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# Descriptive Research Study of the Adverse Events Following Immunization (AEFIs) Surveillance System in Zimbabwe

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## Abstract

**Aim:** Functional national systems that monitor Adverse Events Following Immunization (AEFIs) are vital for implementing evidence-based vaccination policy while ensuring the safe access to these life-saving technologies. These systems can counteract vaccine hesitancy by increasing public trust and uptake in vaccination minimizing the burden of vaccine-preventable diseases (VPDs). Ensuring that these systems function optimally is a critical public health imperative. This is a novel study evaluating AEFI surveillance system including causality assessment, in Zimbabwe. This study provides a review of Zimbabwe's national AEFI surveillance system since its launch in 1998, highlighting strengths, weaknesses, and opportunities for improvement.

**Materials and Methods:** We conducted an in-depth analysis of all AEFI reports received until 2021, assessing reporting trends and overall performance of the AEFI system in terms of investigation, causality assessment. The WHO Global Benchmarking Tool (GBT) was used to assess regulatory performance in terms of AEFI surveillance. Duplications were excluded and reports with evidence of AEFI(s) after vaccination were included by examining the WHO 25 AEFI form core variables.

**Results:** There was a steady increase of AEFI reports per annum particularly from 2006 to 2021 with a more dramatic increase during the COVID-19 epidemic with an AEFI reporting ratio of 43.46/million adults for COVID-19 vaccinations in 2021. The reporting ratio exceeded the WHO recommended minimum AEFI reporting ratio of 10 per 100000 surviving infants during eleven years (47.84%) out of the twenty-three years since inception of the surveillance. The GBT assessment demonstrated that the AEFI surveillance system evolved for all manufacturers or license holders.

**Conclusion:** Close partnership between the immunization program and regulatory authority has enhanced AEFI surveillance in Zimbabwe. Incomplete AEFI case investigations for and timely AEFI detection are challenges that need to be addressed. System strengthening should include consideration of digital innovations to improve detection, optimizing case investigation of serious AEFI including post-mortems and utilizing VigiPoint disproportionate analysis for signal detection.

## Article History

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## Keywords

AEFI surveillance system; AEFI causality assessment; mHealth active participant centered (MAPC) AEFI surveillance; VigiGrade completeness score and WHO global bench marking tool Version VI(GBT)

## Introduction

Globally, immunization is one of the most cost-effective ways of preventing or reducing the severity of infectious diseases including, most recently severe acute respiratory syndrome coronavirus (SARS-CoV-2). Ensuring that vaccines are safe, effective, and of good quality is a responsibility shared by manufacturers, members of the distribution chain, national immunization programs (NIPs) and the national medicines regulatory agencies such as the MCAZ [1]. Timely detection and investigation of adverse events following immunization (AEFIs), causality assessment, identification of signals, response and appropriate communication are essential for promoting the safety of public health vaccines (2, 3). In rare instances, however, AEFIs might result in diminished public trust in vaccination and hence the immunization program's ability to achieve high coverage (4-6). The World Health Organization and Council for International Organizations of Medical Science (CIOMS) define AEFI as "any untoward medical occurrence which follows immunization and does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease" [4, 7].

In Zimbabwe, AEFI surveillance is an activity that is overseen as a partnership between the national medicines regulatory agency (NMRA), which is the Medicines Control Authority of Zimbabwe and the national immunization programme (NIP), the Zimbabwe Expanded Program on Immunization (ZEPI), the latter being housed within the Ministry of Health and Child Care (MoHCC) [8-11].

The MCAZ National Pharmacovigilance Center (NPC) has been delegated the responsibility of overseeing AEFI surveillance since 1998 and is a full member of the WHO International Drug Monitoring Program (12-14). As a contributing member, Zimbabwe transmits all AEFI reports into the VigiBase® Database, aggregated AEFI data for the AEFI Joint Reporting Form (JRF) and electronic AEFI (eJRF) for COVID-19 vaccines that are global indicators for vaccine safety surveillance and trends in AEFI reporting [11, 13-15]. The WHO Global Benchmarking Tool (GBT) is an objective tool used for evaluating national regulatory systems, identifying strengths and opportunities building regulatory capacity for medicines and vaccines, including AEFI surveillance, harmonization, and reliance [16].

Serious AEFIs should be reported within 24 hours to ZEPI to ensure immediate AEFI case investigation and non-serious AEFI reported within 24 hours to 28 days. MCAZ processed all AEFIs received from ZEPI for causality assessment done monthly or may be expedited by the national AEFI committee if deemed necessary for fatal cases or cases causing community concern or reflected in the media. The AEFI signal detection may use VigiBase database disproportionate analysis, including reporting to the WHO AEFI Joint Reporting Form (JRF) for vaccines and eJRF for COVID-19 vaccines [11]. Figure 1 below illustrates Zimbabwe's AEFI process flow, steps for AEFI reporting.

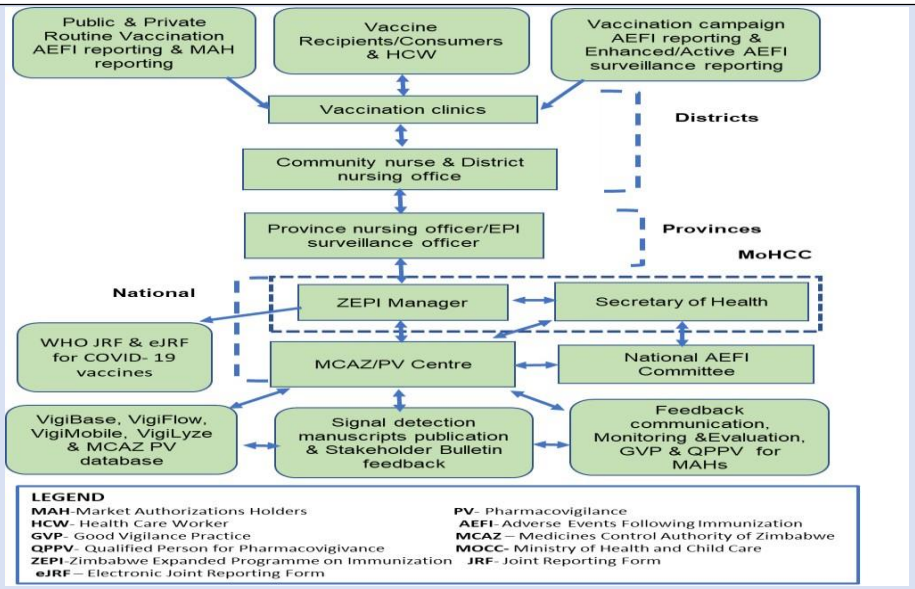



**Figure 1:** Zimbabwe AEFI surveillance process flow.

Several joint ZEPI-MoHCC and MCAZ NPC enhanced AEFI surveillance initiatives were implemented over the years to strengthen passive AEFI surveillance, especially during immunization campaigns and during the introduction of new vaccines, through quarterly EPI review and monitoring and evaluation sessions(12, 15, 17-21). The training of trainers' approach increased the quarterly and annual trainings of healthcare workers (HCWs) based at vaccination clinics in all 11 provinces and 63 districts from 2010 to 2022. This resulted in an increased AEFI reporting ratio of childhood (22, 23). ZEPI-MoHCC and MCAZ NPC successfully participated from 2018 to 2020 in the background study of estimating baseline rates of adverse perinatal and neonatal outcomes using a facility-based surveillance approach of the WHO Global Vaccine Safety Initiative Multi-Country Collaboration on safety in pregnancy [24-27].

ZEPI launched several novel COVID-19 vaccines for SARS-CoV-2 since February 2021. ZEPI and MCAZ conducted enhanced and active AEFI surveillance for COVID-19 vaccinations through a variety of initiatives aimed at preventing, rapidly detecting, and responding to all AEFIs associated with COVID-19 vaccines. This included surveillance of adverse events of special interest, and feasibility of an mHealth participant centered active AEFI surveillance study.

In this report we aim to provide a descriptive review of the AEFI surveillance system and AEFI reporting trends in Zimbabwe since 1998, highlighting strengths, weakness, and opportunities for improvement.

## Study Goals and Objectives

The objectives of this review of the AEFI surveillance system in Zimbabwe are:

1) To describe the AEFI reports received according to the vaccinees' demographic characteristics, suspected vaccine(s), and AEFIs characteristics.
2) To reflect on the trends in the national AEFI reporting rate per 100 000 surviving infants between 1998 and August 2022 for childhood vaccines and adult COVID-19 vaccines.
3) To describe the case investigation and causality assessment system of serious AEFI reports and its performance in terms of completeness.
4) To describe the AEFI immunization programmatic, errors/clusters identified through the spontaneous AEFIs causality assessment.
5) To assess the trend in the quality of the Zimbabwean AEFI reports VigiGrade® completeness score.
6) To report the geographical distribution of AEFI reporting sites.
7) To assess the performance of the AEFI system according to the independent WHO GBT assessment AEFI surveillance indicators.
8) To identify opportunities to strengthen Zimbabwe AEFI surveillance system.

## Materials and Methods

**Inclusion criteria:** The study included all deduplicated AEFI reports received by the MCAZ NPC and ZEPI, verifiable by original AEFI hard copies or AEFI electronic copies reports processed and uploaded onto the inhouse ePV system database, VigiFlow®, VigiBase® and VigiLyze® databases.

For objective 1, the AEFI reports were summarized based on the seriousness, type of antigen, and type of AEFI reported, and demographic data of the vaccinees. MedDRA system organ class (SOC) and preferred terms (PTs) were used to summarize the types of AEFIs reported. MedDRA is a globally harmonized medicines and vaccines safety terminology and classification dictionary utilized within the VigiBase database [28, 29].

The annual AEFI reporting rates for objective 2 were calculated separately for childhood vaccines and COVID-19 vaccines. The AEFI reporting rate for childhood vaccines was calculated by dividing the total number of pediatric AEFI (serious and non-serious) reports received in a year over the total number of surviving infants per year and reported as per 100 000 surviving infants per year (annual UNDP statistics for surviving infants per year for Zimbabwe 1998 to 2021). The denominator for the COVID-19 vaccine reporting rate was the total number of adults vaccinated with either 1 or 2 doses from February 2021 to August 2022 based on ZEPI data since each vaccination was seen as a separate opportunity for AEFI(s).

For objective 3, causality assessment was done by the national AEFI committee for non-serious AEFIs and serious AEFIs. The initial report and supporting case investigation forms, and postmortem results were

reviewed in accordance with the WHO AEFI causality assessment algorithm and Aide-memoire 2019 [30-32]. The National AEFI Committee were trained and experienced in using the old Bradford Hill criteria and current WHO AEFI causality assessment Aide-memoire/ Algorithm 2019 illustrated in **Figure 2** below.

