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ORIGINAL RESEARCH ARTICLE

Signal Monitoring for Adverse Events Following Immunisation with COVID-19 Vaccines During the SARS-CoV-2 Pandemic: An Evaluation of the South African Surveillance System

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Abstract

Introduction Monitoring of adverse events following immunisation (AEFI) is recommended for post-licensure surveillance. We investigated whether the South African surveillance system could detect signals of disproportionate reporting and whether these signals aligned with globally identified AEFI and adverse events of special interest (AESI) post-coronavirus disease-2019 (COVID-19) vaccination.

Methods This retrospective pharmacovigilance study undertook disproportionality analysis of the National Department of Health AEFI database from the start of the COVID-19 vaccine rollout on 17 May 2021 to 31 December 2022. We complemented this with AEFI reports for vaccines not on the routine Expanded Programme on Immunisation schedule, to address potential masking of signals due to the high reporting rate of COVID-19 vaccine AEFI.

Results During the study period, 3846 AEFI were reported for 37,537,009 doses of COVID-19 vaccines (BNT162b2 and Ad26.COV2.S) administered. The overall reporting rate was 10.2 per 100,000 doses, 18.1/100,000 and 7.9/100,000 for Ad26.COV2.S and BNT162b2, respectively. Comparison with other countries suggests underreporting. Disproportionate reporting signals were obtained for three and seven AEFI following BNT162b2 and Ad26.COV2.S vaccines, respectively. An additional three AEFI signals from Ad26.COV2.S emerged in the augmented dataset, indicating masking. All Ad26.COV2.S signals, and one BNT162b2 signal, appear in the vaccines' product information. Among nine AESI evaluated, myocarditis/pericarditis presented as a signal of disproportionate reporting following BNT162b2 vaccination.

Conclusions This study is one of the first from a lower-middle-income country, using a spontaneous reporting system for signal detection post-COVID-19 vaccination. Signals aligned with those reported globally. The study highlights the need to further investigate underreporting, masking, and system attributes for system strengthening.

1 Introduction

The South African adverse events following immunisation (AEFI) surveillance system, established in 1998, is focused on the monitoring and evaluation of AEFI reported in relation to the Expanded Programme on Immunisation (EPI) [1, 2]. Since 17 May 2021, when the national coronavirus disease-2019 (COVID-19) vaccination rollout began, the South African AEFI surveillance system has been responsible for monitoring AEFI and

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Key Points

Reporting rates revealed underreporting of AEFI following COVID-19 vaccines in South Africa compared with other countries.

Analysis of spontaneous reporting system data revealed disproportionate reporting following both BNT162b2 and Ad26.COV2.S vaccines and BNT162b2.

This is one of the first studies from a low- and middle-income country using a spontaneous reporting system for signal detection, and we detected several signals in relation to the COVID-19 vaccines.

adverse events of special interest (AESI) from both the EPI and COVID-19 vaccine rollout. AEFIs are defined as untoward medical occurrences following immunisation, where a causal relationship between the vaccine and the event(s) cannot be assumed; they can include abnormal laboratory findings, symptoms or diseases. AESI are pre-specified, medically significant events that may be causally linked with the vaccine and require diligent monitoring [1]. Vaccines are generally safe and effective and adverse events (AEs) are rare; however, strong pharmacovigilance systems are necessary. An effective system for monitoring AEFI is essential to ensure vaccine safety and prevent a consequential decline in vaccine confidence [1, 2]. Administration of vaccines to otherwise healthy persons means that the public is often less tolerant of risks associated with vaccines, than of those associated with drugs used to treat disease. This emphasises the need for strong pharmacovigilance systems for post-licensure surveillance of vaccines. Post-licensure surveillance often identifies AEs that may not have been seen in the controlled environment of a clinical trial and contributes to understanding the safety profiles of marketed vaccines [3].

Spontaneous reporting systems (SRS), such as the South African AEFI surveillance system, can rapidly identify potential vaccine risks, a process known as signal detection. The World Health Organization Uppsala Monitoring Centre (WHO-UMC) defines a signal as not directly indicative but suggestive of a causal relationship between an AE and drug [4]. Disproportionality analysis is commonly used in pharmacovigilance to identify associations between vaccine/drug-AE pairs in SRS databases. It is based on the principle that incomplete reporting of events will impact all events equally, making the ratio of vaccine/drug-AE combinations to the total reported AEFIs relatively constant. A disproportionate ratio for a vaccine/drug-AE combination relative to others suggests an association that needs investigation but is not synonymous with causality. It indicates a quantitative dependency that requires further investigation to identify possible risks [5]. Disproportionality analysis methods are based on frequentist or Bayesian approaches [5]. These analyses are dependent on the data used to calculate the background rate and having an adequate number of background reports. Calculations can be carried out using a vaccine and/or drug database. The large volume of COVID-19 vaccine reports worldwide has distorted the background rate and consequently created challenges when using disproportionality methods to detect signals of disproportionate reporting.

The UMC is a WHO collaborating centre that manages VigiBase, the WHO's database of all reported side effects of medicinal products and vaccines across all countries, which are part of the WHO Program for International Drug Monitoring. VigiBase uses disproportionality analysis to detect and report quantitative dependencies between vaccine/drug-AE combinations. Identification of signals of disproportionate reporting is the first step in the signal detection process, followed by expert reviews and causality assessment [6].

