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Vaccine safety surveillance in South Africa through COVID-19: A journey to systems strengthening

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ABSTRACT

Background: Surveillance systems for monitoring and reporting adverse events following immunisation (AEFI) and adverse events of special interest (AESI) are vital in understanding safety profiles of post-marketed vaccines. Evaluation of surveillance systems is necessary for systems strengthening. We conducted the first evaluation of the South African AEFI surveillance system in its current form, established in 2018.

Methods: Using CDC guidelines for evaluation of surveillance systems, we conducted a cross-sectional evaluation of system attributes, including quantitative analyses of AEFI/AESI data from 17 May 2021 to 31 December 2022 and qualitative analyses through semi-structured interviews with AEFI surveillance personnel. Findings were used to generate recommendations for system strengthening.

Results: The system collects and manages AEFI data, employs investigative tools and has an established AEFI review committee conducting causality assessment, thus meeting WHO minimal capacity for vaccine safety. System adaptation through inclusion of digital applications facilitated public reporting, whilst increasing complexity of database management. Respondents demonstrated engagement with the system through accounts of their roles in AEFI surveillance. Between 17 May 2021 and 31 December 2022, 37,537,009 COVID-19 vaccine doses (BNT162b2 and Ad26.COV2·S) were administered, and 3846 AEFI reported in relation to these vaccines (reporting rate: 10.2/100,000 doses). AEFI reporting rates varied considerably across provinces, ranging from 1.6 to 59.5 AEFI/100,000 doses. In this time period 283 AEFI were reported in relation to non-COVID-19 vaccines. By 31 December 2022, 73.5 % of severe cases that were investigated were causality assessed.

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Conclusion: We observed a functional, useful, flexible system with high reported stakeholder and public acceptability levels. System challenges included low reporting rates from particular provinces, weak co-ordination between paper and digital reporting and human resource constraints. Recommendations include integration of paper-based and digital surveillance reporting systems to enhance signal detection and eliminate data duplication, provision of dedicated human and financial resources at provincial level and inclusion of active AEFI surveillance through cohort event monitoring.

1. Introduction

1.1. Importance of pharmacovigilance in the context of COVID-19 vaccine roll-out

During the COVID-19 pandemic, following emergency use authorisation (EUA), the national roll-out of vaccines against SARS-CoV-2 began in South Africa on the 17th of May 2021; 14 months after the World Health Organization (WHO) declared the outbreak a global pandemic [1]. From the start of the vaccine roll-out till the 31st of December 2022, 37,537,009 COVID-19 vaccine doses have been administered in South Africa [2]. The magnitude of the distribution and administration of these vaccines to adults necessitated close monitoring of pharmacovigilance surveillance systems post EUA.

Surveillance systems for monitoring and reporting adverse events following immunisation (AEFI) and adverse events of special interest (AESI) are vital in assuring vaccine confidence [3–5]. An AEFI is known as any untoward medical event that occurs following immunisation and that does not necessarily have a causal relationship with the use of the vaccine. An adverse event (AE) can be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease [3–5]. An AESI is defined as a preidentified and predefined medically significant event that has a potential causal link to the vaccine and therefore requires careful monitoring and confirmation through further studies [5,6]. The WHO Global Vaccines Safety Blueprint defines the minimal capacity for vaccine safety surveillance as a monitoring system that has national vaccine pharmacovigilance capacity, with designated staff for this purpose, stable funding, clear mandates and well-defined structures and roles that align with the WHO Programme for International Drug Monitoring (WHO-PIDM) [6]. The system should consist of a national database and a national AEFI review committee [6]. Post-licensure surveillance often identifies AEs that may not have been identified in the controlled environment of a clinical trial and contributes to understanding the safety profiles of marketed vaccines [7].

The WHO's Global Advisory Committee on Vaccine Safety (GACVS) initially recommended two indicators to assess country performance in terms of vaccine safety surveillance, namely to have an established national causality review committee, and to report ≥10 AEFI per 100,000 surviving infants per year. During the pandemic, GACVS recommended a new case-based vaccine safety indicator for monitoring AEFI surveillance in all age groups i.e. to report at least one serious AEFI per million persons per year [8–10].

1.2. Surveillance of adverse events following immunisation in South Africa

The National Department of Health (NDoH) in South Africa has had a rudimentary surveillance system for monitoring AEFI in place since 1998, managed by the South African Expanded Programme on Immunisation (EPI-SA) [4]. From inception, AEFI surveillance was integrated into general pharmacovigilance. However, in 2018, following WHO recommendations, a dedicated pharmacovigilance system for AEFI was established with links to the existing South African Health Products Regulatory Authority (SAHPRA) AE monitoring system. In addition, a national causality review committee was established, referred to as the National Immunisation Safety Expert Committee (NISEC). The new system facilitates detection, investigation and response to reported AEFI [4]. From the start of the COVID-19 vaccination roll-out, the South African AEFI surveillance system has been responsible for monitoring AEFI reported for all vaccines administered in the public and private healthcare sector in the country, including the COVID-19 vaccines. The introduction of COVID-19 vaccines resulted in further developments to this system, to also monitor and evaluate AESI.

1.3. Evaluation of surveillance systems

Evaluation of surveillance systems is necessary for systems strengthening and can help to ensure effective operation and optimisation of system processes. Evaluation of AEFI surveillance systems has been used to advocate for and drive system strengthening. For example in Pakistan and Ethiopia, recommendations generated through qualitative and indicator-based evaluations of their AEFI surveillance system during their COVID-19 vaccine roll-outs, contributed towards advocacy for implementation of interventions to improve pharmacovigilance [11–13]. The WHO Global Benchmarking Tool (GBT), which is a set of indicators used to assess regulatory systems for medical products, aims to evaluate the overarching regulatory framework and provides a set of global standards based on international guidelines and best practices in terms of maturity level (ML) [14]. Since 2022, South Africa has been operating at maturity level 3 (ML3) for vaccines [15]. The WHO Global Vaccines Safety Blueprint and GBT are both situated within the context of pharmaceutical regulatory systems, and whilst helpful overlook important surveillance principles and system attributes. The GACVS recommendations provide broad indicators for assessing country level surveillance. Since 2001, the CDC guidelines for evaluating public health surveillance systems have been used to guide assessment of surveillance systems in numerous settings [16–25], the focus of which is to observe operational aspects and systematically evaluate specific system attributes within the national context (Table 1).