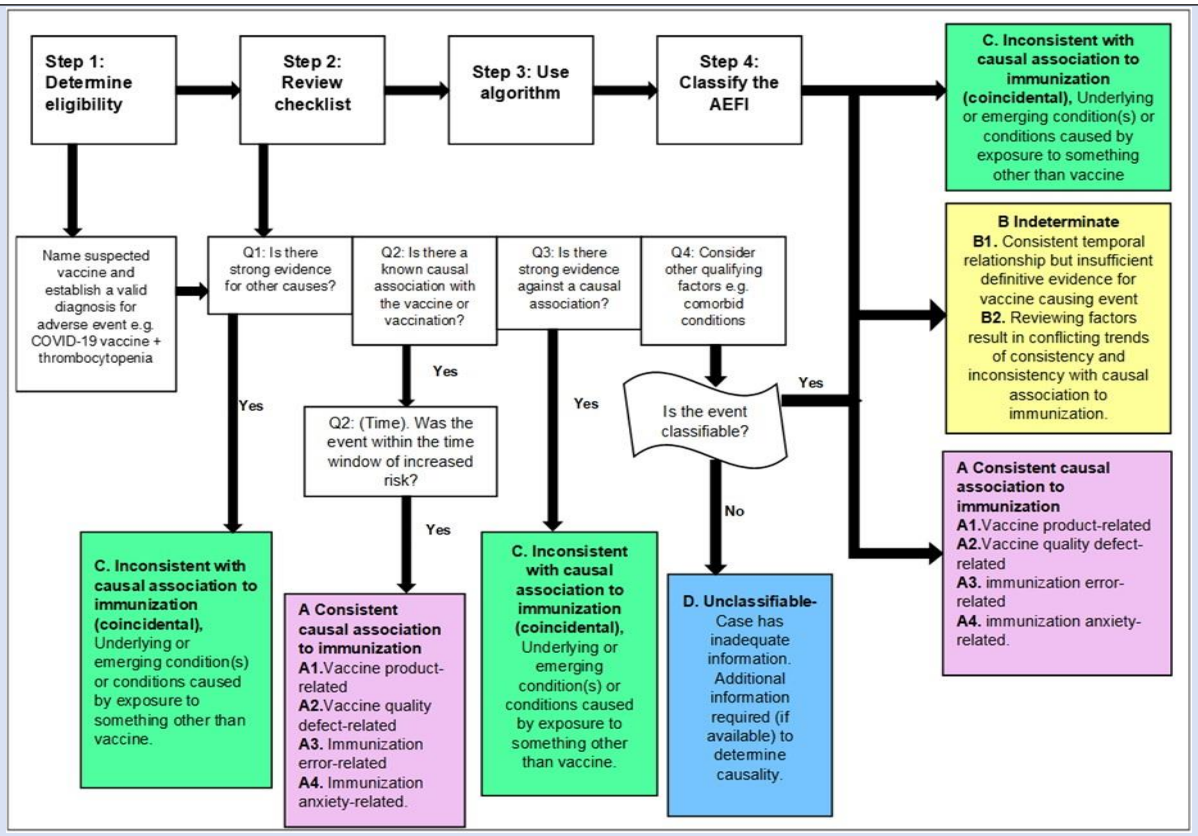



**Figure 2:** Adapted from WHO AEFI causality assessment valid diagnosis eligibility criteria 2019 [30, 31, 33].

The AEFI causality assessment algorithm illustrated in **Figure 2** is used by the Zimbabwe National AEFI Committee to determine all AEFI reports causality assessment from step 1 to step 4. Objective 4 aimed to assess the system's ability to detect programmatic errors and clusters. The WHO definition of AEFI immunization programmatic errors includes AEFIs caused by errors in the preparation, administration, storage, and /or handling of vaccines that tend to occur as clusters. A cluster occurs in more than one vaccinee at a vaccination site or region and is completeness criteria that includes patient information (sex, age, medical history, concurrent conditions); adverse event information (event description, outcome of reaction); medicine/ vaccine information (vaccine generic/trade name, time to onset, indication for use ); and availability of additional information (challenge, rechallenge, case narrative, AEFI case investigation, laboratory results, including postmortem reports) [34]. The quality of the AEFI report determines the extent usually batch related. Programmatic errors were identified by the AEFI national committee through causality analysis of the AEFI reports. Feedback of the causality assessment outcomes was provided to the reporters through letters, medicines information bulletins and ZEPI quarterly review trainings. The assessment of completeness and quality of the Zimbabwe AEFIs reports for objective 5 was determined by the VigiBase VigiGrade® completeness score (34). The maximum VigiGrade completeness score is 1 and the minimum is zero based on four AEFI to which the report can be reliably assessed for causality, and can be incorporated into risk-benefit decision-making [34]. The annual median score of the VigiGrade completeness was measured for three types of ICSRs, that is, VigiGrade vaccines AEFIs, combined vaccines and non-vaccine reports, and non-vaccine reports received by MCAZ mostly via hard copy reporting by HCWs. For objective 6, the geographical distribution of AEFI reports was based on the reporting site names

that determined the province (s) from which these reports arose. The heat map reflected the relative frequency of AEFI reports by each province.

Objective 7 was achieved by reviewing the results of the independent WHO GBT assessment of MCAZ's National Pharmacovigilance Centre (NPC) in August 2021. This study highlighted GBT vigilance assessment results and corrective actions in the context of the AEFI surveillance system such as legal requirements for vaccine manufacturers good vigilance practice (GVP), qualified person for pharmacovigilance (QPPV), and system for AEFI reporting.

For objective 8, the identification of opportunities to strengthen the national AEFI system of Zimbabwe was achieved by examining gaps and weakness identified in objectives 1 to 7 results stated above including the WHO GBT vigilance indicators.

## Results

From 1998 to August 2022, a total of 6001 ICSRs were received by the MCAZ NPC of which 1442 (24.0%) were AEFIs, 3551 (59.2%) were ADRs, 546 (9.1%) SAEs from clinical trials and 462 (7.7%) ADRs/SAEs from pharmaceutical industry. No AEFI report associated with pregnancy and no AEFI report(s) were received from pharmaceutical industry.

Tables 1 and 2 and Figures 3 to 6 shows the reports received according to the type of suspected and co-reported vaccines (Table 1), the types of AEFIs reported (Table 2, figures 3 and 4) and age distribution of vaccinees (Figure 5) and year of report (Figure 6).

| Co-reported active ingredients (WHODrug) | Suspected or Interacting vaccine | Co-reported active vaccines | Total | %Suspected/ Interacting vaccine | % Co-reported medicines or vaccines Percentage |
|---|---|---|---|---|---|
| Polio vaccine | 299 | 20 | 319 | 16.6% | 1.0% |
| Measles vaccine | 218 | 1 | 219 | 11.4% | 0.1% |
| Covid-19 vaccine | 338 | 0 | 338 | 17.6% | 0.0% |
| Measles: Rubella vaccine | 172 | 1 | 173 | 9.0% | 0.1% |
| Pentavalent vaccine | 170 | 1 | 171 | 8.9% | 0.1% |
| Pneumococcal vaccine | 106 | 1 | 107 | 5.6% | 0.1% |
| Typhoid vaccine | 102 | 0 | 102 | 5.3% | 0.0% |
| DTP vaccine | 82 | 0 | 82 | 4.3% | 0.0% |
| Rotavirus vaccine | 61 | 1 | 62 | 3.2% | 0.1% |
| HPV vaccine | 39 | 0 | 39 | 2.0% | 0.0% |
| BCG vaccine | 32 | 1 | 33 | 1.7% | 0.1% |
| Bacterial and viral vaccines, combined | 21 | 1 | 22 | 1.1% | 0.1% |
| Hepatitis B vaccine | 18 | 0 | 18 | 0.9% | 0.0% |
| Vaccines | 17 | 1 | 18 | 0.9% | 0.1% |
| Tetanus vaccine | 16 | 0 | 16 | 0.8% | 0.0% |
| Diphtheria vaccine | 11 | 0 | 11 | 0.6% | 0.0% |
| Cholera vaccine | 10 | 0 | 10 | 0.5% | 0.0% |
| OTP vaccine; HIB vaccine | 5 | 0 | 5 | 0.3% | 0.0% |
| Rabies vaccine | 3 | 0 | 3 | 0.2% | 0.0% |
| DTP vaccine, Hepatitis vaccine | 2 | 0 | 2 | 0.1% | 0.0% |
| Rubella vaccine | 1 | 0 | 1 | 0.1% | 0.0% |

**Table 1:** AEFI reports by suspected vaccines and Co-reported vaccines.

As reflected in Table 1, COVID-19 vaccines were the most frequently implicated vaccines (n=338; 17.6% of all AEFI reports) with no concomitant or co-reported vaccines. Oral polio vaccine was the second most frequently suspected or co-reported vaccine vaccine (1.7%).

**Figure 3** below shows that the majority of AEFIs were known non-serious events in infants in line with what is reflected in the Summary of Product Characteristics (SPC) of those products. The most reported general disorders and site administration. (n=319; 16.6% of all AEFI reports) followed by measles vaccine (11.4%), Measles, Rubella vaccine (9.0%), Pentavalent vaccine (8.9%), pneumococcal vaccine (5.6%), Typhoid vaccine (5.3%), Rotavirus vaccine (3.2%), HPV vaccine (2.0%), and BCG conditions (26.0%) included events such as local injection site reactions, pain, swelling and reduced mobility as well as persistent crying. Skin and subcutaneous tissue disorders (21.3%), gastrointestinal disorders (15.5%), and infections /infestations (13.3%).