Since 1998, the South African National Department of Health (NDoH) maintained a basic surveillance system for AEFI as part of general pharmacovigilance. In 2018, in line with WHO recommendations, a dedicated AEFI surveillance system was introduced, including the establishment of the National Immunisation Safety Expert Committee (NISEC) to allow for causal assessment of cases reported as serious or severe. The system uses case reporting forms (CRFs) completed by healthcare facilities when a patient presents with a suspected AEFI. These CRFs are submitted via email to provincial and national AEFI surveillance coordinators and manually entered into an MS Excel® spreadsheet database.

In 2021, the South African Health Products Regulatory Authority (SAHPRA) introduced the Med Safety application (https://medsafety.sahpra.org.za/) as a second reporting modality. The Med Safety application was developed by the application development project WEB-Recognising Adverse Drug Reactions, in collaboration with the WHO, UMC and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. The application is utilised by SAHPRA to facilitate reporting of AEs through submission of an electronic form by both health professionals and members of the public. The data reported on the electronic form feeds directly into VigiBase. Prior to the introduction of the Med Safety application, AEFI-related reports in the SAHPRA database (VigiBase) were primarily those notified by the

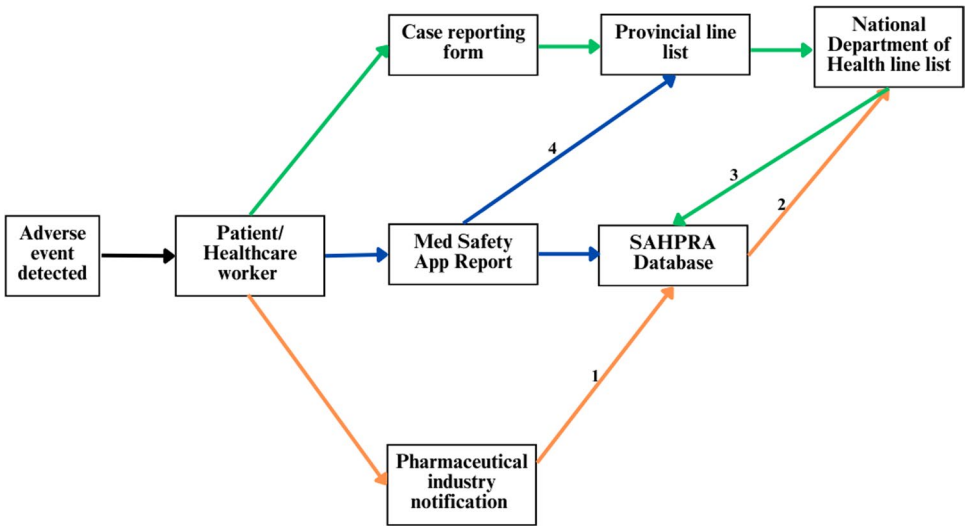

Fig. 1 Structure of the South African AEFI surveillance system. *AEFI* adverse events following immunisation, *CRF* case reporting form, *SAHPRA* South African Health Products Regulatory Authority. Arrows: direction of data flow following AEFI notification (1) Pharmaceutical industry AEFI reports are de-identified and sent to SAHPRA; (2 and 3) data sent via email; and (4) Med Safety reports accessible to provincial surveillance officers

pharmaceutical industry, which were provided without unique identifiers and were anonymised. Owing to the presence of this anonymised data in the SAHPRA database, full integration of the NDoH database into Vigibase became challenging, as there was a risk of creating duplicate entries. Provincial surveillance officers had access to the Med Safety reports and routinely added them to the Excel-based database (NDoH database), as the Med Safety form collects enough metadata to allow for patient identification. With access to both Med Safety reports and paper-based CRFs, provincial surveillance officers were able to carry out investigations of all serious and severe events and submit these investigations for causality assessment. For this reason, from the period of introduction of the paper-based AEFI surveillance system in 2018, the NDoH database was the more comprehensive, but each database has unique data elements. Figure 1 illustrates the information flow when AEs are reported.

We aimed to investigate associations between AEs and COVID-19 vaccines in the NDoH-EPI database. We hypothesised that the South African AEFI surveillance system is adequate to detect signals of disproportionate reporting that align with the most frequently detected AEFI and AESI following COVID-19 vaccination, globally.

2 Methods

2.1 Study Design and Data Sources

This retrospective pharmacovigilance study was a disproportionality analysis of data from the NDoH-EPI and SAHPRA AEFI databases, from the start of the COVID-19 vaccine rollout on 17 May 2021 to 31 December 2022.

2.2 Data Management

2.2.1 NDoH-EPI Dataset (A)

AEFI line list data were standardised and validated using original category definitions. Following this, data were de-duplicated. AEs were separated to create a vaccine AEFI reaction database and then manually reviewed. AEs were coded by two investigators using the medical dictionary for regulatory activities (MedDRA). All five levels of the MedDRA hierarchy were used; Lowest Level Terms were mapped to Preferred Terms, High Level Terms, High Level Group Terms, and System Organ Classes using the MedDRA browser.