To date, no evaluation of the South African AEFI surveillance system has been conducted. We therefore aimed to evaluate specific attributes of the South African vaccine safety surveillance system, using the CDC guidelines [25] in order to generate recommendations for system strengthening.

2. Methodology

2.1. Study context

The AEFI surveillance system in South Africa relies on spontaneous reporting of all minor, severe and serious AEFI and AESI by health care professionals (HCPs) and members of the public, within 24 h of occurrence (Fig. 1). Reports can be submitted electronically through the Med Safety App and database, managed by SAHPRA, which is the preferred reporting modality, or using a paper-based case reporting form (CRF) submitted via email to the National AEFI coordinator [3,26]. All reported data from paper-based CRFs and electronic data submitted via the Med Safety App, are listed manually on an MS Excel spreadsheet, maintained by the secretariat of NISEC. This spreadsheet also includes case metadata (dates of reporting, investigation and classification), patient demographic data and limited details about the case (severity, diagnosis and outcome).

Data reported to SAHPRA through the Med Safety App feeds into VigiBase, the WHO-Uppsala Monitoring Centre (WHO-UMC) global

Table 1
CDC criteria by which the evaluation of the South African surveillance system for AEFI was conducted, including data sources, data collection methods, analytical approaches and reporting methods.

Criteria	Definition applied to AEFI surveillance	Data source	Data collection methods	Analysis method and reporting of results
Purpose	Purpose and objectives of the South African AEFI surveillance system	NISEC terms of reference and procedures	Desk review	Described the purpose, objects and intended use of the collected data and how the information is disseminated and utilized
Resources	Resources required to have the AEFI reporting system operating at full capacity	NISEC terms of reference Semi-structured interviews*	Desk review Interviews with key stakeholders	Ascertained and evaluated: • Funding Sources • Personnel required • Other costs including but not limited to, equipment, supplies, travel budgets
Simplicity/Design	Structure of the reporting system and ease of operation Design and size of the system	Terms of reference and procedures Semi-structured interviews*	Distillation of explanations and figures in the data sources. Interviews with key stakeholders	Ascertained and evaluated: • Quantity and type of information required to establish a diagnosis • Number of reporting sources • Chain of reporting and number of organizations involved • Methods of dissemination of reports and communication between different organizations • Amount of follow up required • Ease of data management and time spent on data management
Flexibility	Adaptable to shifts in requirements or operating conditions regarding time constraints, staffing and funding	Semi-structured interviews*	Interviews with key stakeholders	Ascertained and evaluated: • Participants' perceptions of how the system coped during the COVID-19 pandemic and how the Med Safety App was developed • Participants' reflections on what needed to be done to include surveillance for AEFI post COVID-19 vaccination
Data Quality	Completeness of data recorded by the AEFI system. Data quality is affected by the clarity of forms, questions being asked, and quality of training.	AEFI database Semi-structured interviews*	Data from the AEFI reporting database was imported into R-studio and analysed using summary statistics, including the number of complete CRFs/CIFs, and additional documentation provided. Interviews with key stakeholders	Ascertained and evaluated: • Understanding of CRFs/CIFs and their clarity • How much training was provided • Which database fields are critical for completion of investigations and causality assessment • Level of completeness of the data
Acceptability	Willingness of persons and organizations to participate in the AEFI surveillance system and reporting processes.	Semi-structured interviews*	Interviews with key stakeholders	Evaluated: • Participants' perceptions of the willingness of members of the public and HCPs to engage with AEFI surveillance
Representativeness	Accurate description of the occurrence of vaccine-related AEFI over time and its distribution by place and person.	AEFI database Semi-structured interviews*	Reviewed demographic data that has been collected for each case Interviews with key stakeholders	Ascertained and evaluated: • Differences in distribution of reports by province, age, gender, vaccine type, person reporting, public vs private sector • Reasons behind differences in distribution of reports
Timeliness	Speed between steps in the AEFI reporting process.	AEFI database Semi-structured interviews*	Review of the line list of data that has been collected by the reporting system Interviews with key stakeholders	Ascertained and evaluated: • Turnaround times between when information is requested and complete documentation is received for submission to NISEC
Stability	Reliability of the system; does the AEFI reporting system allow one to collect, manage, and provide data without failure. Availability of responsible persons supporting surveillance.	Semi-structured interviews*	Interviews with key stakeholders	Ascertained and evaluated: • Issues around system availability and points at which there may have been system failures • Sustainability of funding
Usefulness	Usefulness of the AEFI surveillance system	Semi-structured interviews*	Interviews with key stakeholders	Evaluated:

(*continued on next page*)

Table 1 (*continued*)

Criteria	Definition applied to AEFI surveillance	Data source	Data collection methods	Analysis method and reporting of results
				• Participants' perceptions on whether the objectives of the system were achieved • Impact of the system on policy decisions and vaccine-related regulations as reported by participants

AEFI – adverse events following immunisation; CRF- case reporting form; CIF- case investigation form; SAHPRA – South African Health Products Regulatory Authority; NISEC – National Immunisation Safety Expert Committee; NDoH – National Department of Health; HCP – Health care professional.

* Semi-structured questions are provided in the Supplementary Materials.

database. An advantage of electronic reporting is that once a report is submitted, it can be accessed immediately by provincial officers through the backend of the Med Safety App system, known as the Vigilance Hub (Fig. 1).

Provincial surveillance officers review all reports of AEs, electronic and paper-based, to identify serious/severe cases and clusters that require investigation. These cases are then investigated by district or provincial surveillance officers. Findings of case investigations are recorded on a paper-based case investigation form (CIF), with available clinical records attached, and submitted via email to a dedicated email address at the NDoH. Upon completion of the investigation of a case, the status of the 'investigation conducted' field in the MS Excel database is modified by the NISEC secretariat. Once all documentation on a case is available, it is submitted to NISEC for causality assessment, using the WHO causality assessment methodology [27]. NISEC is a ministerial appointed advisory committee of independent technical experts, responsible for causality assessment of serious/severe cases (Supplementary table 1). All authors except for CS serve on this committee.

