was to estimate the risk of predefined adverse events of special interest (AESIs) with acute onset and short period of increased risk following immunization of the COVID-19 vaccine using a self-controlled risk interval (SCRI) study design (see supplemental materials, table S1). Additionally, the studies contributed data to GVDN's multi-site meta-analysis on the association between COVID-19 vaccines and AESIs (listed in table S1). The results of the SCRI analyses and multi-site meta-analyses will be detailed elsewhere.

Patients presenting to hospital with an acute illness suggestive of one of the predefined AESIs were screened for study participation. AESIs under surveillance were events that had the potential to be causally associated with a COVID-19 vaccine. The AESI list was based on the **S**afety **P**latform for **E**mergency **V**a**cc**ines (SPEAC) project list version 23 December 2020 [8], and include generalized convulsions, myocarditis, pericarditis, anaphylaxis, thrombocytopenia, thrombosis with thrombocytopenia syndrome (TTS), Guillain Barré syndrome (GBS), Miller Fisher Syndrome (MFS), Acute Disseminated encephalomyelitis (ADEM), encephalitis, and myelitis. Inclusion criteria for the SCRI analysis were: [1] potential AESI case receiving at least one dose of COVID-19 vaccine in the observation period, [2] residence in the catchment area of the participating hospital, [3] informed consent for study participation from patient or next-of-kin.

2.2. Study oversight, administration and funding.

The SA-CVSS was coordinated by Wits Vaccines and Infectious Diseases Analytics (Wits-VIDA), and the ACVaSS study was coordinated by Wits African Leadership in Vaccinology Expertise (Wits-Alive), both at the University of the Witwatersrand, Johannesburg, South Africa.

GVDN was the technical partner for both studies. The SA-CVSS study was funded by a US CDC Grant to the GVDN (grant reference: CDC Funder Award Number: 1 NU38CK000485–01-00), the South African Medical Research Council (SAMRC) and the Task Force for Global Health (RVD_CDC-COV). Gavi, The Vaccine Alliance, funded the ACVaSS study (Agreement reference: MEL10500921).

Table 1
Country site details.

	Ethiopia	Eswatini	Ghana	Kenya	Mali	Malawi	Mozambique	Nigeria	South Africa
Data collection start date	20th April 2022	N/A	25th April 2022	12th Sept 2022	9th May 2022	25th July 2022	25th July 2022	30th May 2022	28 September 2021
Country population**	126,972,372	1,212,402	34,213,655	55,254,695	23,394,176	21,007,634	34,031,233	224,550,958	60,499,531
Provinces/ states where sites based	Amhara	N/A	Upper East Region	Kilifi County, Uasin Gishu County, Kisumu County, Nairobi County	Korofina	Mzuzu Lilongwe Blantyre Zomba	Great Maputo Area (Maputo city and province)	Lagos, Ogun, Delta, FCT, Kano and Bauchi.	Gauteng, Western Cape
Number of healthcare facilities utilized	1	N/A	15	4	11	4	4	7	5
Type of facility (ies)	Tertiary [1]	N/A	Secondary [1] Primary [14]	Tertiary [4]	Tertiary [4] Secondary [1] Primary [6]	Tertiary [4]	Tertiary [4]	Tertiary [7]	Tertiary [5]
Funding of facility(ies)	Public [1]	N/A	Public [9], Private [5]	Public [4]	Public [9], Private [2]	Public [4]	Public [4]	Public [7]	Public [5]
Location of facility(ies)	Urban [1]	N/A	Mixed urban & rural	Urban [3] Peri-urban, serving rural population [1]	Urban [11] (Bamako)	Urban [4]	Urban [3] peri-urban [1]	Urban [6], Peri-urban [1]	Urban [5]
Electronic medical records	No	No	Yes	Yes	No	Yes	No	No	No
Paper medical records	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medical record held by	Facility	Facility	Facility & patient	Facility & patient	Facility	Facility & patient	Facility	Facility	Facility
Is COVID-19 notifiable?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Format of COVID-19 vaccination cards	Paper: patient & facility#	Electronic and Paper: patient	Electronic, Paper: patient & facility#	Electronic	Paper: patient	Electronic and Paper: patient	Paper: patient	Electronic and Paper: facility#	Electronic: patient & DOH
Established AEFI process & committee for COVID-19	No	Yes	Yes	Yes	No	No	No	No	Yes
First COVID-19 vaccine administered (adults)	13th March 2021	19th March 2021	1st March 2021	5th March 2021	31st March 2021	11th March 2021	8th March 2021	5th March 2021	17th Feb 2021 (HCW), other adults 17th May 2021
Unique national patient identifier utilized for healthcare	No*	N/A	No	Yes for vaccination; No for admissions	No	No	No	No	No
What population is served by facilities (urban, rural)	Urban-based hospital but referral for >13-million people. National proportion of urban-dwellers is 22.1 %	N/A	Urban (~30 %) and rural (~70 %)	Yes for 2 facilities. No for 2 facilities with 86 % and > 50 % of patients from rural areas	Yes, urban	Urban and rural (~30 %-50 % depending on facility.) All tertiary referral hospitals	Mainly urban & peri-urban. (~30 % rural)	Mainly urban; rural (25–30 %)	Urban

** Country population data downloaded from https://www.worldometers.info/population/africa/ on 21st August 2023.
# vaccination facilities, paper-based logs of daily vaccinations.
* Ethiopia launched national unique identifier in September 2024, after completion of this study.