To address potential masking of AEFI-vaccine signals, the NDoH-EPI dataset was augmented as described below with the addition of data:

2.2.2 Dataset Based on NDoH-EPI Line List and Data from SAHPRA (B)

- Data from the SAHPRA database, reported from 17 February 2021 to 31 December 2022 for vaccines that were not part of the EPI or COVID-19-related (e.g. influenza, pneumococcal vaccines) were added. To avoid adding duplicates, the few cases of non-EPI and non-COVID-19 vaccine-related AEFI in the NDoH-EPI database were removed. De-duplication was not possible with SAHPRA's de-identified data.

2.2.3 Dataset Based on the NDoH-EPI Line List and Data from SAHPRA (C)

- Data from the SAHPRA database, reported from 17 February 2021 to 31 December 2022 for vaccines that were not part of the EPI or COVID-19-related (e.g. influenza, pneumococcal vaccines) were added. To avoid adding duplicates, the few cases of non-EPI and non-COVID-19-vaccine-related AEFI in the NDoH-EPI database were removed. De-duplication was not possible with SAHPRA's de-identified data.
- Data for all vaccines from the SAHPRA database from 1 January 1992 to 16 February 2021 were added.

2.3 Statistical Analyses

Statistical analyses were executed in R Studio version 2023.06.1 [5]. Summary statistics were generated. Preferred Terms were used in disproportionality analysis, which condense complex data into two-by-two contingency tables (Table 1) to assess vaccine/drug-AE combinations [6]. The Bayesian Confidence Propagation Neural Network (BCPNN) method used by WHO-UMC aims to detect disproportionality between observed and expected reporting of a vaccine/drug-AE combination [7, 8]. BCPNN is rooted in Bayesian methodology that uses a measure of disproportionality, called an information component (IC), to show the strength of the association between the specific states of two variables [9]. The reporting odds ratio (ROR) and IC were calculated for vaccine/drug-AE pairs using the NDoH-EPI AEFI database as a comparator (Table 2). The ROR, a widely used frequentist calculation, compares the reporting rate for a vaccine/drug-AE combination with the reporting rate for the same AE amongst other vaccines [10]. The IC is the logarithm (base 2) of the observed/expected ratio [11].

Table 1 Two-by-two contingency table used in disproportionality analyses

	Reports for event of interest	Reports for all other events
Reports for drug of interest	*a*	*b*
Reports for all other drugs	*c*	*d*

Whether a vaccine/drug-AE combination is considered quantitatively distinctive depends on the selected threshold. Varying the threshold can either generate more false positive signals and identify more signals or reduce false positives but potentially miss signals. When observed and expected counts are low there is a risk of detecting false positive associations. False positives can be mitigated by the use of the lower limits as thresholds for signal detection [6]. Confidence and credibility intervals will be wider when observed and expected counts are lower; allowing for this uncertainty can reduce false positive signals [11].

Credibility intervals for ICs are calculated as follows [12]:

$$\mathrm{IC}_{025} = \mathrm{IC} - 3.3(a+0.5)^{-\frac{1}{2}} - 2(a+0.5)^{-\frac{3}{2}}$$

$$\mathrm{IC}_{075} = \mathrm{IC} + 2.4(a+0.5)^{-\frac{1}{2}} - 0.5(a+0.5)^{-\frac{3}{2}}.$$

The lower limit of the confidence interval is used to interpret RORs. An $\mathrm{ROR}_{025} > 1$ is considered indicative of a quantitative dependency [13]. The lower limit of the credibility interval is used to interpret ICs. An $\mathrm{IC}_{025} > 0$ is considered indicative of a quantitative dependency [7, 12].

There is much debate around the use of frequentist versus Bayesian approaches for signal detection. Where there are low observed and/or expected cell counts, the ROR can be less stable and present large values, whereas the IC calculation employs methods that give lower relative reporting rate ratios. The IC provides an approach to mitigating identification of false positives; however, there is also the risk of missing credible associations. The ROR ratio is considered a more easily interpretable measure as it is a commonly used statistic for assessing association. Therefore, both measures of association have been presented in this paper, as concurrent use of both measures can assist in ensuring adequate identification of signals [6].

2.4 AEFI and AESI

Signals of disproportionate reporting of AEFI in South African databases were evaluated against the vaccine professional information (PI).

Signals of disproportionate reporting of AESI were evaluated against AESI that literature revealed to be relevant to COVID-19 vaccines and disease. Voss et al., in a multi-national cohort study, have shown some AESI to

Table 2 Formula and thresholds for disproportionality measures

Measure of association	Formula	Thresholds
Reporting odds ratio (ROR)	$\frac{ad}{cb}$	Lower limit of 95% CI > 1
Information component (IC)	log2 ([*a*+0.5]/[(*a*+*b*) × (*a*+*c*)/(*a*+*b*+*c*+*d*)+0.5])	Lower limit of 95% CrI > 0

CI confidence interval, *CrI* credibility interval

have potential associations with COVID-19 vaccines and disease and that their link to COVID-19 disease allows for understanding AESI signals related to COVID-19 vaccination in the context of the broader risk–benefit of COVID-19 vaccination. In this evaluation, we included Guillain–Barré syndrome, myocarditis/pericarditis, and coagulation disorders [14].