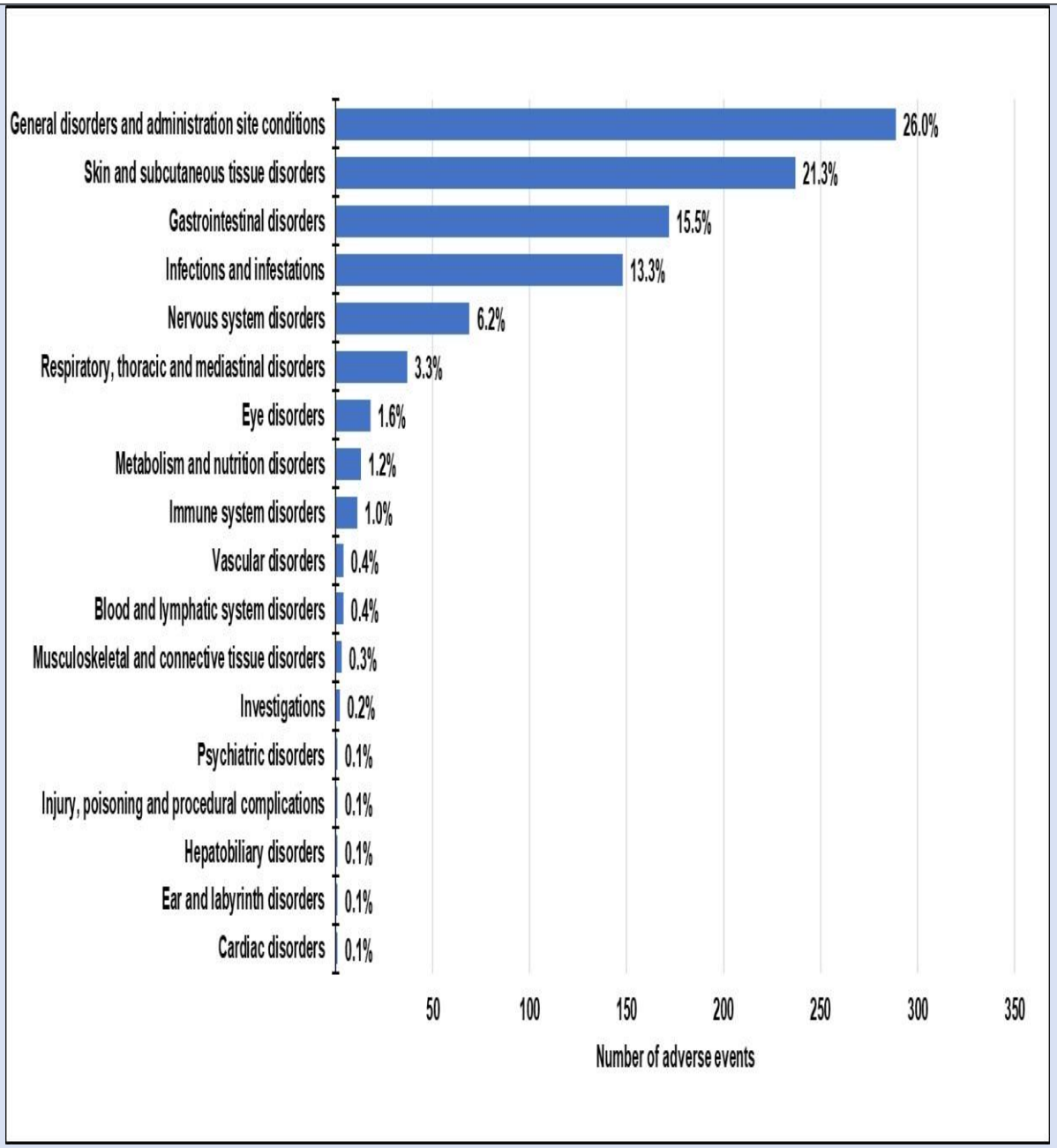



**Figure 3:** Suspected AEFIs and MedDRA system organ classification (SOC).

| AEFI Reaction (MedDRA) System | Count | Percentage | AEFI reaction MEDRA Preferred Terms (PT) |
|---|---|---|---|
| SOC: General disorders and administration site conditions | 289 | 26.0% | Injection site reactions 227(20.6%), crying 29(2.6%), Swelling 8(0.7%), Paralysis 6(0.5%), Hyperthermia 3(0.3%), Pain in extremity 2(0.2%), Mobility decreased 1(0.1%), Peripheral swelling 1(0.1%), Extensive swelling of vaccinated limb 1(0.1%) |
| SOC: Skin and subcutaneous tissue disorders | 237 | 21.3% | Rash 204(18.4 %), Pruritus 35(3.2%), Skin reaction 4(0.4%), Dermatitis bullous 3(0.3%), Skin discolouration 2(0.2%), Skin exfoliation 2(0.2%), Skin swelling 2(0.2%), Stevens-Johnson syndrome 1(0.1%) |
| SOC: Gastrointestinal disorders | 132 | 15.5% | Vomiting 135(12.2%), Diarrhoea 110(9.9%), Abdominal pain 19(1.7%), Decreased appetite 9(0.8%), Poor feeding infant 4(0.4%), Nausea 3(0 3%), Abdominal discomfort 1(0.1%), Abdominal distension 1(0.1%), Diarrhoea haemorrhagic 1(0.1%), Gastroenteritis 1(0.1%), intussusception 1(0.1%) |
| SOC: Infections and infestations | 148 | 13.3% | Pyrexia 133(12.0%), Chills 3(0.3%), Pneumonia 2(0.2%), Measles 1(0.1%), Tonsilitis 1(0.1%), Sepsis 1(0.1%), Upper respiratory tract infection 1(0.1%), cellulitis 1(0.1%), Toxic Shock Syndrome (TSS) 1(0.1%) |
| SOC: Nervous system disorders | 69 | 6. 2% | Seizure 28 (2.5%), Headache 22 (2.0%), Asthenia 14 (1.3%), Dizziness 11 (1.0%), Malaise 5 (0.5%), Fatigue 2 (0.2%), Febrile convulsion 2 (0.2%), Lethargy 2 (0.2%), Loss of consciousness 2 (0.2%), Syncope 1(0.1%) |
| SOC: Respiratory, thoracic and mediastinal disorders | 37 | 3. 3% | Cough 14(1.3%), Dyspnoea 10(0.9%), Respiratory distress 2(0.2%), Pulmonary embolism 1(0.1), Pulmonary oedema 1(0.1%), Breath sounds abnormal 1(0.1%), Chest discomfort 1(0.1%), Chest pain 1(0.1%), Hypoxia 1(0.1%), Aspiration 2(0.2%), Tachypnoea 1(0.1) |
| SOC: Eye disorders | 18 | 1.6% | Ocular hyperaemia 5 (0.5%), Eye inflammation 4(0.4%), Conjunctivitis 3(0.3%), Eye irritation 3(0.3%), Eyelid oedema 3(0.3%), Eye discharge 1 (0.1%), Eye pain 1(0.1%), Eye swelling 1(0.1%), Vision blurred 1 (0.1%), Eyelids pruritus 1 (0 1%) |
| SOC: Metabolism and nutrition disorders | 13 | 1.2% | Hyperhidrosis 1(01%) |
| SOC: Immune system disorders | 11 | 1.0% | Anaphylactic reaction 6(0.5%), Hypersensitivity 5(0.5%), Lymphadenitis4(0.4%), Face oedema 3(0.3%), Lymphoedema 1(0.1%), Auricular swelling 1(0.1%), Oedema 1(1.0%), Periortital oedema 1(0.1%), Swelling face 1(0.1%), Lip swelling 1(0.1%), Angioedema 1(0.1) % |
| SOC: Vascular disorders | 4 | 0.4% | Oedema peripheral 4(0.4%), Gangrene 1(0.1%), Shock 1(0.1%), Shock symptom 1(0.1%) |
| SOC: Blood and lymphatic system disorders | 4 | 0.4% | Epistaxis 5(0 5%), Haemorrhage 1(0.1%) |
| SOC: Musculoskeletal and connective tissue disorders | 3 | 0.3% | Dystonia 1(0.1%), Diplegia1(0.1%) |
| SOC Investigations | 2 | 0. 2% | Medication error 1(0.1%) |
| SOC: Psychiatric disorders | 1 | 0. 1% | Sleep disorder 1(0.1%) |
| SOC: Injury, poisoning and procedural complications | 1 | 0. 1% | Tenderness 1(0.1%) |
| SOC: Hepatobiliary disorders | 1 | 0. 1% | Jaundice 1(0.1%) |
| SOC: Ear and labyrinth disorders | 1 | 0. 1% | Rhinitis 1(0.1%) |
| SOC: Cardiac disorders | 1 | 0. 1% | Cardio-respiratory arrest 1(0.1%) |

**Table 2:** AEFI Reactions MedDRA, SOC and PTs.

**Table 2 Foot note:**

**'Injection site reactions'** includes the following MedDRA PTs: injection site abscess, injection site abscess sterile, abscess, injection site reaction, injection site swelling, injection site inflammation, injection site pain, vaccination site swelling, injection site haemorrhage, injection site erythema, injection site necrosis, injection site urticaria, injection site cellulitis and application site cellulitis. **'Rash'** includes the following MedDRA PTs: urticaria, rash pruritic, rash macular, rash erythematous and septic rash. **'Seizures'** includes the following MedDRA PTs: febrile convulsion and seizures. **'Death'** includes the following MedDRA PTs: sudden death, death neonatal, and sudden infant death syndrome.