2.3. Sites and study populations

Individuals residing in the catchment area of participating hospitals and healthcare facilities were screened on admission to hospital in relevant departments (medical), and eligible, consenting patients were enrolled. Information about participating facilities in each country are detailed in Table 1.

2.4. Data collection process

Enrolment was initiated in SA-CVSS in September 2021 and in the ACVASS study in April 2022; however, countries initiated enrolment at different times during the study period determined by receipt of approval by their respective Research Ethics Committees.

During the screening and enrolment process, study staff were required to complete study-specific electronic case report forms on the Research Electronic Data Capture tools (REDCap) [9,10], a free, secure, web-based application designed to support data capture for research studies hosted at the University of the Witwatersrand, Johannesburg, South Africa (see supplemental material & Fig. S1). Details of enrolment and data collection procedures are included in Supplemental material.

Patients' COVID-19 vaccination information was obtained through patient-held- and/or facility-held- vaccination cards and/or interviews with the patient (or the patient's representative/family member). Vaccination history was verified through the national electronic (South Africa only) or paper-based vaccination registers (Table 1). A patient's verbal report of vaccine history was accepted only if no written documentation was available. The AESI level of certainty (LOC) was computed according to the diagnosis specific Brighton Collaboration Case Definition (BC-CD).

2.5. Evaluation of active surveillance system based on its attributes.

A self-administered questionnaire (see supplementary materials) was circulated to Principal Investigators (PIs) 8 months after initiation of enrolment, to gather updated site information, and determine the quality of implemented surveillance systems. Seven of the nine attributes suggested by the CDC guidelines for evaluating a public health surveillance system [11] were investigated as detailed in Table 2.

Table 2
Attributes for evaluating public health surveillance systems.

	Attribute	Process of evaluation
1	*Simplicity* (structure and ease of operation)	A data flow chart was used to illustrate the process of screening and enrolment of patients and data collection. Simplicity was measured by the complexity of case definitions, the process of data collection and capture, the ease of use of the database and the amount and type of data that were collected were assessed.
2	*Flexibility* (how system adapts to change)	Any changes made to the system in the study period were investigated and the subsequent ease of change was evaluated.
3	*Acceptability* (the willingness of individuals to participate in the surveillance)	As a proxy, participation rates and data completeness were assessed
4	*Data quality* (completeness of information)	Case report forms (CRFs) were reviewed to ascertain alignment of data elements in the CRF with the Brighton Case Definition. Additions or revisions to the data collection tools were considered. Validity of data and logical checks were performed on the data fields (e.g. chronological events and realistic date checks).
5	*Representativeness* (if disease accurately described over time and place in population)	The proportion of cases identified from each area (city/region) was compared to the proportion of the population residing in that area
6	*Timeliness* (the speed at which data flow between the different components of the surveillance system)	The average time between enrolments, collection of patient outcome information, COVID-19 vaccination information were used to assess timeliness of the system. Possible factors causing delays were investigated
7	*Stability* (the reliability and availability of the system)	assessed by identifying electronic database down times, laboratory test result delays
8	*Sensitivity* (the proportion of cases of a health-related event detected by the surveillance system)	Not evaluated due to limited data on the number of individuals hospitalized for rare AESI within specific sites
9	*Predictive value positive* (proportion of reported cases that actually have the health-related event under surveillance)	Not evaluated due to limited data on the number of individuals hospitalized for rare AESI within specific sites

Guidelines utilized detailed in MMWR [11].

2.6. Ethical and regulatory review and approval

The studies were approved by the Human Research Ethics Committee (HREC), University of the Witwatersrand (Wits-HREC references: ACVaSS: M220139; SA: 210810). ACVaSS participating partners obtained approval from local ethics committees, and in certain countries, additional institutional reviews and approvals were required prior to study initiation (table S2). Local ethics committee approval was not obtained due to institutional delays, and therefore no data were collected in Eswatini. Regulatory authorities of all participating countries were notified and facility specific approvals were obtained by local PIs. The studies were conducted under the international ethical guidelines for health-related research involving humans issued by the Council for International Organizations of Medical Sciences (CIOMS) [12], good epidemiological practice (GEP) guidelines, the Declaration of Helsinki and its amendments [13] and any applicable national laws, regulations, and guidelines.