The corresponding MedDRA term for each AESI was identified. The database is symptoms-based, and patients can self-report without a clinician's formal diagnosis. We therefore created two definitions, an exact definition and an inclusive definition that includes probable cases on the basis of the presence of characteristic symptoms of the AESI. When there were no cases meeting an exact definition, only the inclusive definition was used (Table 3).

3 Results

From 17 May 2021 to 31 December 2022, 37,537,009 doses of BNT162b2 and Ad26.COV2.S were administered, for which 3846 persons reported AEs (reporting rate of 10.2 per 100,000 doses). Of these AEs, 1676 (43.6%) were classified as serious/severe. AEFI reporting rates for BNT162b2 and Ad26.COV2.S were 7.9/100,000 and 18.1/100,000, respectively. Reporting rates of serious/severe AEs were 4.7 and 4.4 for the Ad26.COV2.S vaccine and BNT162b2 vaccine, respectively (Table 4). The bolded values in all the tables represent the overall values for each of the vaccine types or for all vaccine types.

Female recipients of Ad26.COV2.S had a higher reporting rate (24.2/100,000) compared with males (9.7/100,000). Most recipients of Ad26.COV2.S were in the 18–34 (40.7%) and 35–49 (37.2%) year age groups, with persons aged 18–34 years receiving 40.7% of the COVID-19 vaccines but reporting 26.0% of AEFI. Amongst BNT162b2 recipients,

Table 3 AESI definitions

Pre-specified AESI	Corresponding MedDRA preferred terms	Exact and inclusive definitions
Guillain–Barré syndrome	Guillain–Barré syndrome	Exact definition: Guillain–Barré syndrome
Myocarditis/pericarditis	Myocarditis/pericarditis Cardiac flutter Cardiac fibrillation Sinus tachycardia Tachycardia	Exact definition: myocarditis/pericarditis Inclusive definition: myocarditis/pericarditis + cardiac flutter + cardiac fibrillation + sinus tachycardia + tachycardia
Non-haemorrhagic stroke	Ischaemic stroke Embolic stroke	Exact definition: ischaemic stroke + embolic stroke
Haemorrhagic stroke	Subarachnoid haemorrhage Cerebral haemorrhage Traumatic intracranial haemorrhage	Exact definition: subarachnoid haemorrhage + cerebral haemorrhage + traumatic intracranial haemorrhage
Deep vein thrombosis	Deep vein thrombosis Thrombosis Pulmonary thrombosis Subclavian vein thrombosis	Exact definition: deep vein thrombosis Inclusive: deep vein thrombosis + thrombosis + pulmonary thrombosis + subclavian vein thrombosis
Pulmonary embolism	Pulmonary embolism Embolism	Exact definition: pulmonary embolism Inclusive definition: pulmonary embolism + embolism
Disseminated intravascular coagulation	Coagulopathy	Exact definition: NA Inclusive definition: coagulopathy
Immune thrombocytopenia	Immune thrombocytopenia Thrombocytopenia	Exact definition: immune thrombocytopenia Inclusive definition: immune thrombocytopenia + thrombocytopenia
Thrombosis and thrombocytopenia	Thrombosis + thrombocytopenia Cerebral venous sinus thrombosis (CVST)	Exact definition: reviewed cases of thrombosis that reported low platelets (thrombocytopenia) + reviewed cases of CVST that reported low platelets (thrombocytopenia)

Table 4 Number of doses administered, and AEFI reported, by vaccine type in South Africa, 17 May 2021 to 31 December 2022

Vaccine type	Total # of vaccine doses administered (% of total)	Total # of AEFI reported (% of total)	Rate per 100,000 doses administered	*P* value (x^2)
Ad26.COV2.S	**8,627,230 (23.0%)**	**1561 (40.6%)**	**18.1**	**< 0.0001**
Serious/severe AE's	8,627,230	403 (25.8%)	4.7	
BNT162b2	**28,909,779 (77.0%)**	**2285 (59.4%)**	**7.9**	
Serious/severe AE's	28,909,779	1273 (55.7%)	4.4	
Total	**37,537,009**	**3846**	**10.2**	

AEFI adverse events following immunisation

the distribution of reported AEFI was weighted towards person's ≥ 60 years, with this age category receiving 25.8% of vaccines but reporting 35.5% of AEFI (Table 5).

Table 6 presents the distribution of Ad26.COV2.S and BNT162b2 doses across South African provinces. AEFI reporting rates varied considerably, with the Western Cape and North West provinces having the lowest and highest reporting rates, 1.6 and 59.5 among Ad26.COV2.S recipients and 2.5 and 11.5 among BNT162b2 recipients.

Table 7 presents the number of reported AEFIs by vaccine type for datasets A (NDoH-EPI database), B (augmented NDoH-EPI database) and C (augmented NDoH-EPI database). To elicit a masking effect due to over-reporting of AEFI from COVID-19 vaccines, datasets B/C were created. Datasets B and C include an additional 221 and 7146 AEFI for non-COVID vaccines, respectively. Analyses included here focus on datasets A and C, so as to stabilize the background rate with the addition of a sufficient amount of non-COVID AEFI data. Results of dataset B analyses are included as supplementary tables to demonstrate the effect of the incremental addition of non-COVID vaccine AEFI to elicit masking.