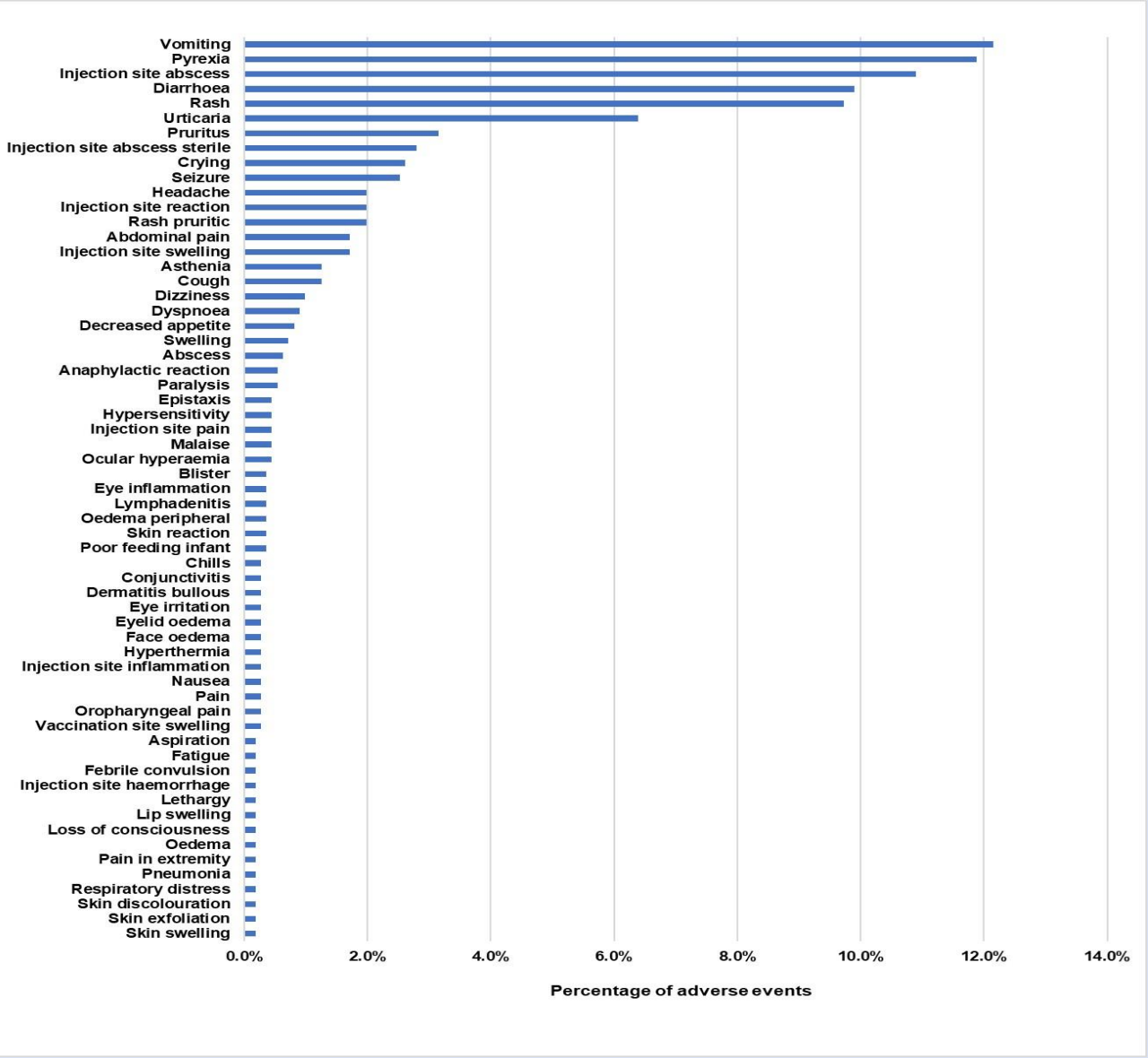
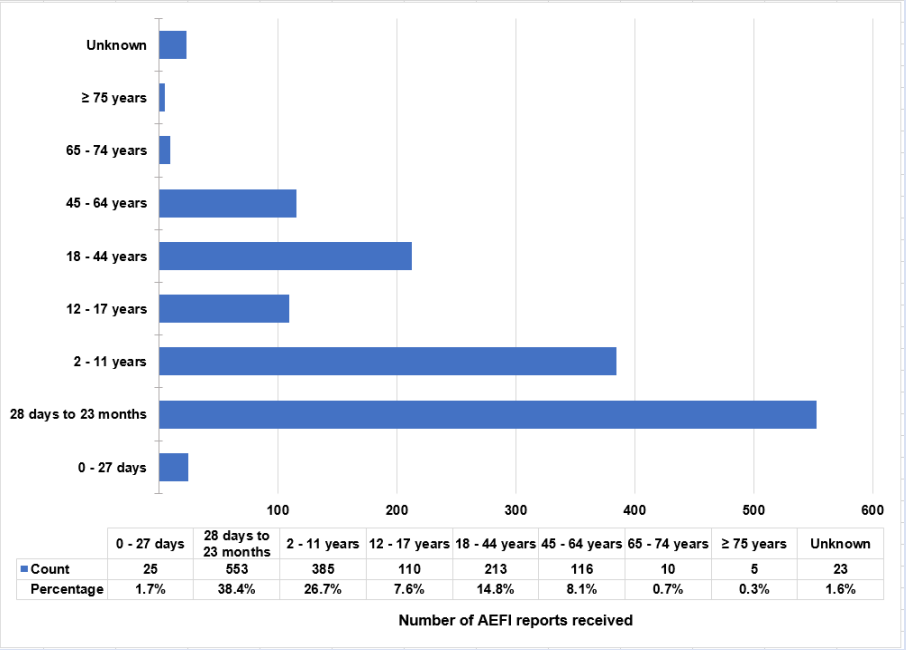



**Figure 4:** Suspected AEFIs classified as MedDRA Preferred Terms (PTs).

Figure 4 shows that the majority AEFIs were vomiting (12.2%), pyrexia (12%), injection site abscess (11%), diarrhoea (9.9%), rash (9.8%) and urticaria (6.3%). Figure 5 below shows vaccinees reported in infants between 28 days and 23 months (38.4%), 2 to 11 years (26.7%) and adults 18 to 44 years (14.8%). Most adult AEFI reports were related to COVID-19 vaccines.

demographic characteristics that 653 (45.4%) were males, 755 (52.4%) were females and 32 (2.2%) were of unknown sex. Majority of AEFI reports were related to routine childhood vaccines




| | 0 - 27 days | 28 days to 23 months | 2 - 11 years | 12 - 17 years | 18 - 44 years | 45 - 64 years | 65 - 74 years | ≥ 75 years | Unknown |
|---|---|---|---|---|---|---|---|---|---|
| Count | 25 | 553 | 385 | 110 | 213 | 116 | 10 | 5 | 23 |
| Percentage | 1.7% | 38.4% | 26.7% | 7.6% | 14.8% | 8.1% | 0.7% | 0.3% | 1.6% |

**Figure 5:** Vaccines' demographic characteristics who experienced AEFIs.

Figure 6 shows the annual AEFI reporting ratios for surviving infants and COVID-19 vaccines adult vaccinees as well as percentage of AEFIs that were non-serious, non-fatal serious and fatal. AEFI reporting ratios ranged from 0 to 38 per year per 100000 surviving infants with peak reporting rates noted in 2009 (28), 2010 (24), 2016 (24), and the highest in 2021 [37]. The reporting ratio exceeded the WHO recommended minimum AEFI reporting ratio of 10 per 100000 surviving infants for 11 years (47.8%) out of the 23 years since inception of the surveillance system. The COVID-19 vaccination program in adults yielded a total of 338 reports (23% of all AEFI reports) over a 7-month period from February 2021 to August 2022 with an AEFI reporting ratio of 44.36 per 1 million COVID-19 vaccinees.

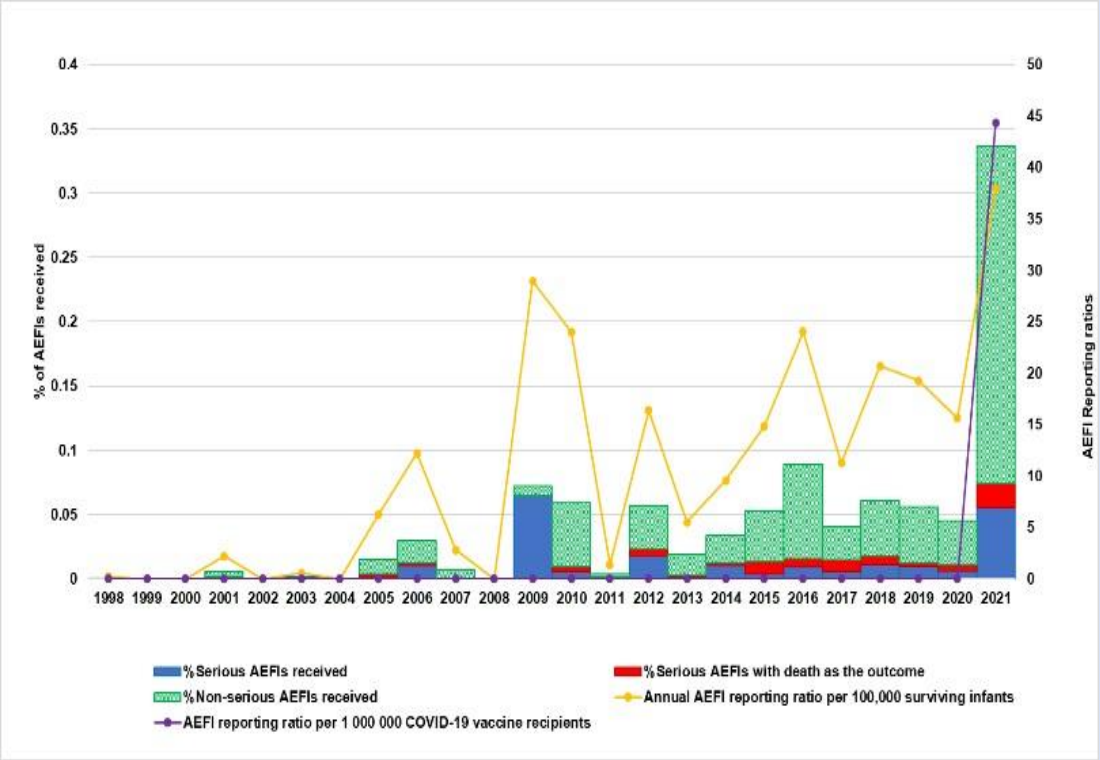



**Figure 6:** Annual AEFI reporting ratios, serious and non-serious AEFIs.

**Table 3** below indicates that 780 (54.2%) AEFI reports were non-serious, 427 (29.7%) were non-serious medically important conditions, 116 (8.1%) were fatal and 95 (6.6%) caused/prolonged hospitalization.

| Seriousness criteria | Number of AEFI reports | Percentage of total AEFI reports |
|---|---|---|
| Death | 116 | 8.1% |
| Life threatening | 19 | 1.3% |
| Caused/prolonged hospitalization | 95 | 6.6% |
| Disabling/incapacitating | 2 | 0.1% |
| Congenital anomaly/birth defect | 1 | 0.1% |
| Other med1caltyimportant condition | 427 | 29.7% |
| Unknown | 780 | 54 .2% |
| TOTAL | 1.440 | 100.00% |