Informed consent was required from all participants/ representatives before enrolment. Consent forms were available in local language/s and aligned with local ethics requirements.

3. Results

A total of 60,959 patients admitted to the 50 healthcare facilities across eight African countries were screened between September 2021 and 31 March 2023 (see supplemental material). Of these, 26.3 % (16007) were eligible for enrolment based on potentially comparable diagnoses and after informed consent, 13,047 (81.9 % of eligible) were enrolled into these studies (See Fig. 1, Fig. 2.)

Almost 40 % of screened patients were aged 20 to 29 years (20.4 %, 12,457/60959) and 30 to 39 years (18.0 %, 10,943/60959), whereas a third (33.4 %) of the individuals enrolled into the study were aged 30 to 39 years (16.8 %, 2191/13047) and 40 to 49 years (16.6 %, 2163/13047). Just over half of screened (53.2 %, 32,255/60959) and enrolled (52.8 %, 6884/13047) individuals were female (Table 3). The most common admission diagnoses of screened patients were diseases of the circulatory system (21.9 %, 13,365/60959). The most common admission diagnoses of the patients who were screened but not enrolled were diseases of the circulatory system (13.7 %, 6556/47912), diseases of the respiratory system (12.1 %, 5807/47912), and diseases of the digestive system (10.7 %, 5116/47912). (see table S3).

Only 28.8 % (3657/12707) of enrolled patients were eligible for inclusion in the SCRI analysis, the results of which will be detailed elsewhere. Ineligible patients were excluded due to one or more of the following reasons [1] patient not vaccinated (52.5 %, 6665/12707), [2]

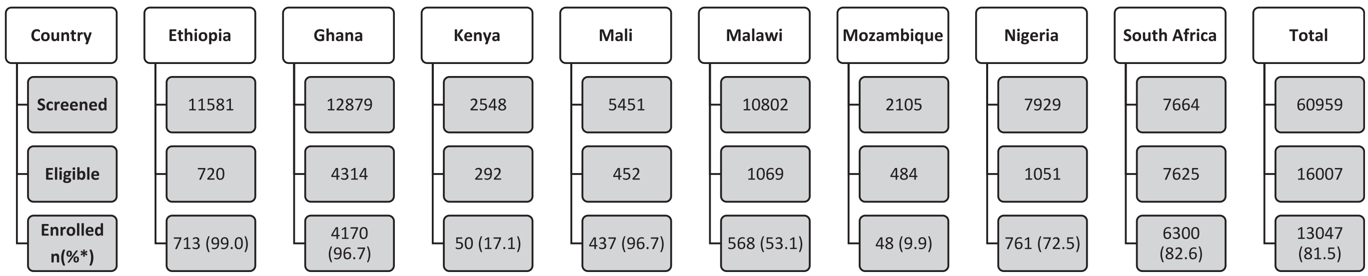

Fig. 1. Flow diagram of screening and enrolments per country. %* percentage of eligible. # Only 8 of the 9 countries initiated screening and enrolment into studies.