Table 5 The number of doses administered and AEFI reported by vaccine type, sex and age group, 17 May 2021 to 31 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 (23.0%)**	**1561 (40.6%)**	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 (77.0%)**	**2285 (59.4%)**	7.9	< 0.0001
Male	12,652,680 (43.8%)	834 (36.5%)	6.6	
Female	16,257,099 (56.2%)	1417 (62.0%)	8.7	
Unknown	0 (0%)	34 (1.5%)		
Age group (years)				
Ad26.COV2.S	**8,627,230 (23.0%)**	**1561 (40.6%)**	18.1	< 0.0001
12–17	391 (0.005%)	0 (0%)	0	
18–34	3,515,409 (40.7%)	406 (26.0%)	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 (77.0%)**	**2285 (59.4%)**	7.9	< 0.0001
12–17	3,027,972 (10.5%)	64 (2.8%)	2.1	
18–34	6,887,150 (23.8%)	296 (13.0%)	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%)		

AEFI adverse events following immunisation

Table 6 The number of doses administered and AEFI reported by vaccine type and province, 17 May 2021 to 31 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%)**	**14,235**	**1561 (40.6%)**	18.1	< 0.0001
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%)**	**47,702**	**2285 (59.4%)**	7.9	< 0.0001
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 (2.0%)	8.6	
Western Cape	4,772,575 (16.5%)	66,174	548 (24.0%)	11.5	
Unknown	0 (0%)		184 (8.1%)		

AEFI adverse events following immunisation

Table 7 Number of adverse events reported to NDoH for Ad26.COV2.S, BNT162b2, and non-COVID-19 vaccines for dataset A (NDoH-EPI), dataset B (NDoH-EPI augmented) and dataset C (NDoH-EPI augmented)

Vaccine	Total number of reported vaccine reactions (%)		
	Dataset A	Dataset B	Dataset C
Ad26.COV2.S	4195 (45.4%)	4195 (44.3%)	4195 (25.6%)
BNT162b2	4732 (51.2%)	4732 (50%)	4732 (28.9%)
Non COVID-19 vaccines	315 (3.4%)	536 (5.7%)	7461 (45.5%)
Total	**9242**	**9463**	**16,388**

The most frequently reported AEFI for datasets A and C are presented in Table 8.

Table 9 presents the results of the disproportionality analyses of the top ten most frequently reported AEs in relation to the Ad26.COV2.S vaccine. All events in dataset C presented as signals of disproportionate reporting, while seven presented in dataset A.

Figure 2 further illustrates this positive shift of IC lower bound values in dataset C for all AEFI excluding pyrexia, compared with dataset A. It also highlights the shift of fatigue, pain and injection site swelling past the boundary.

Table 10 presents the results of the disproportionality analyses of the top ten most frequently reported AEs in relation to the BNT162b2 vaccine. In dataset A, dyspnoea, chest pain, and rash present as signals of disproportionate reporting. In the augmented dataset C, rash no longer appears as a signal; however, dataset C elicited signals for dizziness and fatigue.

Figure 3 further illustrates the shift of IC lower bound values in dataset C, compared with dataset A. It also highlights the shift of fatigue and dizziness past the boundary.

Table 11 presents the results of the disproportionality analyses of relevant AESI reported in relation to the Ad26.COV2.S vaccine. In datasets A and C, IC lower bound values indicate no signals of disproportionate reporting. In dataset C, positive and negative shifts are seen in IC lower bounds; however, no signals of disproportionate reporting are elicited.

Table 12 presents the results of the disproportionality analyses of relevant AESI reported in relation to the BNT162b2 vaccine. In datasets A and C, IC lower bound values indicate signals of disproportionate reporting for

Table 8 Most frequently reported adverse events following BNT162b2, Ad26.COV2.S, and non-COVID-19 vaccines in datasets A (NDoH-EPI) and C (NDoH-EPI augmented) by vaccine, as determined using the MedDRA preferred terms

BNT162b2		Ad26.COV2.S		Non-COVID vaccines		Non-COVID vaccines	
Adverse events	Total	Adverse events	Total	Adverse events	Total	Adverse events	Total
	A & C		A & C		A		C
Headache	356	Headache	670	Injection site swelling	38	Pyrexia	448
Dizziness	209	Myalgia	334	Lymphadenitis	28	Rash	245
Dyspnoea	183	Pyrexia	282	Pyrexia	20	Vomiting	215
Pyrexia	160	Dizziness	268	Crying	17	Vaccine failure	199
Injection site pain	159	Injection site pain	243	Rash	17	Seizure	182
Chest pain	125	Fatigue	144	Abscess	16	Drug ineffective	165
Fatigue	124	Pain	125	Seizure	15	Crying	148
Injection site swelling	120	Nausea	124	Injection site erythema	14	Diarrhoea	139
Myalgia	114	Injection site swelling	123	Injection site pain	11	Pneumonia	117
Rash	113	Chills	104	Peripheral swelling	9	Injection site swelling	114

Table 9 Results of disproportionality analyses of the top ten reported adverse events following immunisation for the Ad26.COV2.S COVID-19 vaccine for datasets A (NDoH-EPI) and C (NDoH-EPI augmented)