2.2. Study design

For the purpose of this study, we considered the CDC framework for evaluating surveillance systems. The framework focuses on evaluating specific attributes of the system and is based on attributes deemed essential for the maintenance of an adequate surveillance system (Supplementary table 2).

We developed a conceptual framework that linked CDC criteria with system outputs including AEFI detection, causality assessment, interpretation of findings and subsequent public health actions (Fig. 2). We then conducted a cross-sectional evaluation of system attributes informed by the CDC criteria [25], focusing on attributes that were of importance and feasible to evaluate. Findings were then used to generate recommendations for strengthening South African AEFI surveillance.

2.3. Study participants and setting

The quantitative study population included all AEFI case records from vaccine recipients and HCPs, that were reported through the Med Safety App or through submission of a CRF to the NDoH. The qualitative study population included purposively identified personnel involved in reporting, investigating, evaluating, and acting on AEFI surveillance data, including two NISEC secretariat members from EPI-SA, two technical experts from NISEC, and one SAHPRA pharmacovigilance specialist (Fig. 1). AEFI surveillance members at the national operating level of the AEFI surveillance system were purposively selected for semi-structured interviews, to ensure detailed and in-depth information on the surveillance system is obtained. Some participants also contributed to the review of the findings and the manuscript.

2.4. Data collection

For each of the attributes that were identified as feasible to assess from Table 1, data was collected from sources described in Table 1. Table 1 also summarizes the analytic approach for each of the criteria. After obtaining informed consent, interviews were conducted on Zoom, recorded and transcribed.

2.5. Data management and analysis

All recorded interviews were transcribed verbatim using Zoom Video Communications, Inc. and subsequently corrected for AI transcription errors. We then used a thematic analysis to identify, interpret and report on themes using the selected conceptual framework (Fig. 2). Data relevant to identified themes was gathered and collated in MS Excel [28].

AEFI line lists were imported into R-studio, cleaned, and de-duplicated. Only AEFI reports that included a vaccine type were included in the analysis. Individual variables were reviewed for consistency and categories standardized. Variables were evaluated using summary statistics.

3. Results

A total of 4129 AEFI reported between 17th May 2021 to 31st December 2022 were collated for inclusion in the quantitative evaluations. This included 1561 AEFI reported following administration of the Ad26.COV2·S vaccine, 2285 AEFI reported following administration of the BNT162b2 vaccine and 283 AEFI following administration of all other non-COVID-19 vaccines, including those administered as part of the EPI (routine immunisation) and vaccines available in the private sector (Table 2). NISEC only assesses serious/severe AEFI cases for causality. In total 1877 cases were identified by the NISEC secretariat as severe local and/or severe systemic reactions based on information provided in CIFs. Table 2 shows the number of AEFI reported by vaccine type, the proportion of cases classified as severe/serious, the investigative status and the number of cases causality assessed. 73.5 % (534) of serious/severe cases that were investigated, had been causality assessed as of the 31st of December 2022. In some instances, a case initially classified as severe/serious, was reclassified as non-serious, following discussion by NISEC.

3.1. Attributes of the south African AEFI surveillance system

3.1.1. Purpose

The AEFI surveillance system is a pharmacovigilance system used to monitor the safety of administered vaccines and to ensure appropriate responses to safeguard vaccine confidence. Data collected contributes directly to understanding the safety profile of vaccines post-authorisation. Data is managed and maintained by the NDoH. The NISEC determines, where possible, the causal role of the vaccine in relation to each reported AEFI. SAHPRA is responsible for collation of causal assessments and for determining the subsequent appropriate

regulatory actions.

3.1.2. Simplicity

Participants reported that since 1998, the AEFI surveillance system had a single line of reporting through completion of a CRF submitted to a single database. The addition of the Med Safety App (in 2021) as a reporting medium, lead to the existence of a second database (Fig. 1). A participant outlined the different lines of reporting by explaining *"…we introduced the Med Safety App in May 2021…it allows people in the public or a health care worker to report an adverse event…so that's one way of reporting, another way of reporting is that in health facilities if you can't use the app you can still fill in a CRF, which is a paper-based document"*. Complexity arises, as the pharmaceutical industry submits anonymised AEFI reports electronically to SAHPRA in the International Conference on Harmonisation (ICH) E2B format [2]. SAHPRA is responsible for uploading these data-sparse reports into Vigibase. Participants observed that multiple lines of reporting, two databases and anonymised data create the risk of duplicate AEFI reports, should databases be merged. The complexity around data management also arises from the transfer of information and data between SAHPRA, the NDoH and the pharmaceutical industry. Participants demonstrated a strong desire to have a single line of reporting, with one participant stating *"I think the agreement on minimum variables is essential…we should all collect the same data on the same platform so that it's easy for us to identify and update cases rather than create duplicates within the system"*. Issues were also noted around the time-consuming relay of information on causality assessment outcomes to the provinces via the Ministry of Health.

3.1.3. Flexibility

All interviewees mentioned shifts in complexity of the system during the COVID-19 vaccine roll-out with high numbers of AEFI case reports, changes in frequency of NISEC meetings from quarterly to weekly and the introduction of the Med Safety App as an additional reporting modality. Interviewees were asked how safety surveillance adapted with the vaccine roll-out. One participant stated that, *"it waskind of [a] sink or swim situation because all the provinces were under strain during the COVID-19 response and vaccine introduction"*. When asked about changes in complexity and time with the roll-out, a participant noted that there were *"improvements in system flow of data, so how we receive data, who is responsible for what and how we collect it [data] and keep it all together because we were jumping from an odd 150-200 cases a year to suddenly having over 1000 cases in 9 months"*.

A member of the secretariat noted that flexibility of the system is limited if a new vaccine were to be introduced, stating *"I'm not sure if the system would be able to cope,"* as particular provinces already struggle to investigate cases and to provide the necessary information for causality assessment. Thus, the need for additional training and personnel for case investigations. One participant elaborated on why the training is so crucial, explaining that, *"training people in the public and also health care workers on the expected AEFI so that they can manage them effectively and report them in an accurate way…understanding what technical data might be required…so they can be properly investigated"*.

Difficulty in providing adequate personnel to fulfil these functions is a source of system inflexibility.