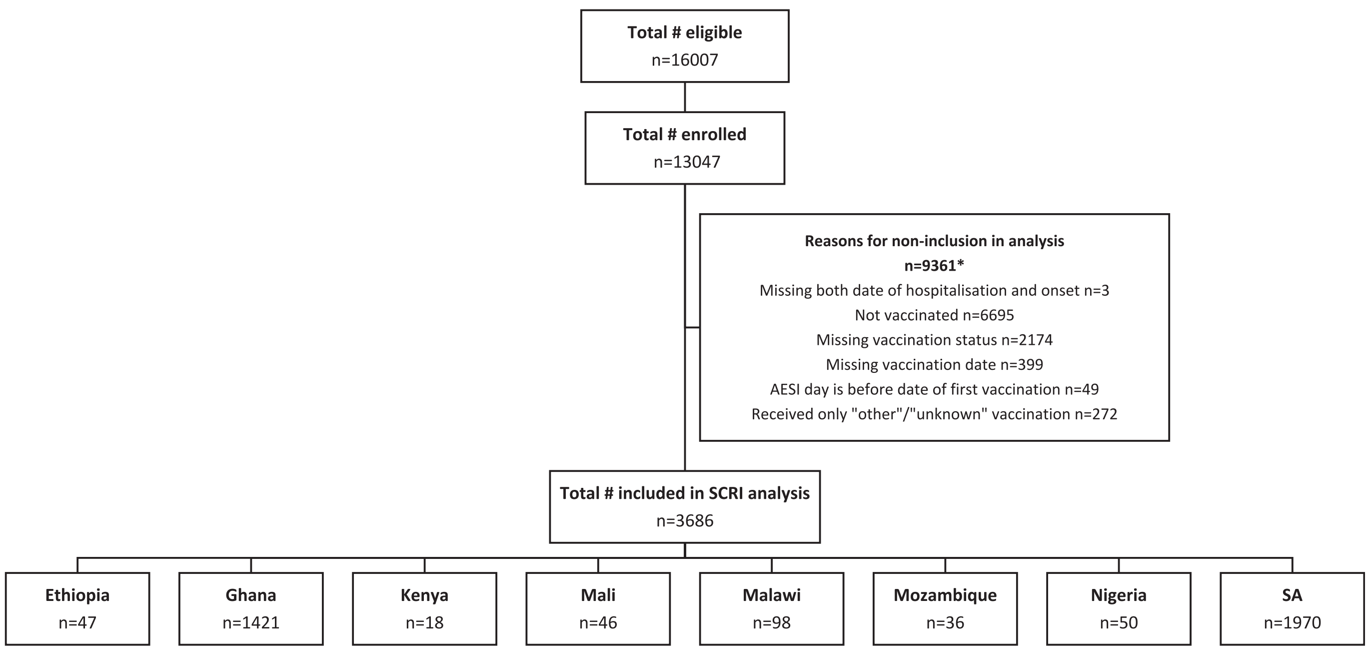

Fig. 2. Flow diagram of patients included into the Self-controlled Risk Interval (SCRI) analysis, stratified per country. *Some events had multiple reasons for non-inclusion in the SCRI analysis.

patient received “other” or “unknown” vaccination brand/platform (37.9 %, 4819/12707), [3] missing vaccination status (14.9 %, 1890/12707), [4] missing vaccination date/s (3.3 %, 415/12707), [5] AESI occurred before date of first vaccination (1.3 % of vaccinated participants, 48/3745) and [6] missing both date of hospitalisation and date of symptom onset (0.0 %, 3/12707).

The average time taken for sites to obtain ethics approval from time of submission was 46 days. Four sites exceeded 60 days (range: 60 to 125 days), which delayed or prevented initiation of data collection (table S2).

3.1. *Simplicity*

There was a clear flow of data through the system (Fig. S1); however, some BC-CDs are complex due to the nature of the condition. In some BC-CDs, subjective symptoms and observable clinical signs were included, which led to variable interpretation. Several variables required for BC-CD are not routinely recorded in medical records in some countries, leading to missing clinical criteria documentation, for example: the presence or absence of a severe headache in patients with thrombosis and the type of motor manifestations in a patient with generalized convulsions. All sites have, however, agreed that the screening and enrolment procedures were easy to follow, and automated calculation of BC-CD level of certainty simplified the process.

3.2. *Flexibility*

The studies were able to adapt to updated BC-CDs, demonstrating flexibility. The database was restructured several months into data collection to allow for collection of raw data (which contributed to multi-factorial criteria in BC-CDs), rather than requiring data collection staff to interpret or combine multiple variables in the field before entering data. All AESI-specific forms, were revised by a working group consisting of GVDN, Wits-VIDA and Wits-Alive members and data collection was transitioned to an updated database in mid-July 2022. Sites provided input into database amendments and study staff were informed timeously about the date of and procedures for transition to updated database. A study process flow diagram was provided to sites as part of retraining (Fig. S1).

When minor amendments were required to improve functionality and simplicity of data capture, data collection was halted before the changes were made to avoid corruption or loss of data. Minor amendments were made over weekends, when database was offline and restored before data collection resumed.

3.3. *Acceptability*

Training slides were developed by the Wits-VIDA (for SA sites), Wits-Alive (for ACVaSS sites) and GVDN (all sites) teams and were shared with site teams via the Open Science Framework portal. Recorded voice-over English MS PowerPoint presentations were made available for

Table 3
Demographics of screened and enrolled patients.