	Dataset A (NDoH-EPI)				Dataset C (NDoH-EPI augmented)			
Preferred term	*a*	ROR	ROR CI	IC CrI**	*a*	ROR	ROR CI*	IC CrI**
Headache	670	2.47	2.16	0.39	670	5.11	4.50	1.10
Myalgia	334	3.74	3.01	0.53	334	7.45	6.09	1.27
Pyrexia	282	1.95	1.61	0.23	282	1.35	1.17	0.10
Dizziness	268	1.54	1.28	0.09	268	3.28	2.75	0.81
Injection site pain	243	1.76	1.44	0.16	243	3.44	2.85	0.83
Fatigue	144	1.41	1.11	-0.03	144	2.81	2.23	0.64
Pain	125	1.29	0.99	-0.11	125	1.96	1.56	0.34
Nausea	124	1.76	1.33	0.08	124	2.72	2.13	0.60
Injection site swelling	123	0.93	0.73	-0.35	123	1.52	1.22	0.11
Chills	104	2.54	1.81	0.25	104	4.75	3.47	0.92

Shaded cells represent signals of disproportionate reporting on the basis of lower 95% credibility limit

EPI expanded programme on immunisation, *IC* information component, *NDoH* National Department of Health, *ROR* reporting odds ratio

*(95% confidence interval (CI) lower boundary)

**(95% credibility interval (CrI) lower boundary)

myocarditis/pericarditis. Signals of disproportionate reporting also appear for deep vein thrombosis (DVT) and disseminated intravascular coagulation (DIC) in dataset C.

4 Discussion

4.1 AEFI Reporting Rates

South Africa's first case of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was reported on 5 March 2020, and by 12 October 2023, there were 4,072,522 laboratory-confirmed cases and 102,595 deaths reported [15]. In this retrospective pharmacovigilance study of AEFI and AESI reported to NDoH during the COVID-19 vaccine rollout, we observed several signals of disproportionate reporting for both Ad26.COV2.S and BNT162b2 vaccines. These signals largely aligned with AEFI observed globally. AEFI reporting rates varied across demographic features. A comparison of reporting rates with those of other countries revealed underreporting. Augmented database analyses revealed potential masking, highlighting data limitations.

Overall, 3846 AEFI were reported from 17 May 2021 to 31 December 2022, during which 37,537,009 doses of BNT162b2 and Ad26.COV2.S were administered. The overall AEFI reporting rate was 10.2 per 100,000 doses

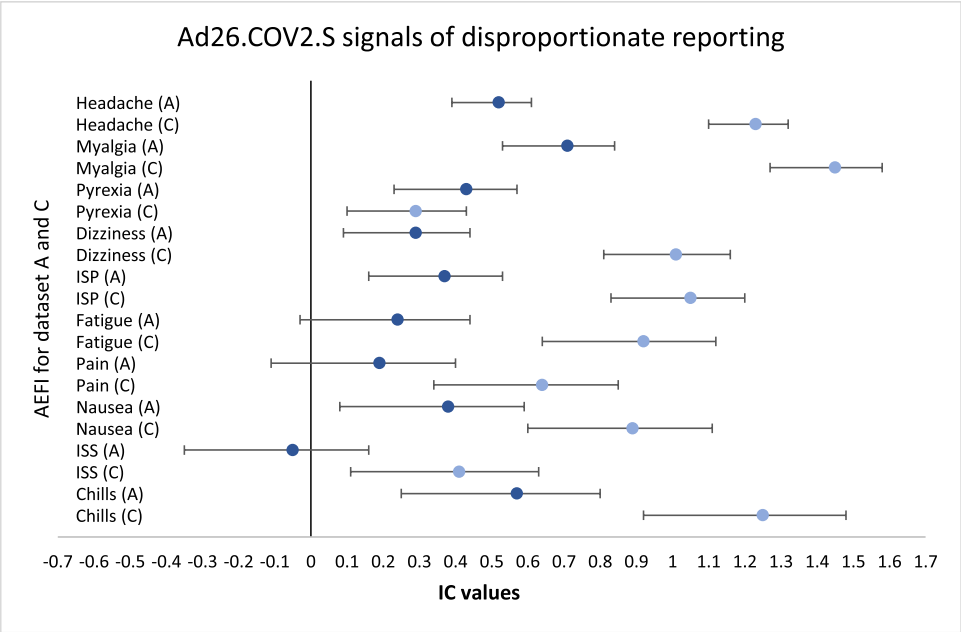

Fig. 2 Plot of the disproportionality analyses (indicating the lower limit of the 95% credibility interval of the information component (IC) on the *x*-axis) of the top ten reported AEFI for the Ad26.COV2.S vaccine for dataset A (NDoH-EPI) and C (augmented NDoH-EPI)

ISS: injection site swelling; ISP: injection site pain

Table 10 Results of disproportionality analyses of the top ten reported adverse events following immunisation with the BNT162b2 vaccine for datasets A (NDoH) and C (NDoH augmented) (shaded cells represent signals of disproportionate reporting)