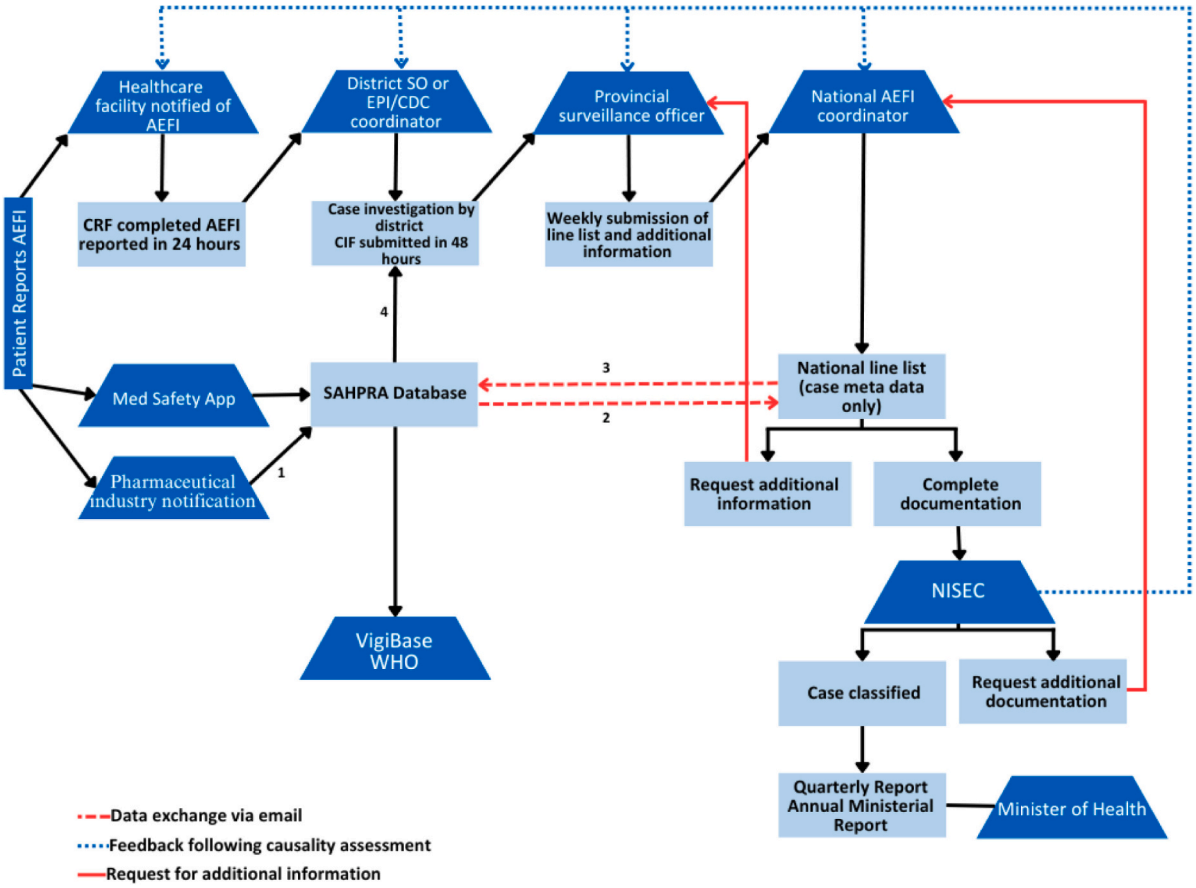

Fig. 1. Key: Adverse events following immunisation (AEFI); Case reporting form (CRF); Expanded programme on immunisation (EPI); Centre for Disease Control (CDC); South African Health Products Regulatory Authority (SAHPRA); World Health Organization (WHO); Case investigation form (CIF); National Immunisation Safety Expert Committee (NISEC); Department of Health (DoH). Arrows indicate the direction of data flow following notification of AEFI: 1: Pharmaceutical industry notifications are de-identified and sent to SAHPRA; 2 and 3: Data is sent via email; 4: Med Safety App reports are accessible to provincial surveillance officers. Schematic of the national AEFI surveillance system.

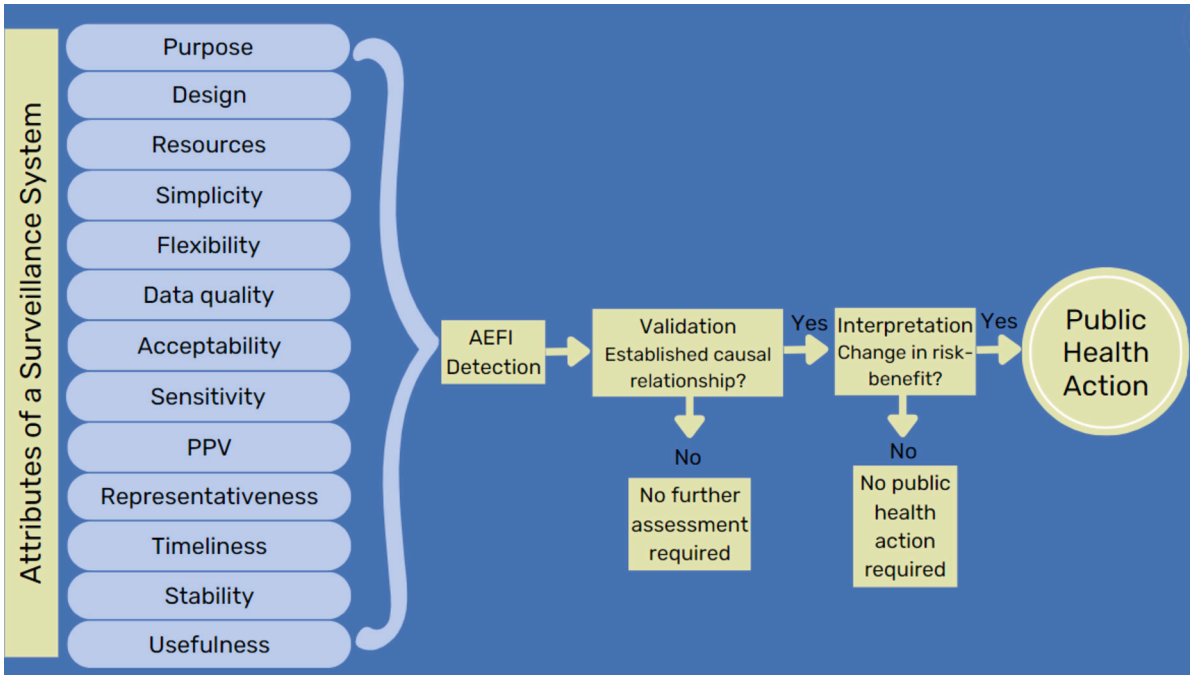

Fig. 2. Conceptual framework outlining CDC attributes for evaluating a surveillance system and how these attributes can be used to evaluate the national AEFI surveillance system.