	Ethiopia	Ghana	Kenya	Mali	Malawi	Mozambique	Nigeria	South Africa	Total
Total screened	11,581	12,879	2548	5451	10,802	2105	7929	7664	60,959
Total enrolled	713	4170	50	437	568	48	761	6300	13,047
Age group	**Enrolled/screened (% of screened who were enrolled)**								
≤19 years	31/987 (3.1 %)	273/1230 (22.2 %)	4/207 (1.9 %)	24/637 (3.8 %)	68/1147 (5.9 %)	0/42 (0 %)	7/174 (4 %)	106/132 (80.3 %)	513/4556 (11.3 %)
20–29 years	112/3174 (3.5 %)	706/2871 (24.6 %)	8/438 (1.8 %)	36/12964359 (2.6 %)	103/2569 (4 %)	3/238 (1.3 %)	63/973 (6.5 %)	688/835 (82.4 %)	1719/12457 (13.8 %)
30–39 years	112/2095 (5.3 %)	645/2269 (28.4 %)	11/436 (2.5 %)	44/1118 (3.9 %)	111/2103 (5.3 %)	11/345 (3.2 %)	76/1150 (6.6 %)	1181/1427 (82.8 %)	2191/10943 (20 %)
40–49 years	96/1596 (6.0 %)	618/1797 (34.4 %)	13/352 (3.7 %)	67/647 (10.4 %)	104/1712 (6.1 %)	6/371 (1.6 %)	109/1488 (7.3 %)	1150/1394 (82.5 %)	2163/9357 (23.1 %)
50–59 years	108/1323 (8.2 %)	591/1552 (38.1 %)	5/281 (1.8 %)	83/539 (15.4 %)	72/1104 (6.5 %)	11/353 (3.1 %)	157/1575 (10 %)	1122/1354 (82.9 %)	2149/8081 (26.6 %)
60–69 years	107/1257 (8.5 %)	433/1090 (39.7 %)	7/347 (2 %)	100/604 (16.6 %)	48/962 (5 %)	10/367 (2.7 %)	175/1307 (13.4 %)	1102/1321 (83.4 %)	1982/7255 (27.3 %)
70–79 years	94/818 (11.5 %)	414/932 (44.4 %)	2/288 (0.7 %)	58/387 (15.0 %)	42/773 (5.4 %)	6/258 (2.3 %)	116/851 (13.6 %)	645/785 (82.2 %)	1377/5092 (27 %)
≥ 80 years	53/330 (16.1 %)	490/1138 (43.1 %)	0/196 (0 %)	25/160 (15.6 %)	17/379 (4.5 %)	1/131 (0.8 %)	58/411 (14.1 %)	288/365 (78.9 %)	932/3110 (30 %)
Age missing	0/1 (0 %)	0/0 (0 %)	0/3 (0 %)	0 (0 %)	3/53 (5.7 %)	0/0 (0 %)	0/0 (0 %)	18/51 (35.3 %)	21/108 (19.4 %)
Sex	**Enrolled/ screened (% of screened who were enrolled)**								
Female	361/5648 (6.4)	2521/7864 (32.1)	18/1419 (1.3)	211/3398 (6.2)	306/6141 (5)	21/1020 (2.1)	363/3572 (10.2)	3083/3193 (96.6 %)	6884/32255 (21.3 %)
Male	352/5932 (5.9)	1649/5012 (32.9)	32/1128 (2.8)	226/2052 (11.0)	262/4658 (5.6)	27/1085 (2.5)	398/4356 (9.1)	3181/3319 (95.8 %)	6127/27542 (22.2 %)
Unknown	0/1 (0 %)	0/3 (0 %)	0/1 (0 %)	0/1 (0 %)	0/3 (0 %)	0	0/1 (0 %)	14/32 (43.8 %)	14/42(33.3 %)

NOTE: Only eight of the nine countries participating in study are included in this table, as data collection was not initiated in Eswatini.
Lessons learnt during establishment of COVID-19 active vaccine safety surveillance in nine[#] African countries:

training purposes. The PowerPoint slide decks were shared with country PIs, who adapted slides as required for local requirements. Additionally, local PIs could deliver training in their home languages. The database was developed in English and was not translated due to a single database being utilized by all sites. Some local PIs translated the data dictionary and developed MS Word-based case report forms in relevant languages as a tool that field staff utilized. Languages spoken by study staff included English, Portuguese, French, Amharic (Ethiopia), Tumbuka and Chichewa (Malawi), Hausa, Yoruba, Igbo (Nigeria), Kiswahili, Giriama (Kenya), Changana (Mozambique), Bambara (Mali), Akan, Nankam, Frafra, Kasem, Buli Tale and Dagbani (Ghana), Sesotho, isiZulu, Afrikaans and isiXhosa (South Africa).

Data collection teams were established by local PIs, and included dedicated study staff, and attending health care providers in the facilities. At several sites, data collection was hampered by the large routine workload of attending clinicians, however this was mitigated by the study teams providing support with administrative aspects of the study. Acceptability of the study was increased by the availability of an electronic database, which can be used for the development of routinely required reports and site-specific research projects being conducted by study staff and associated clinicians.

A typographical error in the inclusion criteria of the synopsis of the ACVaSS protocol resulted in restriction of enrolment in one country (Mozambique) to patients with confirmed COVID-19 vaccination only, which hampered enrolment. This emphasizes the importance of careful review and update of all sections of standardized protocol templates.

3.4. Data quality

To ensure data quality, a monitoring plan was developed and full-time data management study team members were employed at Wits-VIDA and Wits-Alive coordinating centers. Key variables were monitored and regular progress reports were generated by data management teams and shared with site teams for data correction and cleaning. The data quality monitoring feature in REDCap was utilized by both internal (site-level) and external (regional/ coordinating centre) monitoring teams. Out of 50 facilities (8 countries), 55 % (27/50) of sites utilized paper based medical records and 46 % (23/50) used a combination of electronic and paper records.