**Table 3:** Categories of Zimbabwe seriousness of suspected AEFI reports received from 1998- 2023.

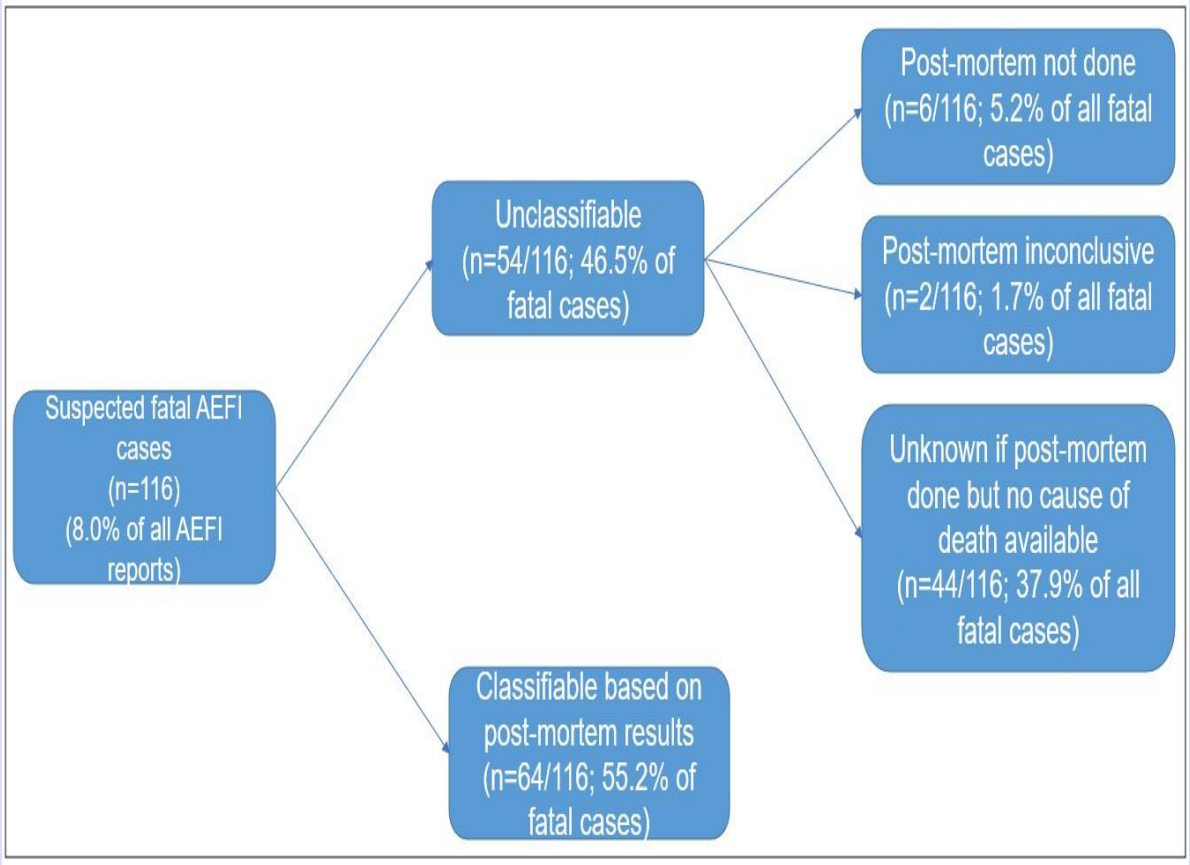



**Figure 7:** Zimbabwe suspected fatal AEFI reports received from 1998-2022 National AEFI

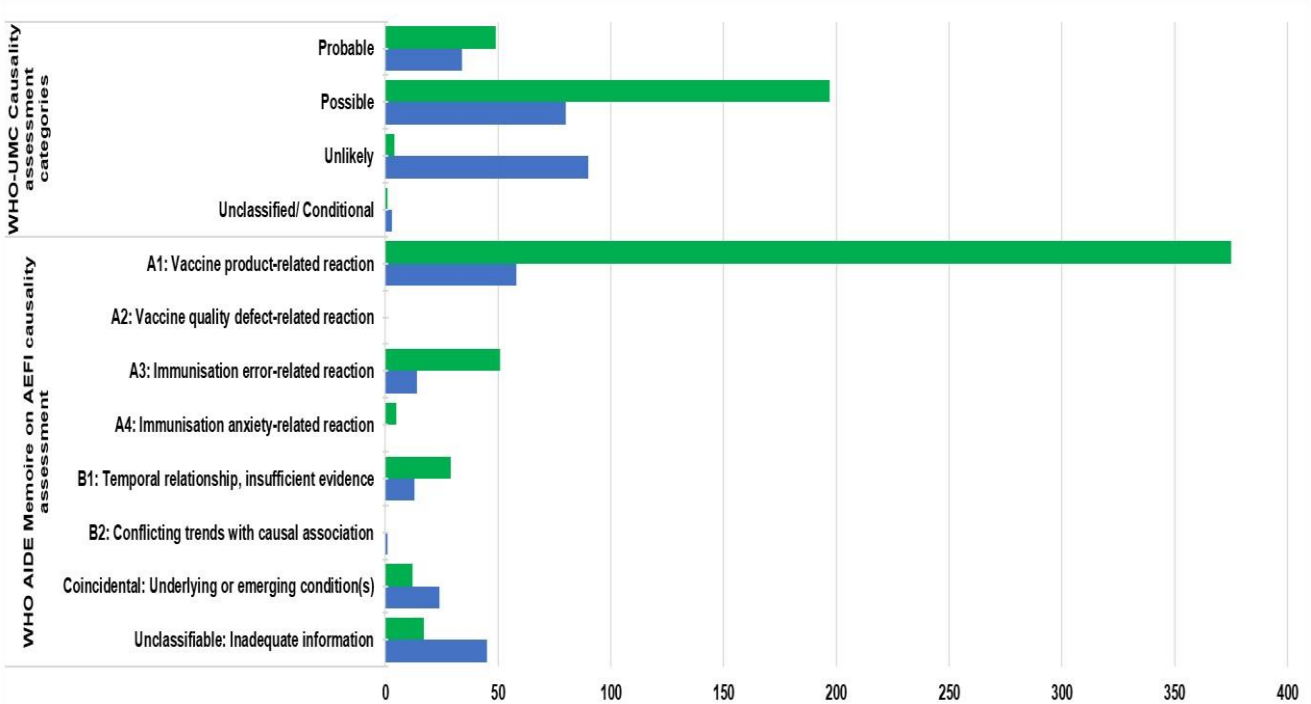
## Committee causality assessment outcomes

**Figure 7** above shows 116 (8.0%) of all suspected death AEFIs cases, of which 64/116 (55.2%) were classifiable in terms of causality assessment due to the availability of postmortem results. However, 54/116 (46.5%) were unclassifiable due to no postmortem in 6/116 (5.2%) cases so no cause of death was evident. There was inconclusive postmortem for 2/116

(1.7%) cases, and for 44/116 (37.9%) cases, it was not known if postmortem was done or not, but no cause of death was evident. The suspected AEFI death cases 101/116 (87.1%) were associated with children's antigens, and 15/116 (12.9 %) suspected AEFI death cases were associated with adult COVID-19 vaccines. All fatal AEFI cases were investigated however the limiting factor was the lack of postmortem results due to unavailability of postmortem facilities and in some cases next of kin refused to have postmortem done, hence no cause of death was evident.

**Figure 8** below shows the National AEFI Committee causality assessment of 1104 children's vaccinees suspected AEFIs' initially using Bradford Hill based criteria from 1998-2013, and then the WHO Aide-memoire from 2014-2019 including revisions. 375 (34%) AEFI reports were classified as vaccine product related reaction (A1), 51 (4.6%) as immunization error-related reaction (A3), 29 (2.6%) as demonstrating a temporal relationship but with insufficient evidence to prove causal association (B1), 17 (1.5%) were unclassifiable due to inadequate information (D), 12 (1.1%) as coincidental underlying or emerging conditions (C), and 5 (0.5%) as immunization anxiety-related reaction (A4). The serious AEFIs included 58 (5.3%) A1 vaccine product related reaction;14 (1.3%) A3 immunization error-related reaction; 13(1.2%) B1 temporal relationship insufficient evidence; 45(4.1%) unclassifiable due to inadequate information; and 24 (2.2%) coincidental underlying or emerging conditions.

A total of 338 COVID-19 AEFIs were reported to MCAZ NPC and ZEPI. Most adult COVID-19 vaccines AEFIs 260/338 (77%) were non-serious, and many adverse events (87%) were resolved. Causality assessment outcomes for non-serious.

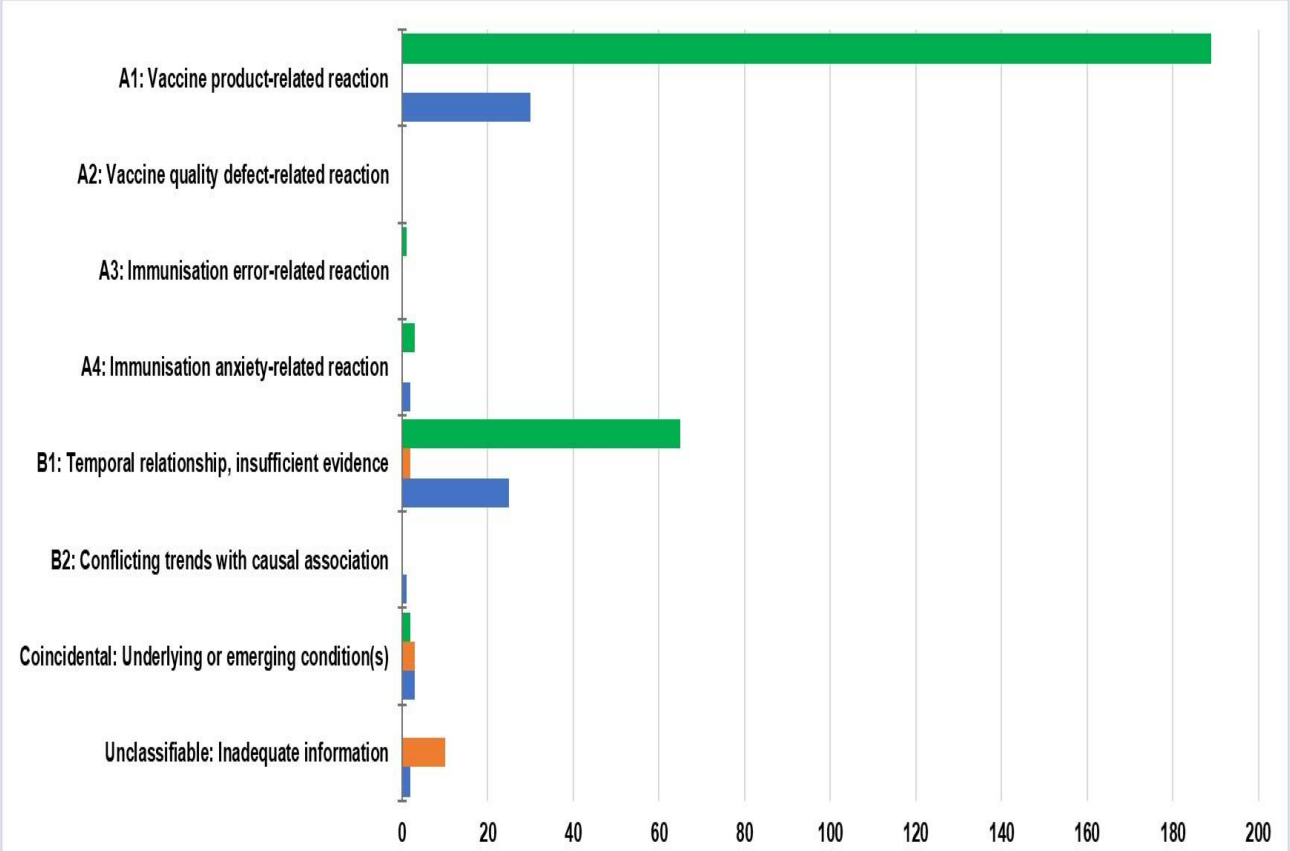



| | WHO AIDE Memoire on AEFI causality assessment | | | | | | | | WHO-UMC Causality assessment categories | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unclassifiable : Inadequate information | Coincidental: Underlying or emerging condition(s) | B2: Conflicting trends with causal association | B1: Temporal relationship, insufficient evidence | A4: Immunisation anxiety-related reaction | A3: Immunisation error-related reaction | A2: Vaccine quality defect-related reaction | A1: Vaccine product-related reaction | Unclassified/ Conditional | Unlikely | Possible | Probable |
| Number of non-serious AEFIs | 17 | 12 | 0 | 29 | 5 | 51 | 0 | 375 | 1 | 4 | 197 | 49 |
| Number of serious AEFIs | 45 | 24 | 1 | 13 | 0 | 14 | 0 | 58 | 3 | 90 | 80 | 34 |