Table 2
AEFI reported by vaccine type, number of cases classified as severe/serious, investigated and causality assessed.

Vaccine type	# of AEFI reported	# of cases classified as severe/serious (percentage of total # reported)	# investigated (percentage of total # reported)	# of severe /serious cases causality assessed (percentage of total # of cases classified as severe/ serious)
BNT162b2 vaccine	2285	1273 (55.7 %)	421 (18.4 %)	331 (78.6 %)
Ad26.COV2·S vaccine	1561	403 (25.8 %)	163 (10.4 %)	108 (66.3 %)
BCG vaccine	44	28 (63.6 %)	19 (43.2 %)	9 (47.4 %)
Bivalent oral polio vaccine	33	27 (81.8 %)	24 (72.7 %)	15 (62.5 %)
DTaP-IPV-Hib-HepB	56	47 (83.9 %)	31 (55.4 %)	19 (61.3 %)
Hepatitis B vaccine	2	1 (50 %)	0 (0 %)	0 (0 %)
Human papillomavirus vaccine	16	5 (31.3 %)	4 (25 %)	5 (NA)
Influenza vaccine	2	1 (50 %)	1 (50 %)	1 (100 %)
Measles containing vaccine	31	17 (54.8 %)	17 (54.8 %)	9 (52.9 %)
Meningitis vaccine	2	1 (50 %)	0 (0 %)	1 (NA)
Onvara (varicella)	1	0 (0 %)	0 (0 %)	1 (NA)
Pneumococcal conjugate vaccine	45	38 (84.4 %)	25 (55.6 %)	15 (60 %)
Measles, mumps, rubella vaccine (MMR)	1	0 (0 %)	0 (0 %)	1 (NA)
Rotavirus vaccine	34	32 (94.1 %)	20 (58.8 %)	15 (75 %)
Snake antivenom	1	0 (0 %)	1 (100 %)	0 (0 %)
Tetanus diphtheria vaccine	10	1 (10 %)	1 (10 %)	2 (NA)
Tetanus toxoid vaccine	4	2 (50 %)	0 (0 %)	1 (NA)
Verocell vaccine	1	1 (100 %)	0 (0 %)	1 (NA)
TOTAL	4129	1877 (45.5 %)	727 (17.6 %)	534 (73.5 %)

3.1.4. Data quality

A member of the secretariat mentioned that the quality of reports declined with the inclusion of self-reporting by members of the public via the Med Safety App.

Table 3 shows the proportion of missing data elements from the CRF and the Med Safety App fields that are essential for identification and investigation of serious/severe AEFI. The outcome of the cases (recovery or vital status) had a large proportion of missing data (22 %). As much as 24 % of reports were missing the final diagnosis in the line list database. Participants also noted that the overall database quality improved during the pandemic due to evident familiarity of the secretariat and investigation teams with the CIF and data collation processes.

3.1.5. Acceptability

Participants demonstrated evidence of engagement with the system through their accounts of their roles in investigation and assessment of cases, with a secretariat member explaining, *"I've definitely learned a lot about surveillance…and you learn the skills to work with different people to access information,"* while another stated, *"it taught me about the tools used to determine causality"*. They displayed a thorough understanding of the processes and commitment to seeing improvements, with a participant noting *"doing the right type of training will improve the system"*. Participants mentioned that through their role in the system, they learned about the role of policy informing decisions, WHO causality assessment tools, engaging with the public around vaccine hesitancy,

Table 3
Completeness of fields identified as critical to be completed during case investigation and for the purpose of causality assessment of cases among AEFI reports submitted from 17th of May 2021 to 31st of December 2022.

Field	Number of reports with missing data ($n = 4129$)	Proportion of total
Name	73	1.8 %
Surname	198	4.8 %
Date of birth	399	9.7 %
Sex	59	1.4 %
Date of vaccination	333	8.1 %
Date of onset of AEFI	399	9.7 %
Date of reporting	1306	31.6 %
Severity (Classification)	343	8.3 %
Outcome	897	21.7 %
Final diagnosis	1007	24.4 %

and variety of adverse reaction profiles. We also noted that committee members dedicate their time to do causality assessment reviews voluntarily for altruistic reasons, namely to support public health.

3.1.6. Representativeness

A total of 3846 AEFI were reported for the period of the 17th of May 2021 to the 31st of December 2022 during which 37,537,009 doses of both SAHPRA registered COVID-19 vaccines (BNT162b2 and Ad26.COV2·S) were administered (Table 4, AEFI reporting rate of 10.2/100,000 doses) [2]. Over 75 % of vaccinees received the BNT162b2 vaccine, for which 2285 AEFI were reported (7.9 AEFI/100,000 doses) whilst 1561 AEFI were reported for the AD26.COV2·S vaccine (18.1 AEFI/100,000 doses), p-value indicates that observed differences were not due to chance (<0.0001). Female recipients of the Ad26.COV2·S vaccine had a much greater reporting rate of AEFI (24.2/100,000) compared to males (9.7/100,000, $P < 0.0001$). Regarding age distribution, most recipients of the Ad26.COV2·S vaccine were in the 18–24 year (40.7 %) and 35–49 year (37.2 %) age groups. Among Ad26.COV2·S recipients, the distribution of AEFI in relation to vaccine doses administered in each age group was uneven ($P < 0.0001$), with persons aged 18–34 years receiving 40.7 % of vaccines but reporting 26 % of AEFI. Among BNT162b2 recipients, the distribution of reported AEFI was weighted towards persons >60 years, with those in this age category receiving 26 % of vaccines but reporting 36 % of AEFI ($P < 0.0001$).