The WHO has a recommended list of data elements to be included in vaccine safety surveillance for adverse events following immunization. [14] Most of the recommended variables were included in the REDCap data collection tools (table S4). The vaccine batch LOT number was included in the REDCap data collection tool; however, LOT number was not recorded on vaccination records at most sites. Pregnancy status was included in the data collection tool, however, details of lactation were not included.

Some BC-CDs were newly developed when these studies were initiated; therefore, some companion guides detailing critical variables needed were not finalized. Some of the BC-CDs, for example Generalized Convulsions and Guillian Barré Syndrome, were challenging to integrate into the REDCap data collection tools because the pathways indicated in the pictorial algorithm were not always included in the tables embedded within the full case definition. Despite extensive testing, there were a few errors in the automated REDCap database LOC calculations, requiring verification of LOCs in statistical software (STATA and/or R) to ensure data quality. Independent programming of automatic LOC calculations should be duplicated, for verification.

Verification of COVID-19 vaccination data for enrolled patients was challenging across sites. South Africa has an individual-level patient digital vaccination database (Electronic Vaccine Data System or EVDS), from which vaccinees could obtain an electronic vaccination record.

However, access to the EVDS was restricted, leading to delays in monitoring. At some sites, vaccinees did not receive a vaccination card, and details were logged in facility-held registers. Therefore field teams had to conduct home visits, or review paper-based, hand-written vaccination registers at multiple healthcare facilities to obtain vaccination data, adding to travel costs and personnel time.

Other challenges with verifying vaccination records included: (i) patients not carrying vaccination cards at hospital admission, (ii) lost vaccination cards, (iii) incorrect patient contact details recorded, complicating tracing, (iv) patients deceased, and (v) patient migration. Due to initiation of the vaccine safety surveillance platform late into the pandemic (May 2022 to March 2023), there were few active country-specific vaccination campaigns and demand for vaccination was low. Consequently, very few recently vaccinated patients presented with an AESI at the participating hospitals or healthcare facilities. The Ethiopian team reported difficulties obtaining patients' vaccination cards due to regional conflicts; however, this was resolved within a month of recruitment initiation.

The Ethiopian or Ge'ez calendar, used as the civil calendar in Ethiopia, is similar to the Coptic - and Julian calendars. The database did not support this calendar format, so the Ethiopian team converted dates to Gregorian calendar format prior to data entry. Although this was not a challenge for the Ethiopian team, due to their familiarity with both calendars, monitoring teams needed to take this into account.

3.5. Electronic REDCap data capturing systems

The data capture process was dependent on an internet connection, therefore data were either: [1] entered on paper-based data collection instruments and later entered onto electronic database, [2] captured directly in to database using the web-link or [3] captured on tablets using the offline REDCap mobile app, and synchronized data with REDCap server once tablets were online. Despite the convenience of offline data entry, some challenges were encountered with synchronization of data when uploading data onto the server, requiring manual reconciliation of data on tablets and the database. Although all the enrolled patients' data were retrieved and uploaded onto the REDCap database, approximately 500 screening records were lost due to data synchronization issues in the first months of screening. To ensure no further loss of screening data, the 'emergency data dump' feature in REDCap was used. This entails that data collected from the tablets were uploaded onto the REDCap server as a comma-separated value (CSV) file. Thereafter, the coordinating team consolidated the data and synchronized it back to the REDCap project database. In addition, copies of databases were created as a backup by the coordinating team in case records went missing or were accidently deleted.

Despite pilot testing of the database prior to patient enrolment initiation, extensive amendments needed to be made to the database to allow for collection of raw data rather than collection of composite variable data. To avoid confusion at the point of data entry, the coordinating teams decided to roll out a new database from July 2022, and merge data entered into the two databases at the time of analysis, rather than implementing amendments into existing database. The complexity of the adverse events of special interest necessitated development of very detailed BC-CDs, sections of which were open to interpretation. The two databases used to collect data needed to be merged and appended at the time of data cleaning and analysis. In addition, some data were not collected or verified in the initial database, which impacted on the ability to calculate LOCs for myocarditis, pericarditis, ADEM, encephalitis and myelitis. This highlights the importance of collecting raw data and pilot testing all the data collection tools on-site, in conjunction with relevant case definitions, before data collection commences.

Many hospitals and healthcare facilities in LMICs have limited capacity, finances and other resources to conduct laboratory and imaging tests as part of routine care. Some centers offer testing at the patient's expense; however, patients are seldom able to pay for these tests. This contributed to missing data needed for the LOC calculation, which resulted in several clinically-reported AESIs not being able to fulfil criteria for LOC1–3 due to insufficient evidence being available.