**Figure 8:** Children vaccinees AEFIs causality assessment outcomes.

AEFIs were 189 (55.9%) A1 vaccine product related reaction, 65 (19.2%) B1 temporal relationship insufficient evidence, 3 (0.9%) A4 immunization anxiety related reactions, 2 (0.6%) coincidental

underlying or emerging conditions, 1 (0.3%) A3 immunization error related reaction. Serious AEFIs causality assessment outcomes were 30 (8.9%) A1 vaccine product related reaction, 25 (7.4%) B1 temporal relationship insufficient evidence, 3 (0.9%) coincidental underlying or emerging conditions, 2 (0.6%) A4 immunization anxiety related reaction, and 2 (0.6%) unclassifiable due to inadequate information. As shown in **Figure 9**, outcomes for COVID-19 serious AEFIs deaths were 10 (3.0%) unclassifiable due to inadequate information, 3 (0.9%) were coincidental underlying or emerging conditions, and 2 (0.6%) were B1 temporal relationship due to insufficient evidence. In **Figure 9**, most (189) of the non-serious COVID-19 vaccines suspected AEFIs were classified as A1, vaccine-product related reaction, and 65 classified as B1, temporal relationship insufficient evidence.




| | Unclassifiable: Inadequate information | Coincidental: Underlying or emerging condition(s) | B2: Conflicting trends with causal association | B1: Temporal relationship, insufficient evidence | A4: Immunisation anxiety-related reaction | A3: Immunisation error-related reaction | A2: Vaccine quality defect-related reaction | A1: Vaccine product-related reaction |
|---|---|---|---|---|---|---|---|---|
| Number of non-serious AEFI reports | 0 | 2 | 0 | 65 | 3 | 1 | 0 | 189 |
| Number of serious AEFI reports with death as the outcome | 10 | 3 | 0 | 2 | 0 | 0 | 0 | 0 |
| Number of serious AEFI reports | 2 | 3 | 1 | 25 | 2 | 0 | 0 | 30 |



**Figure 9:** Adult Covid-19 vaccinees AEFIs causality assessment outcomes.

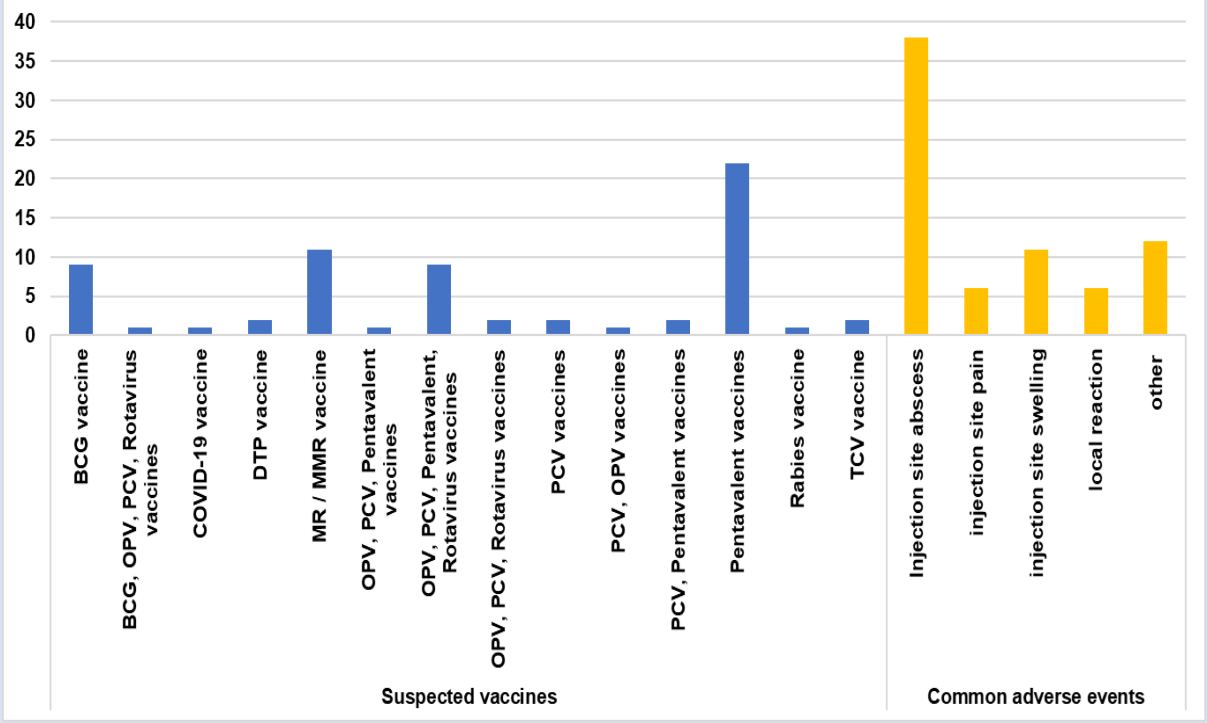



**Figure 10:** AEFIs programmatic immunization error-related reactions.

Figure 10 above shows that most injectable vaccines used were associated with injection site abscess as also noted in an Australian study [37] although some occurred when combination vaccines were administered. Pentavalent (DPT-HepB-Hib) was associated with the highest injection site abscesses in thirty cases, then MR/ MMR vaccine eleven cases and BCG vaccine nine cases. Figure 10 focused mostly on those AEFIs where the reporter stated the suspected antigen(s) to have caused the injection site reaction. In most cases those injectable antigens were usually administered in combination hence difficult to single out one antigen except of course for the pentavalent that is formulated and administered as a multi-antigen preparation.

In 2009, a cluster of one hundred serious AEFI of nausea, vomiting and diarrhea were reported during a measles vaccination campaign in Hurungwe district, Mashonaland West province. The affected batches were quarantined whilst AEFI case investigations were conducted by joint MCAZ NCP and ZEPI throughout the vaccine cold chain. The MCAZ laboratory analyzed the vitamin A, OPV, measles vaccine and diluent batch for sterility test in accordance with manufacturers' finished product specifications/certificate of analysis (COA). The measles vaccine diluent batch samples evaluated did not meet sterility specification hence the affected batch was quarantined and recalled. The OPV vaccine and vitamin A however met the finished product specification on analysis. The measles vaccine manufacturer had delivered acceptable quality of vaccines, but challenges arose in the cold chain. The cluster was considered a programmatic error due to local storage conditions in that district. MCAZ engaged the vaccine procurement agent to strengthen all vaccination clinics countrywide to prevent similar AEFI clusters.

Figure 11, Figure 12, and Figure 13 shows the Zimbabwe AEFIs reports VigiGrade completeness scores ranging from 0.53 to 0.90 for combined vaccines and 0.40 to 0.90 for non-vaccines (concomitant medicines). The non-vaccines medicines alone ADR/SAEs report VigiGrade completeness scores ranging from 0.61 to 0.97. The results demonstrated that Zimbabwe AEFIs are of high-quality including ADR and SAEs reports. The quality for the AEFI reports however slightly decreased from 2020 to 2022 due to the inherent COVID-19 pandemic disease during the same period including infected staff quarantines, lockdowns and extremely limited health services, and staff attrition. A MoHCC press reports stated that since 2021 more than, four thousand HCWs had left Zimbabwe for greener pastures. Reports for 2022 data was however limited in that it only showed reports for quarter 1 and 2, 2022, at the time of data analysis.