Table 4
The number of doses administered and AEFI reported by vaccine type, sex and age group, 17th May 2021 to 31st December 2022.

Sex	Total number of vaccine doses administered (% of total)	Total number of AEFI reported (% of total)	AEFI rate per 100,000 doses	*P*-value (x^2)
Ad26.COV2·S	**8,627,230 (23 %)**	**1561 (41 %)**	18.1	<0.0001
Male	3,817,765 (44.3 %)	371 (23.8 %)	9.7	
Female	4,809,465 (55.7 %)	1166 (74.7 %)	24.2	
Unknown	0 (0 %)	24 (1.5 %)		
BNT162b2	**28,909,779(77 %)**	**2285 (59 %)**	7.9	<0.0001
Male	12,652,680 (43.8 %)	834 (36.5 %)	6.6	
Female	16,257,099 (56.2 %)	1417 (62 %)	8.7	
Unknown	0 (0 %)	34 (1.5 %)		
Total	**37,537,009**	**3846**	**10.2**	
Age group				
Ad26.COV2·S	**8,627,230 (23 %)**	**1561 (41 %)**	18.1	<0.0001
12–17	391 (0.005 %)	0 (0 %)	0	
18–34	3,515,409 (40.7 %)	406(26 %)	11.5	
35–49	3,209,123 (37.2 %)	553 (35.4 %)	17.2	
50–59	1,354,036 (15.7 %)	341 (21.8 %)	25.2	
≥ 60	547,632 (6.3 %)	82 (5.3 %)	15	
Unknown	639 (0.01 %)	179 (11.5 %)		
BNT162b2	**28,909,779 (77 %)**	**2285 (59 %)**	7.9	<0.0001
12–17	3,027,972 (10.5 %)	64 (2.8 %)	2.1	
18–34	6,887,150 (23.8 %)	296 (13 %)	4.3	
35–49	7,157,287 (24.8 %)	477 (20.9 %)	6.7	
50–59	4,378,626 (15.1 %)	347 (15.2 %)	7.9	
≥ 60	7,453,164 (25.8 %)	811 (35.5 %)	10.9	
Unknown	5580 (0.02 %)	290(12.7 %)		
Total	**37,537,009**	**3846**	**10.2**	

Table 5 shows the rate of vaccine administration varied considerably across provinces, ranging from 10,326 to 20,574 doses/100,000 persons for the Ad26.COV2·S vaccine and from 29,576 to 66,174 doses/100,000 persons for the BNT162b2 vaccine (Table 5). AEFI reporting rates varied by province among Ad26.COV2·S vaccine recipients (1.6–59.5/100,000 doses) and BNT162b2 vaccine recipients (2.5–11.5/100,000 doses) with the Western Cape and North West provinces having the highest and lowest reporting rates respectively for both Ad26.COV2·S and BNT162b2 ($P< 0.0001$).

Table 6 shows the cadres of persons and sectors reporting AEFI, either via the Med Safety App or via email to the NDoH. The largest number of reports (71.6 %) were submitted by HCPs and the majority of reports (63.5 %) were submitted in the public sector.

Participants were aware that certain provinces were underreporting AEFI, as one participant explained that, *"it depends on the province itself, that's why you see different reporting [rates] from different provinces…it comes in with structure…the province's [geographical] layout, as well as the management within the province*". Another participant also attributed the differences to resource availability, explaining that *"doing case investigations…even to travel to do these investigations is not equitably distributed across the provinces"* and *"it really has to do with the skills and resources within the provinces; unfortunately it's definitely not standard across all provinces"*. Participants reported that in the smaller provinces, HCP awareness of AEFI reporting systems was poor, staff lacked training and were over-burdened during the pandemic. Attempts to establish provincial immunisation safety expert committees during the pandemic was not very successful because of the lack of available and suitable technical experts. A participant described the challenge, stating *"we were trying to establish provincial safety committees…but then you get other provinces that are very rural with no [medical] universities, so it's difficult for them to establish expert safety committees"*.

3.1.7. Timeliness

Turnaround times from when a serious/severe AEFI is reported to the point of providing feedback on causality assessment, were not assessed quantitatively due to incomplete data fields. However, participants explained that the 30-day turn around time for causality assessment of serious/severe cases, specified in the NISEC terms of reference document is difficult to achieve Interviewees attributed extensive turnaround times to insufficient human resources within the provinces to conduct investigations for serious cases and delays in obtaining clinical notes, with a participant noting that *"the human capacity to do these investigations is not available"*. Furthermore, complex cases take time to be reviewed and discussed, and two-hour weekly expert committee meetings restrict the number of cases that can be discussed. Time availability of experts is also a challenge, with one participant stating that *"once a case is complete it joins the queue for assessment…obviously you can increase the number of assessments done on a weekly basis by having longer meetings but unfortunately it's difficult to find experts for these committees who have [sufficient] time available to do these assessments"* and attend weekly meetings. One of the participants highlighted the implications of all these delays, especially during the pandemic, saying that *"it can be almost a year later [after reporting] when we will be discussing the case at the committee meeting"*.

Table 5
Number of doses administered and AEFI reported by vaccine type and province, 17th May 2021 to 31st December 2022.