3.6. Representativeness

Patients were residents of the areas serviced by the participating facilities. Most facilities (29/50) are tertiary healthcare facilities based in urban settings, and are referral hospitals for peri-urban and rural healthcare facilities. Despite both urban and rural populations being represented in this study, it is likely that there was underrepresentation of the rural population, based on urban location of the majority of the facilities and the well-documented inequalities in access to healthcare between urban- and rural dwellers [15,16]. Most facilities (43/50) are public health facilities, therefore patients utilizing privately-funded healthcare were under-represented (Table 1).

3.7. Timeliness

The average time for study staff to enroll a patient was between 30 and 60 min, with a range of <30 min to >3 h. Most CRFs were completed in less than a week, but this was dependent on the patient's admission duration and completion of laboratory and imaging investigations (Table S5).

3.8. Stability

The REDCap platform was stable with all sites agreeing that it was user friendly and easy to rectify data capture errors. Nevertheless, the automatically assigned screening numbers was an issue for some sites as the same screening numbers were assigned on multiple tablets, leading to duplication of screening numbers once data were synchronized on database. Some medical records were lost, misplaced or not systematically organized at health facilities; therefore, site teams found it challenging to go back to patient files to resolve data-related queries.

Due to limited data on the number of individuals hospitalized for the rare AESIs within the specific study sites, evaluation of the additional two surveillance system attributes (sensitivity and positive predictive value) was not feasible.

4. Discussion

Active vaccine safety surveillance systems serve as a vital early warning mechanism by detecting unexpected signals or clusters of adverse events. This enables regulatory- and public health authorities to make timely, evidence-based decisions regarding vaccine use and recommendations. Resource and capacity constraints have limited the establishment of functional active vaccine safety surveillance platforms in LMICs, compared with the success of establishing such systems in many HICs. Our findings across nine African countries highlight the challenges of developing active vaccine safety monitoring systems in LMICs, but also demonstrated the feasibility of establishing sentinel active vaccine safety surveillance platforms in a short time period.

Access to data is a key challenge in LMICs, as most facilities rely exclusively, or almost exclusively on paper-based medical and vaccination records and vaccination registers. Abstraction of data is therefore time-consuming and missing medical records undermines the success of the platform. Introduction and/or expansion of electronic medical and vaccination records will simplify data collection, enabling more rapid identification of adverse events and assessment of relatedness. To facilitate the data collection process across various sites with language differences, the translation feature within REDCap could be utilized which allows the study instrument designers to automatically change the language of the instrument. However, this was a recent development on REDCap at the time of this study and limited languages were available.

Additionally, medical records should include key variables related to diseases and exposures (e.g., lot number, expiry date, date and body site of vaccination) in standardized formats to allow for pooling of essential data elements. The collection and entry of raw data elements, which can be utilized in BC-CD LOC calculation and analyses, is preferred to entry of multi-component or derived variables interpreted by field staff.

Active vaccine safety surveillance is resource intensive, and requires significant personnel time to collect, validate and analyze data, as well as a dedicated group of experts who can allocate significant time to assessment of potential AESI cases. Implementation of active safety surveillance at sentinel sites would supplement passive reporting processes and restrict costs.

Active safety surveillance for vaccines and other medicines should be integrated into routine healthcare and managed by the national or regional medicines regulatory authority, in collaboration with Ministries of Health and international immunization funding platforms. Patients should be made aware that medicine exposure data are collected and reported routinely as compulsory safety monitoring, with blanket approval from ethics committees and regulatory authorities. Additionally, patients should have access to digital medicines safety reporting platforms, like the Med Safety App [17], to self-report potential adverse events. The Med Safety App has been rolled out successfully in at least 13 African countries through the African Union Smart Safety Surveillance (AU-3S) programme since 2020 [18]. The pharmacovigilance system implemented to monitor for AESIs during the Sisonke trial (a phase 3B open-label trial of Ad26.COV2S (Janssen/ Johnson and Johnson) vaccine which enrolled almost half a million HCWs in South Africa from February 2021), provides an example of successful integration and harmonization of vaccination records, national privately-funded- and publicly-funded healthcare data and active and passive safety surveillance platforms in a LMIC [19].

The BC-CDs were utilized to provide a consistent and scientifically validated framework for assessing and reporting of adverse events of special interest after COVID-19 vaccination. Use of BC-CDs ensures greater accuracy and comparability of safety data collected in varied settings by harmonizing data collection and interpretation, thus enhancing the ability to detect, monitor and evaluate potential safety concerns. Utilization of BC-CDs by multiple stakeholders involved in vaccine safety monitoring facilitates clear communication of safety data and ultimately fosters trust in vaccine safety.