Preferred term	Dataset A (NDoH-EPI)				Dataset C (NDoH-EPI augmented)			
	a	ROR	ROR CI*	IC CrI**	*a*	ROR	ROR CI*	IC CrI**
Headache	356	0.46	0.40	-0.74	356	1.17	0.15	-0.03
Dizziness	209	0.72	0.60	-0.47	209	1.70	1.42	0.25
Dyspnoea	183	2.51	1.90	0.25	183	3.08	2.47	0.67
Pyrexia	160	0.49	0.40	-0.82	160	0.52	0.43	-0.96
Injection site pain	159	0.58	0.47	-0.67	159	1.32	1.08	-0.0003
Chest pain	125	3.57	2.44	0.32	125	7.96	5.55	1.08
Fatigue	124	0.82	0.64	-0.44	124	1.79	1.42	0.23
Injection site swelling	120	0.70	0.55	-0.56	120	1.23	0.99	-0.99
Myalgia	114	0.31	0.25	-1.32	114	0.77	0.62	-0.58
Rash	113	1.73	1.27	0.01	113	0.94	0.76	-0.37

EPI expanded programme on immunisation, *IC* information component, *NDoH* National Department of Health, *ROR* reporting odds ratio

*(95% CI lower boundary)

**(95% CrI lower boundary)

administered. A consolidated global report compiled by the Pan American Health Organization, reported AEFI rates ranging from 10.99/100,000 to 67.8/100,000 doses [16]. AEFI reporting rates for Argentina (67.8/100,000), and Colombia (58/100,000) [16], which have similar economic profiles and population sizes to South Africa, were 5–6 times higher than South Africa's. AEFI surveillance relies on spontaneous reporting, and as such, underreporting is inevitable. Our low reporting rate may be indicative of underreporting in our setting.

Reporting rates by vaccine type differed substantially, with reporting rates of 18.1/100,000 and 7.9/100,000 for Ad26.COV2.S and BNT162b2, respectively. This observation aligned with findings in other countries. Canada reported rates of 243.24/100,000 and 47.32/100,000 for Ad26.COV2.S and BNT162b2, respectively [16]. A descriptive study on the frequency of AEFI with different SARS-CoV-2 vaccines in the Netherlands found that 82% of Ad26.COV2.S recipients reported at least one adverse event, compared with 45.2% of BNT162b2 recipients [17]. In addition, a cross-sectional study in Italy reported

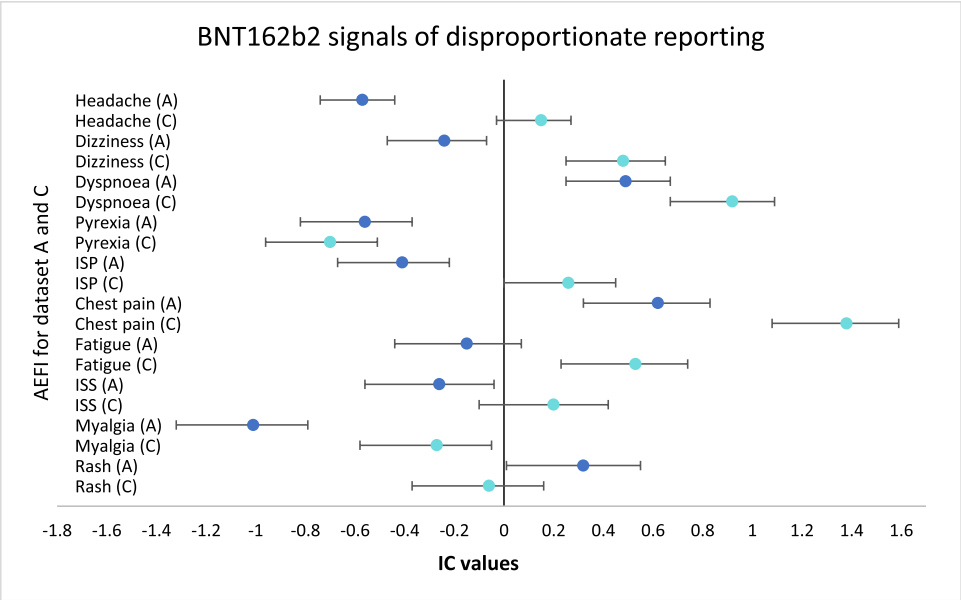

Fig. 3 Plot of disproportionality analyses of the top ten reported AEFI (indicating the lower limit of the 95% credibility interval of the information component (IC) on the *x*-axis) for the BNT162b2 vaccine for dataset A (NDoH-EPI) and C (augmented NDoH-EPI). *ISP* injection site pain, *ISS* injection site swelling

ISS: injection site swelling; ISP: injection site pain

Table 11 Results of disproportionality analyses of relevant reported adverse events of special interest in relation to the Ad26.COV2.S vaccine for datasets A (NDoH-EPI) and C (NDoH-EPI augmented)