Province	Total number of vaccine doses administered (% of total)	Vaccines administered per 100,000 persons	Total number of AEFI reported (% of total)	Rate of AEFI per 100,000 doses administered	*P*-value (x^2)
Ad26.COV2·S	**8,627,230 (24.5 %)**		**1561 (41 %)**		<0.0001
		14,235		18.1	
Eastern Cape	1,023,926(11.9 %)	15,336	223 (14.3 %)	21.8	
Free State	561,991 (6.5 %)	19,236	167 (10.7 %)	29.7	
Gauteng	1,662,334 (19.3 %)	10,326	135 (8.6 %)	8.1	
KwaZulu-Natal	1,356,637 (15.7 %)	11,758	207 (13.3 %)	15.3	
Limpopo	1,222,371 (14.2 %)	20,574	90 (5.8 %)	7.4	
Mpumalanga	955,915 (11.1 %)	20,250	174 (11.1 %)	18.2	
North West	817,671(9.5 %)	19,529	13 (0.8 %)	1.6	
Northern Cape	245,240 (2.8 %)	18,739	37 (2.4 %)	15.1	
Western Cape	781,145 (9.1 %)	10,831	465 (29.8 %)	59.5	
Unknown	0 (0 %)		50 (3.2 %)		
BNT162b2	**28,909,779(75.5 %)**		**2285 (59 %)**		<0.0001
		47,702		7.9	
Eastern Cape	3,251,899 (11.2 %)	48,705	223 (9.8 %)	6.9	
Free State	1,697,843 (5.9 %)	58,113	101 (4.4 %)	5.9	
Gauteng	8,714,366 (30.1 %)	54,131	619 (27.1 %)	7.1	
KwaZulu-Natal	4,494,710 (15.5 %)	38,955	317 (13.9 %)	7.1	
Limpopo	2,552,310 (8.8 %)	42,958	118 (5.2 %)	4.6	
Mpumalanga	1,396,157 (4.8 %)	29,576	93 (4.1 %)	6.7	
North West	1,507,851 (5.2 %)	36,012	37 (1.6 %)	2.5	
Northern Cape	522,068 (1.8 %)	39,891	45 (2 %)	8.6	
Western Cape	4,772,575 (16.5 %)	66,174	548 (24 %)	11.5	
Unknown	0 (0 %)		184 (8 %)		
Total	**37,537,009**		**3846**		
		61,937		**10.2**	

Table 6
Distribution of persons reporting AEFI and distribution of reports by sector (private/public), 17th May 2021 to 31st December 2022.

Person reporting	Total number of reports	Proportion of total
Manufacturer	2	0.01 %
Legal representative	1	0.03 %
NHLS Helpdesk	10	0.3 %
Vaccinee	446	10.8 %
Health care professional	2955	71.6 %
Caregiver	30	0.7 %
Unknown	685	16.6 %
Total	**4129**	**100 %**
Sector (Private/Public)		
Public	2621	63.5 %
Private	542	13.1 %
Unknown	966	23.4 %
Total	**4129**	**100 %**

3.1.8. Stability

Participants reported that whilst the surveillance system was functional, there were risks to system stability, the most significant of which is the lack of sufficient human resources. One participant stated that *"with the volume [of cases] it was almost unmanageable during the pandemic, with the resources we had available"*. They reported that AEFI surveillance responsibilities are often allocated to already overburdened staff, contributing to delays in AEFI investigation. Several participants expressed concern that the addition of new vaccines and changes to the EPI would pose a risk to system stability, with one participant saying that *"it's functional,* [but] *definitely not resilient enough to cope with constant additional challenges to the health system, because the resources are not unlimited"*. They also mentioned that primary financial support for the secretariat during the pandemic came from non-governmental organizations and with this form of funding comes additional risks to stability.

3.1.9. Resources

Human resources, funding, access to medical records and support for communication with the public and stakeholders were considered essential resources to ensure smooth operation of the system. Several participants noted that personnel need to be medically qualified and have experience with working within the health system in order to effectively carry out roles in AEFI effectively, with a participant explaining that *"you need someone who understands the medical terminology, who understands the cases"*. A need for permanent, dedicated administrative staff to assist with data collation was highlighted, with a participant noting that *"an NGO has been providing funding for some of these secretariat support positions but it was only for 6 months or so and then you are back to square one, so we need permanent positions"*. Participants also observed that significant resources were allocated by national and provincial departments for roll-out and administration of vaccines during the pandemic, but limited additional resources were allocated for vaccine safety surveillance.

3.1.10. Usefulness

Participants were unable to recall instances when AFEI data had contributed to a shift in policy, while all interviewees felt that vaccine safety information and AEFI surveillance data provides reassurance that vaccines are safe to use and has the potential to influence policy. A participant reflected that *"…there hasn't been any instance yet, but it does have the potential to influence policy…at this stage I would say it's more about providing reassurance"*. Participants provided an example of causality assessed cases of Guillian-Barrè syndrome following administration of the Ad26.COV2·S vaccine, after which NISEC recommended that changes in policy were *not* necessary in the light of the rarity of the AEFI and the population-level benefit of the vaccine (MEDIA RELEASE-Coronavac Section 21_03.07.2021_FINAL.docx (sahpra.org.za)). At the time of this study, participants elaborated that they were using data to update the provinces on their reporting and investigation performance at quarterly meetings, with one participant explaining that *"the data is*

used to influence performance, I would say more than policy".

Whilst participants believed that the system itself and communication with the public about AEFI contributed towards public confidence in the vaccine roll-out, participants also felt that AEFI surveillance data could be better used to promote pharmacovigilance and its importance to policy makers. If the importance of surveillance and its programmatic implications were better understood, it could potentially lead to allocation of additional resources to strengthen the system.

4. Discussion

In this first evaluation of the South African AEFI surveillance system in its current form, established in 2018, we observed a functional, useful, flexible system with high reported stakeholder and public acceptability levels. Despite these key strengths, we observed low reporting rates from some provinces, weak co-ordination between manual and application-based electronic reporting systems and resource limitations. In comparison with the Zimbabwean AEFI surveillance system, it revealed similar challenges in terms of under-resourcing [29–31]. Authorities could strengthen the South African AEFI surveillance system by increasing resource allocation at a provincial level and introducing active cohort event monitoring surveillance.

4.1. System strengths

During the COVID-19 vaccine roll-out, pharmacovigilance was supported by the presence of an already functional and simple AEFI surveillance system [13]. Overall, the system met the WHO minimal capacity for vaccine safety, described by collating and managing AEFI data, monitoring and investigating AEFIs and completing causality assessments [6]. The timely action by SAHPRA in response to reported Guillian-Barrè cases, provided the public with insight into the AEFI surveillance system, thus strengthening public confidence in vaccines and demonstrating the usefulness of AEFI data to health authorities. This demonstrated that South Africa has a strategy in place for risk communication, another WHO minimal capacity requirement [6].

Adaptation of the system through inclusion of digital applications (Med Safety App) facilitated reporting by members of the public. This additional mode of reporting was introduced as part of the African Union Smart Safety Surveillance (AU-3S) program initiative. The AU-3S program specifically aims to strengthen safety surveillance across Africa and was instrumental in the development of an AEFI reporting form in the Med Safety App [32]. Overall, the introduction of COVID-19 vaccines led to increased awareness among HCPs of AEFI reporting systems and general improvements in database quality.