Limitations of the study include being unable to identify a sufficient number of COVID-19-vaccinated patients with AESIs that had an LOC 1–3 (true cases), as the safety surveillance studies were only implemented in early 2022, when the uptake of COVID-19 vaccines was declining. This highlights the importance of establishing and maintaining strong active PV systems in sentinel sites in multiple countries, which could be scaled up prior to the introduction of new vaccines. Additionally, use of- and access to electronic individual vaccination records and vaccination registries is vital, but was limited in participating countries. Enrolment into these demonstration projects was concluded in March 2023, and was not sustained for ongoing monitoring of adverse events of special interest.

Many LMICs have existing passive vaccine surveillance systems, which are important but inadequate to identify rare AESI related to vaccination roll-out. We have demonstrated that the establishment of active vaccine safety surveillance platforms is time-consuming, but feasible in LMICs. This knowledge will be useful in planning for future vaccine introductions in Africa and other low income setting to assure the safety of new vaccines and maintain vaccine confidence. Vaccine/ medicines safety surveillance systems which can be adapted for new medicines and activated in days to weeks, should be approved by all relevant authorities, and planned prior to any future epidemics. Ideally, vaccine/ medicine safety surveillance should be considered routine care, and therefore should not require separate informed consent or dedicated research teams. National Ministries of Health should identify and support sentinel surveillance sites equipped with electronic medical records and staffed with dedicated personnel responsible for active safety surveillance activities. Field Epidemiology Training Program (FETP) trainees and alumni should be mobilized to strengthen these systems, especially during outbreaks and new vaccine introductions. Regional organizations such as African Vaccine Regulatory Forum (AVAREF) should play a key role in facilitating access to standardized protocols, data collection and reporting tools and qualified reviewers to ensure harmonized and coordinated active vaccine safety assessment across countries.

In conclusion, we appeal that, since many vaccines - including those for Ebola, Nipah, Chikungunya and Lassa Fever - will be introduced primarily or exclusively in LMIC, establishment, maintenance and sustained funding of active vaccine safety surveillance platforms is prioritized by regulatory authorities, vaccine manufacturers, government health departments and immunization support organizations. Active vaccine safety surveillance is essential to ensure that new vaccines are adequately monitored for safety when introduced and used in these populations.

Author Contribution

SAM & SBB conceptualized the study; CLC & KG coordinated the ACVaSS and SA-CVSS studies respectively, SM, JP, NAA, SO, BT, KJ, SS, EWK & SC were site principal investigators; TD was lead country investigator; JAY, AI & JG developed database, JAY & AI coordinated data management and curation, MB contributed to project administration, HC, JG, YJ, AL, JAY, LG & AI analyzed data; CLC wrote original draft of manuscript, and all authors critically reviewed and edited manuscript. XN, BNT, AM, POA, AH, EI, BE, AT, DM, FCH, SS, AS, CK and ES were sub-investigators and/ or study coordiantors at sites. All authors approved final version of manuscript.

CRediT authorship contribution statement

Clare L. Cutland: Supervision, Investigation, Conceptualization, Methodology, Data curation, Writing – original draft, Project administration. **Kimberley Gutu:** Writing – review & editing, Formal analysis, Methodology, Data curation, Project administration, Investigation. **Jessica Ann Yun:** Project administration, Writing – review & editing, Data curation, Formal analysis. **Alane Izu:** Writing – review & editing, Investigation, Methodology, Project administration, Formal analysis. **Sana Mahtab:** Writing – review & editing, Supervision, Investigation, Methodology. **Jonny Peter:** Supervision, Methodology, Writing – review & editing, Investigation. **Nana Akosua Ansah:** Supervision, Project administration, Writing – review & editing, Investigation. **Stephen Obaro:** Project administration, Writing – review & editing, Investigation, Supervision. **Binyam Tilahun:** Writing – review & editing, Investigation, Supervision, Project administration. **Kondwani Jambo:** Supervision, Project administration, Writing – review & editing, Investigation. **Samba Sow:** Project administration, Writing – review & editing, Investigation, Supervision. **Eunice Wangeci Kagucia:** Writing – review & editing, Investigation, Supervision, Project administration. **Sergio Chicumbe:** Supervision, Project administration, Writing – review & editing, Investigation. **Tenelisiwe Dlamini:** Writing – review & editing, Project administration. **Michael Browne:** Writing – review & editing, Project administration. **Hazel Clothier:** Writing – review & editing, Formal analysis. **Jennifer Griffin:** Writing – review & editing, Methodology, Project administration, Formal analysis. **Yannan Jiang:** Writing – review & editing, Project administration, Formal analysis. **Arier Lee:** Writing – review & editing, Formal analysis. **Luam Ghebreab:** Formal analysis, Writing – review & editing. **Shabir A. Madhi:** Supervision, Conceptualization, Writing – review & editing, Funding acquisition. **Steven B. Black:** Writing – review & editing, Funding acquisition, Supervision, Conceptualization.

Declaration of competing 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.

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Appendix A. Supplementary data

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Data availability

Data will be made available on request.

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