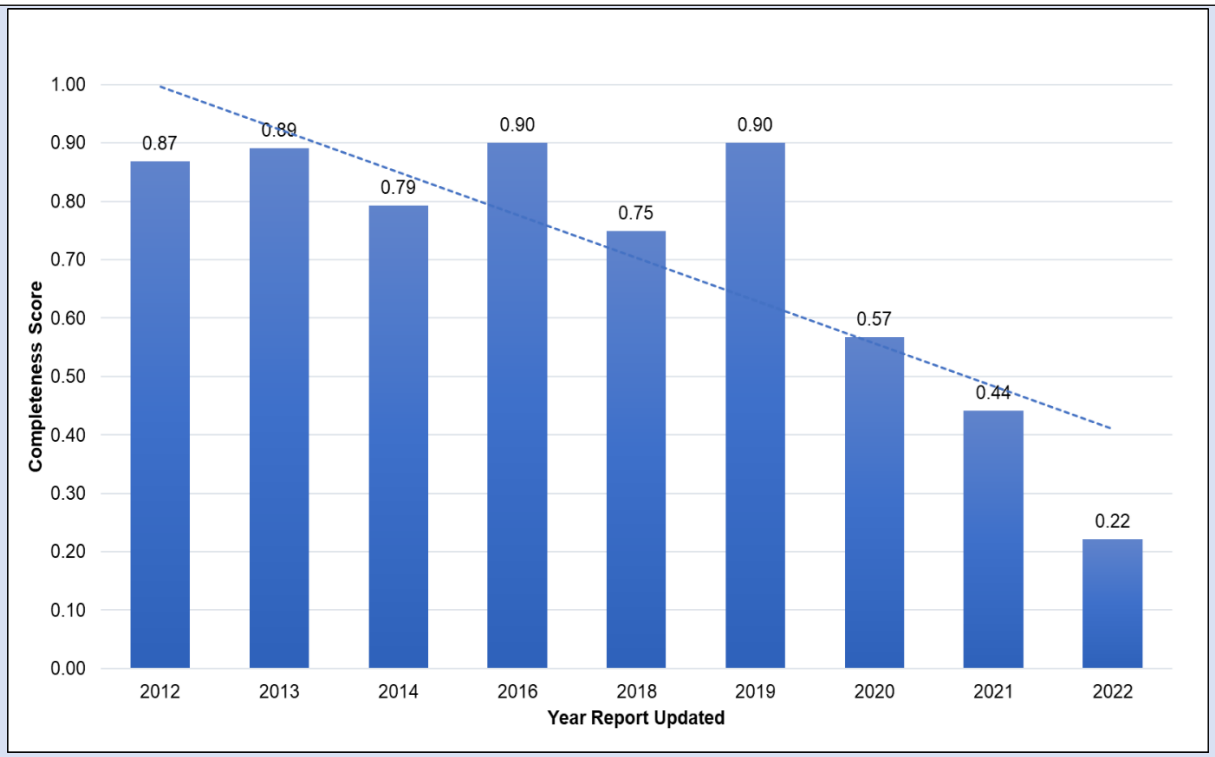



**Figure 11:** Zimbabwe VigiGrade vaccines AEFIs completeness score.

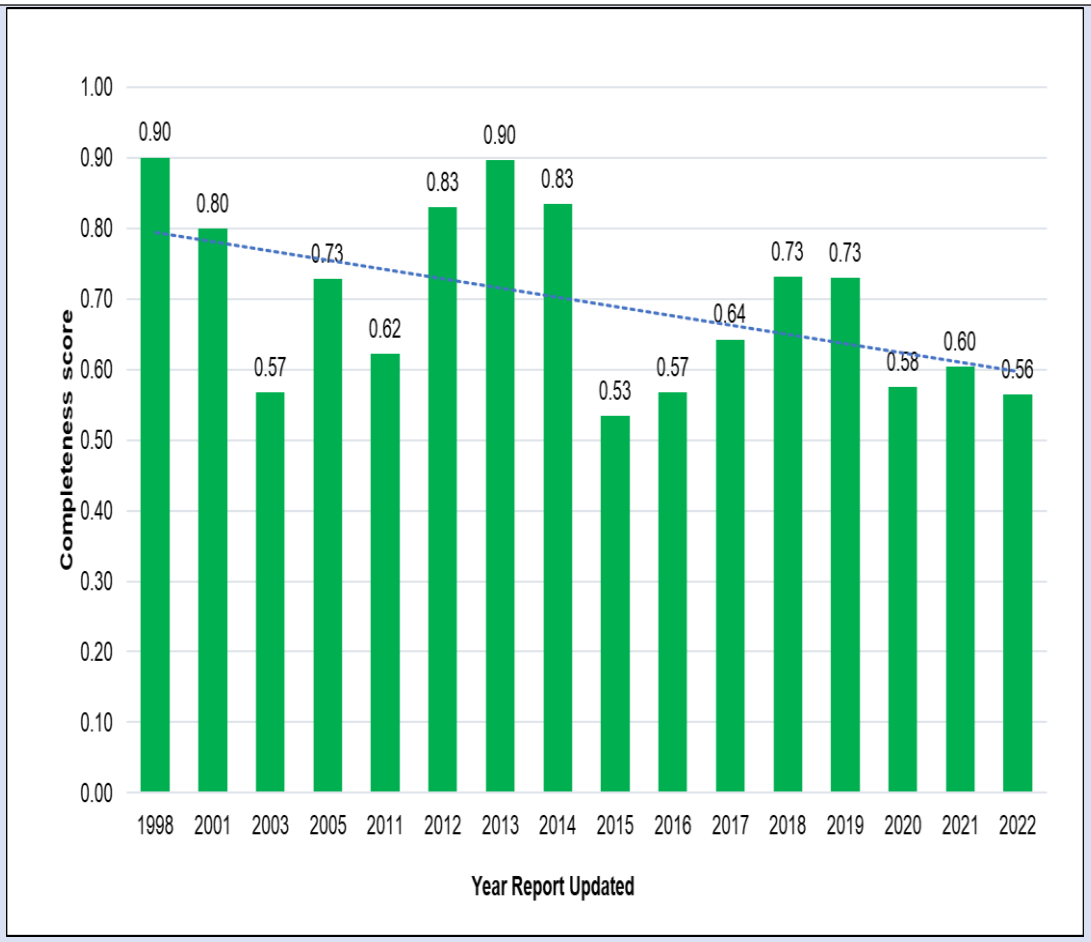



**Figure 12:** Zimbabwe VigiGrade combined vaccine and non-vaccine AEFIs completeness score.

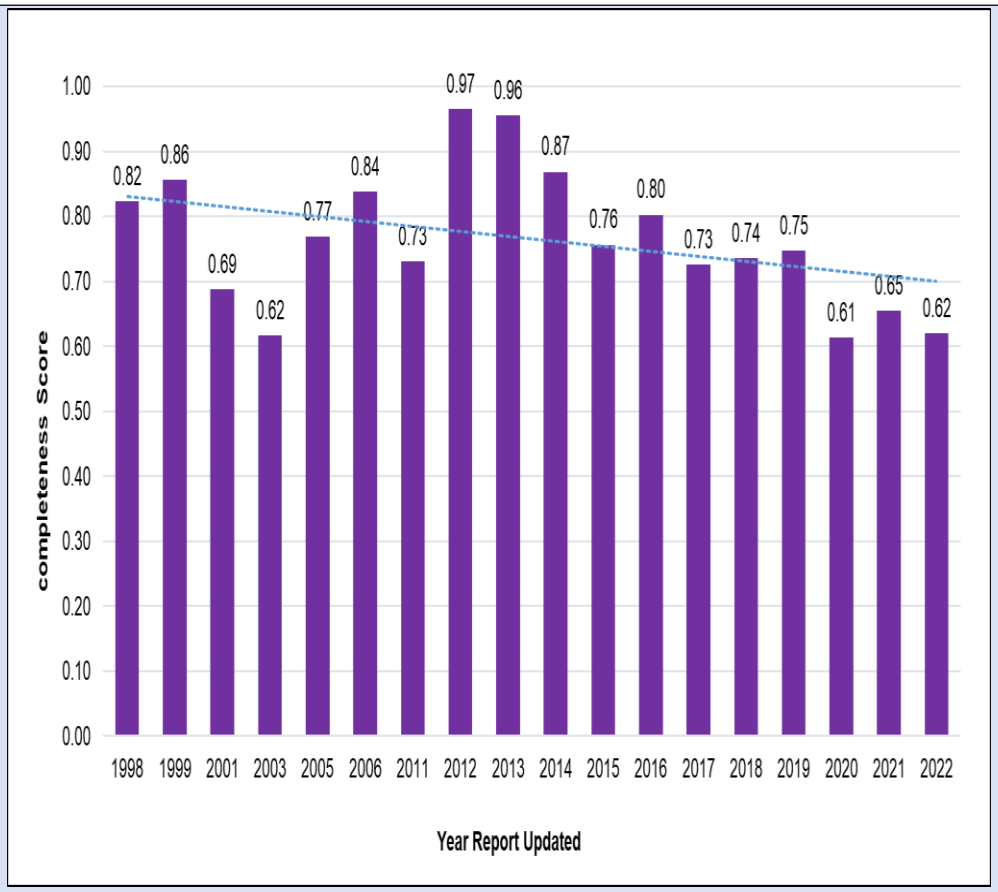



**Figure 13:** Zimbabwe VigiGrade non-vaccines ADRs/SAEs) completeness score.

| Province | AEFI reports | Percentage |
|---|---|---|
| Bulawayo | 119 | 8.3% |
| Chitungwiza | 108 | 7.5% |
| Harare | 373 | 25.9% |
| Manicaland | 165 | 11.4% |
| Mashonaland Central | 43 | 3.0% |
| Mashonaland East | 143 | 9.9% |
| Mashonaland west | 141 | 9.8% |
| Masvingo | 123 | 8.5% |
| Matebeleland North | 85 | 5.9% |
| Matebeleland South | 56 | 3.9% |
| Midlands | 65 | 4 .5/o |
| Unknown | 21 | 1.5% |
| Total | 1442 | 100.0% |

Table 4: Zimbabwe geographical distribution of AEFIs reports.

Table 4 and Figure 14 below shows the geographical distribution of Zimbabwe 1442 AEFI reports from 1998 to August 2022, from all 11 provinces. Most reports arose from the Harare 373 (25.8%) where the capital city is based. Some AEFI reports verifiable by signed hard copies with names of patients/vaccinees did not indicate vaccination clinics hence the provinces were unknown in 21 (1%) of reports although the reports met the inclusion criteria for analysis.

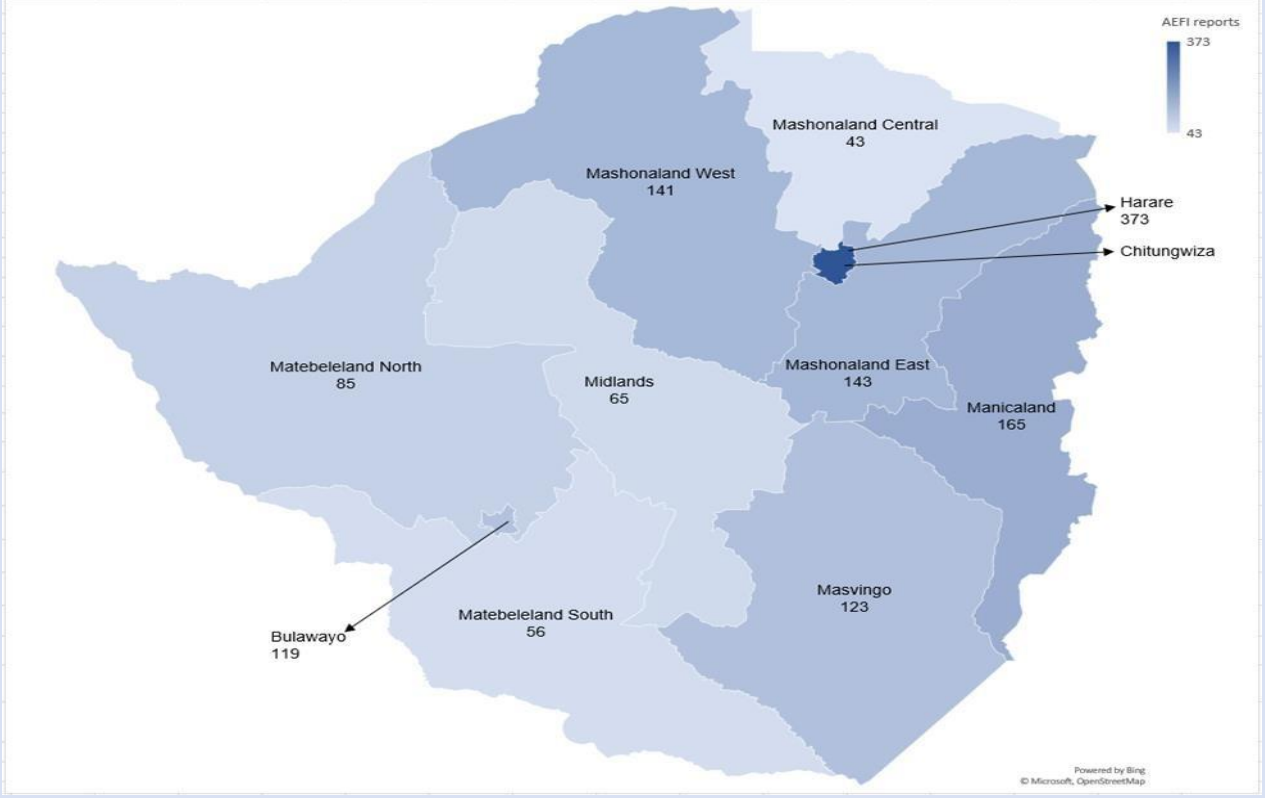



**Figure 14:** Zimbabwe geographical distribution of AEFIs reports.

According to the MCAZ WHO GBT August 2021 assessment report, 85% of the GBT vigilance assessment indicators were complied with such as AEFI reporting guidelines, AEFI reporting, AEFI case investigation and stakeholders' engagement through feedback letters, newsletters, trainings, circulars, and media communications. The WHO GBT August 2021 MCAZ assessment report however recommended strengthening legislation for the vigilance system, manufacturers' Good Vigilance Practice (GVP) and Qualified Persons for Pharmacovigilance (QPPV). These legal requirements were addressed by MCAZ circulars 3/2022 and 13/2022 including signed confirmation by majority of medicines/vaccines manufacturers having GVP/QPPV systems in 2022. The MCAZ NPC developed system for conducting manufacturers GVP/QPPV training sessions and GVP inspections.