Following interviews with members of the secretariat, NISEC and SAHPRA, it became apparent that there was a high level of acceptability of the surveillance system at national level. Committee members review serious/severe AEFI cases and conduct causality assessment voluntarily with no form of compensation. All participants appeared to be significantly invested in their role in the surveillance system and openly discussed areas they felt needed improvement.

4.2. Areas in need of strengthening

The AEFI surveillance system evaluation and review of high-income country systems underscored the presence of areas in need of strengthening and areas necessitating innovation.

The South African AEFI surveillance system, similar to many other LMICs, proved to be significantly affected by under-resourcing [32,33]. Funding, human resources and training are areas where deficiencies have resulted in reduced quality of reporting and data management. The varied and uneven distribution of cases reported across provinces revealed a lack of representativeness in the data. The Western Cape province had a reporting rate of 59.5 per 100,000 doses despite having the second lowest vaccine administration rate (10,831/100,000) whereas the North West province had a reporting rate of 1.6 per 100,000 doses and had the third highest vaccine administration rate (19,529/100,000) among Ad26.COV2·S recipients; a similar pattern was observed for the BNT162b2 vaccine. Differences in provincial reporting were attributed to issues with funding, personnel and general infrastructure, especially in the more rural provinces. Delays of up to a year were mentioned, before cases are assessed for causality. This was again attributed to insufficient personnel to conduct investigations and large numbers of cases in need of expert review. Inadequate resourcing emerged as a primary underlying factor affecting the timeliness, stability, representativeness and data quality of the AEFI surveillance system.

The addition of the Med Safety App digital reporting system resulted in a new database that was not integrated into the existing manual AEFI database, making database management more complex. Issues have also arisen from anonymised forms from the pharmaceutical industry submitted to SAHPRA, possibly resulting in duplicate entries.

At the start of the COVID-19 vaccine roll-out, South Africa had a phase 3B open-label trial, referred to as the 'Sisonke Study', aimed at assessing the safety and effectiveness of the Ad26.COV2·S vaccine. To facilitate reporting of AEFI, each study participant received a SMS with a link to an electronic CRF. This active surveillance component was dependent upon having adequate resources available to facilitate the SMS service. The study demonstrated that in the South African setting, given adequate resources, an active surveillance component would provide timely and accurate AEFI information [32]. The use of participant-centred digital solutions to complement passive surveillance has been demonstrated to address some of the limitations of passive surveillance such as a underreporting, reporting bias and timeliness [34].

4.3. Strengths and limitations of the evaluation framework

The CDC guidelines allow for a structured evaluation and functional assessment of a wide range of surveillance systems [35]. However, these guidelines do not specifically consider the contextual legislative environment, cost-effectiveness or stakeholder expectations of the system. An in-depth review of our regulatory framework would support evaluations of the surveillance system [15]. The CDC guidelines consider the acceptability of the system in relation to the willingness of stakeholders/operating personnel to use the system, however stakeholder perceptions and expectations of the system are not explicitly considered by the guidelines while these also influence acceptability [25,36]. Funding sources are considered by the CDC guidelines, but no comprehensive methodology is provided for evaluating the cost-effectiveness/cost-benefit of a surveillance system. Inclusion of assessment of economic attributes would allow for stakeholders to make informed decisions regarding resource allocation [36]. Groseclose *et al.* adapted the CDC guidelines to include additional attributes; these included cost-effectiveness, security and standard use [37]. Security was defined as methods for keeping available data confidential and accurate, while standards use was defined as the use of data exchange by a surveillance system that enhances communication and information exchange. Several data exchange issues were identified in our study and an attribute focusing on the assessment thereof would have been of value [37].

5. Recommendations

Evaluation of components of the national AEFI surveillance system revealed issues around data linkage and integration between the national AEFI database maintained by the NISEC secretariat and VigiBase maintained by SAHPRA. Integration of these two passive surveillance reporting systems and development of a single database would ensure adequate signal detection, streamlined processes and no duplication of data entries. Pharmacovigilance systems are rooted in signal detection and a single integrated database would allow for adequate detection of

signals. The addition of a digital surveillance component has highlighted the importance of transitioning to a form of surveillance that allows for real-time safety surveillance of vaccines. The Australian and Canadian surveillance systems [33] demonstrated that active, digital, participant-centred surveillance allows for streamlined and expanded collection, automated filtering and triage of reports for priority investigation and causality assessment. The system could be further strengthened by including indicators of performance at various points within the system to ensure that it is operating to a good standard. Provincial capacity for quality investigation needs to be expanded for the purposes of data validation and improvement of turnaround times for causality assessment. Data validation metrics should exist at both a provincial and national level for closed-response and fixed-format fields to improve data accuracy.

It is important that provincial, district and facility level components of the surveillance system are evaluated to ensure that all system developments and modifications address issues at all levels of the surveillance system. Significant differences were noted among AEFI reporting across the provinces and it is therefore essential that provincial level evaluation is conducted in order to identify specific issues, pertaining to individual provinces. Resources, system stability and acceptability are all critical attributes to assess at a provincial level in order to ensure that the AEFI surveillance system operates efficiently and effectively.

Changing the way pharmacovigilance is perceived and underscoring its importance is critical to ensuring that decision-makers understand its vital role in vaccine safety. Recognition of its significance could result in the allocation of sufficient resources to strengthen the system.

CRediT authorship contribution statement

Chenoa Sankar: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Johanna C. Meyer:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Marione Schönfeldt:** Investigation, Data curation. **Hannah Gunter:** Writing – review & editing, Investigation. **Halima Dawood:** Writing – review & editing, Investigation. **Victoria Sekiti:** Data curation. **Naseera Pickard:** Investigation, Data curation. **Lawrence Mubaiwa:** Investigation. **Dini Mawela:** Investigation. **Sipho Dlamini:** Investigation. **Jonny Peter:** Investigation. **David Spencer:** Investigation. **Clive Gray:** Investigation. **Vinod Patel:** Investigation. **Lesley Bamford:** Investigation. **Tohlang Sehloho:** Data curation. **Kerrigan McCarthy:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126535.

Data availability

The authors do not have permission to share data.

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