## Discussion

The Zimbabwe AEFI surveillance system met and exceeded the criteria of the WHO minimum AEFI reporting ratio of 10 per 100 000 surviving infants achieving 11.26 to 43.46 in 2006, 2009, 2010, 2012, 2015 to 2021. The highest AEFI reporting ratio of 43.46 was for the adult COVID-19 vaccinees in 2021. The highest AEFI reporting ratios in 2021 were also contributed in part by the feasibility study of mHealth active participant centered (MAPC) AEFI surveillance study conducted in Zimbabwe, based on the Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) Australian study innovation [43]. There was a gradual improvement of the AEFI reporting ratio from 2009 to 2021 due to joint MCAZ NPC and ZEPI enhanced AEFI surveillance HCWs AEFI reporting trainings, feedback, monitoring and evaluation programs during vaccination campaigns [15, 17, 22].

The Zimbabwe enhanced AEFI spontaneous reporting system managed to generate both serious and non-serious AEFI reports such as fever and febrile convulsions as expected in line with other AEFI surveillance systems study findings in both high-income countries (HICs) and LMICs (2, 5, 6, 13, 35-39). Most serious AEFIs were managed by antipyretic agents, antihistamines, and antibiotics at the vaccination clinics with few hospitalizations. Some children had a history of underlying infections before vaccinations hence the need for antibiotic therapy and/or antiretroviral therapy. ZEPI has a policy of free treatment of all serious AEFIs that occur within 3 to 5 days post-vaccination with limited funding for vaccine injury compensation. Some

HICs have however well-funded systems of vaccine injury compensation schemes [40].

The qualitative aspect of the study results identified areas of the causality assessment that were subsequently made more robust using more accurate, clearer language, semantics in step 1 to 4 of the algorithm illustrated in **Figure 2**. The India-Zimbabwe inter country study results were accepted by the WHO Global Advisory Committee on Vaccine Safety (GACVS) in December 2018 and resulted in the revised WHO AEFI causality assessment algorithm Aide-memoire 2019 Globally, most national AEFI committees, including Zimbabwe, adopted use of this WHO revised AEFI causality assessment algorithm Aid-memoire 2019 that also became useful for COVID-19 vaccines [37, 39]. Italy study evaluated the WHO AEFI causality assessment algorithm using COVID-19 vaccines thrombosis and thrombocytopenia AEFIs with death as an outcome [39]. The study recommended use of robust postmortems techniques to achieve Brighton Collaboration AEFI case definition level 1 diagnostic certainty for COVID-19 vaccines fatal AEFI cases [39].

Consideration of country background rates for rare fatal AEFIs is key to determine the benefit risk profiles. Therefore ZEPI, MCAZ NPC, Mutare hospital and Edith Opperman clinic Harare, successfully participated in a WHO feasibility study of Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) project case definitions based on levels of diagnostic certainty for pregnancy and neonatal outcomes. The study results showed that modification of the GAIA stillbirth definition could help avoid potential misclassification in LMICs [25, 27]. The study underscored the need for greater data literacy and inter-sectoral collaboration among healthcare providers, pharmacovigilance, and health program managers to promote harmonized approaches (case definitions and data elements) for capturing adverse outcomes of pregnancy [24, 25].

The African region contributes a cumulative total of only 0.9% of individual case safety reports (ICSRs) to the WHO global surveillance safety database known as VigiBase [13]. Most of these reports relate to medicines such as antiretrovirals, anti-tubercular and antibiotic medications rather than vaccines (13). Scientific evidence on the local AEFIs is lacking in most Low Middle-Income Countries (LMICs), including Zimbabwe. The challenges and limitations of analysing spontaneous AEFIs reports were that, for most AEFI data collected, there was no denominator data, no total number of exposed patients and no background rates. Reporting biases may arise due to media attention following serious AEFIs during vaccination campaigns. The most pressing national challenges for COVID-19 vaccines deployment included cost, distribution logistics; and addressing the widespread misinformation disseminated via social media that perpetuated vaccine hesitancy [6, 41]. While anaphylaxis after COVID-19 vaccination is rare, few local reports of such events in the media further fueled vaccine hesitancy.

The MCAZ NPC launched an electronic AEFI report system in 2019 with mobile app and desktop offline system; however, the uptake was low because most public vaccination clinics did not have the capacity for online reporting except for the aggregate data sent via the District Health Information Services (DHIS2). The main challenges of AEFI causality assessment were that 54/118 unfortunate death cases were unclassifiable due to lack of postmortems either by refusal by next of kin or unavailability of postmortem facilities. However, no cause of death was evident from the investigations. Some authors advocated that postmortem should be mandatory in all deaths temporarily related to vaccine administration [39]. It is also recommended that such postmortems should be conducted in line with the Letulle technique for clinical and forensic assessment in case of suspected death related to vaccines [39]. The Zimbabwe primary healthcare postmortem services have inadequate resources for the advanced postmortem Letulle technique. Globally, some studies cited few reports of similar cases of suspected post-vaccination sudden infant death syndrome [42]. Such suspected fatal AEFIs led to the development of the active participant-centered AEFI surveillance systems, and requirements for pharmaceutical industry in Europe, Australia, and Canada to conduct enhanced AEFI surveillance of influenzas and COVID-19 vaccines [36, 43, 44].

For this study, there were seven children suspected with anaphylaxis AEFI vaccine cases of which one recovered, one died and five were unknown with no cause of death evident. There was only one reported case of suspected anaphylaxis AEFI for COVID-19 vaccinee and the patient recovered. Some authors found that 85% of cases of anaphylaxis had pre-existing atopic disease such as asthma [45]. Paediatrics analysis of a large-linked post-vaccination

database in Asia found risk of anaphylaxis to be 1.21 cases/million doses for BNT162b2 COVID-19 vaccine [46, 47]. An Australian study found that estimated incidence rate of anaphylaxis for DTaP vaccines was 0.36 cases per 100,000 doses, and 1.25 per 100,000 doses for MMR vaccines [6]. Apparently, removal of gelatin from vaccines may dramatically reduce allergic reactions to these vaccines [6].

Enhanced joint MCAZ NPC and ZEPI-MoHCC AEFI surveillance trainings, monitoring and evaluations during vaccination campaigns and introduction of new vaccines from 2009 to 2021 led to increased AEFI reporting ratios. MCAZ EPI and ZEPI should therefore secure more resources for enhanced and active AEFI surveillance systems. This includes electronic AEFI reporting from vaccine clinics to districts, provinces, and national use of the ZEPI system. Active AEFI surveillance systems should also target improving AEFI detection sensitivity, and AEFI case management by incorporating technologies such as mHealth active participant cantered (MAPC) AEFI surveillance used in HICs [48]. Given the increasing penetration of mobile technology in Zimbabwe, it is possible to conduct such feasibility studies if more resources were generated for MAPC AEFI surveillance [48].

Given that causality assessment was not always conclusive for suspected AEFI fatalities due to inadequate postmortem information, there is a need to strengthen AEFI case investigations and increase postmortem facilities countrywide. The MCAZ NPC, in line with the WHO GBMT indicators for vigilance, should also conduct signal detection of AEFIs in Zimbabwe compared to VigiBase globally using signal disproportionate analysis. Such an approach requires at least 500 ICSRs [49], and Zimbabwe has 6001 ICSRs in VigiBase. It is important for ZEPI, MCAZ NPC and academia to avail resources to conduct facility-based background rates studies to compare prevalence of the specific antigens serious AEFI related cases that may be suspected with death, as part of risk minimization.

## Limitations, confounding factors and/or bias

The limitation of this study is that it is based mostly on spontaneous retrospective AEFI case series from 1998 to 2022 not comprehensive clinical notes/case reviews hence caution is required in interpretation of AEFI symptoms, signs and diagnoses temporarily associated with vaccination but not necessarily causally associated with vaccine(s) [50]. To reduce errors and duplication, only AEFI data uploaded on VigiBase, MCAZ NPC ePV system and Excel databases with verifiable hard copy AEFI reports from ZEPI and the national pharmacovigilance center were used. There is a possibility that, due to underreporting, few AEFIs reports might be missed if they were not reported to ZEPI and/or MCAZ national pharmacovigilance centre. Ethical approval was obtained MRCZ/A/2268 and E/148.The authors acknowledge ZEPI-MoHCC and MCAZ NPC staff, HCWs, vaccinees/guardians and the national AEFI Committee who conducted AEFI surveillance, case management and causality assessment from 1998 to 2022. Thanks to all MCAZ/ZEPI-MoHCC partners, WHO, UNICEF, GAVI, CDC, and UMC.

## Conclusion

The Zimbabwe AEFI surveillance system is producing good results, but it requires strengthening in the areas of timely AEFI detection, AEFI case investigation including completion of postmortems to enable causality assessment, VigiPoint disproportionate analysis signal detection and risk minimization. AEFI case investigation, initiatives ought to prioritize postmortems of fatal AEFI cases as incomplete assessment of causation in such cases can severely compromise public confidence in vaccines. This requires adequate postmortem facilities at vaccination clinics, referral district and provincial hospitals. Effective AEFI detection, case management, risk minimization and promotion of vaccinees safety requires ZEPI and MCAZ to use dependable, efficient, and cost effective electronic AEFI systems such as VigiMobile and MAPC AEFI surveillance. Strong collaboration between the national immunization program and NRA national pharmacovigilance center is critical for strengthening the national AEFI surveillance system in a resource-limited country.

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