	Dataset A (NDoH-EPI)				Dataset C (NDoH-EPI augmented)			
Preferred term	*a*	ROR	ROR CI*	IC CrI**	*a*	ROR	ROR CI*	IC CrI**
Guillain-Barré Syndrome	6	2.41	0.60	-0.91	6	0.90	0.36	-1.52
Myocarditis/Pericarditis	3	0.11	0.04	-4.37	3	0.25	0.08	-3.63
Myocarditis/Pericarditis (inclusive definition)	14	0.33	0.18	-1.95	14	0.70	0.39	-0.94
Non-hemorrhagic stroke	0	0	0	-12.22	0	0	0	-11.68
Hemorrhagic stroke (inclusive definition)	1	0.40	0.04	-4.41	1	0.72	0.08	-5.04
Deep vein thrombosis	8	0.74	0.31	-1.45	8	1.64	0.69	-0.76
Deep vein thrombosis (inclusive definition)	12	0.58	0.29	-1.45	12	1.32	0.67	-0.70
Pulmonary embolism	9	0.77	0.33	-1.34	9	1.43	0.64	-0.80
Pulmonary embolism (inclusive definition)	10	0.75	0.34	-1.31	10	1.43	0.67	-0.73
Disseminated intravascular coagulation (inclusive definition)	2	0.22	0.05	-3.95	2	0.52	0.12	-1.57
Immune thrombocytopenia	0	0	0	-11.26	0	0	0	-12.53
Immune thrombocytopenia (inclusive definition)	9	0.54	0.25	-1.66	9	0.78	0.37	-1.40
Thrombosis with thrombocytopenia	-	-	-	-	-	-	-	-

Shaded cells represent signals of disproportionate reporting

EPI Expanded Programme on Immunisation, *IC* information component, *NDoH* National Department of Health, *ROR* reporting odds ratio

*(95% Confidence Interval (CI) lower boundary)

**(95% Credibility Interval (CrI) lower boundary)

an adjusted odds ratio of 2.06 for AEFI reported in relation to the Ad26.COV2.S vaccine compared with that of the BNT162b2 vaccine [18]. Our reporting rates for serious/severe AEFI for each of the vaccine types were quite similar, with a slightly higher reporting rate for Ad26.COV2.S (4.7/100,000) compared with BNT162b2 (4.4/100,000). Overall, lower levels of reactogenicity have been reported for the BNT162b2 vaccine, compared with

Table 12 Results of disproportionality analyses of relevant reported adverse events of special interest in relation to the BNT162b2 vaccine for datasets A (NDoH-EPI) and C (NDoH-EPI augmented)

Preferred term	Dataset A (NDoH-EPI)				Dataset C (NDoH-EPI augmented)			
	a	ROR	ROR CI*	IC CrI**	*a*	ROR	ROR CI*	IC CrI**
Guillain-Barré Syndrome	3	0.48	0.12	-2.61	3	0.33	0.10	-3.22
Myocarditis/Pericarditis	34	10.87	3.34	0.26	34	20.76	7.36	1.00
Myocarditis/Pericarditis (inclusive definition)	50	3.20	1.79	0.11	50	5.83	3.50	0.78
Non-hemorrhagic stroke	3	0	0	-1.29	3	0	0	-0.72
Hemorrhagic stroke (inclusive definition)	3	2.86	0.30	-1.61	3	3.64	0.61	-1.23
Deep vein thrombosis	13	1.55	0.64	-0.68	13	3.51	1.50	0.03
Deep vein thrombosis (inclusive definition)	25	1.99	1.00	-0.28	25	4.68	2.39	0.47
Pulmonary embolism	14	1.48	0.64	-0.66	14	2.62	1.23	-0.11
Pulmonary embolism (inclusive definition)	16	1.53	0.69	-0.59	16	2.78	1.36	-0.01
Disseminated intravascular coagulation (inclusive definition)	11	5.25	1.16	-0.34	11	13.37	2.96	0.40
Immune thrombocytopenia	1	0	0	-3.22	1	0.40	0.05	-4.54
Immune thrombocytopenia (inclusive definition)	20	2.12	0.96	-0.33	20	2.21	1.21	-0.07
Thrombosis with thrombocytopenia	-	-	-	-	-	-	-	-

Shaded cells represent signals of disproportionate reporting

EPI expanded programme on immunisation, *IC* information component, *NDoH* National Department of Health, *ROR* reporting odds ratio

*(95% confidence interval (CI) lower boundary)

**(95% credibility interval (CrI) lower boundary)

reactogenicity to other mRNA-based and adenovirus-vector vaccines [19, 20].

We observed differential administration rates of both vaccines across provinces in South Africa. However, AEFI reporting rates were not distributed in similar ratios to vaccine administration rates across provinces. The rural North West Province had the lowest AEFI reporting rate (1.6/100,000), despite having the third highest rate of Ad26.COV2.S doses administered per 100,000 persons (19,529/100,000). In contrast, the urban Western Cape Province had one of the lowest rates of Ad26.COV2.S doses administered per 100,000 persons (10,831/100,000), but the highest AEFI reporting rate (59.5/100,000). This pattern, however, is not consistent across other rural and urban provinces. For example, Gauteng Province, South Africa's economic hub, had a relatively small Ad26.COV2.S AEFI reporting rate of 8.1/100,000. Variation of AEFI reporting rates across provinces can likely be attributed to differences in system functionality, provincial capacity and resources.

4.2 Signals of Disproportionate Reporting of AEFI

In dataset A, seven AEFI presented as signals of disproportionate reporting in relation to the Ad26.COV2.S vaccine (Table 9). Headache, nausea, myalgia, and injection site pain all appear on the vaccine PI, listed as 'very common' side effects, occurring at a frequency of ≥ 1/10 recipients [21]. Therefore, despite underreporting, our AEFI surveillance system detected signals that concur with AEFI frequencies from clinical trials and post-marketing surveillance. Pyrexia and chills are also listed in the Ad26.COV2.S PI as common side effects (≥ 1/100 to < 1/10), and dizziness as uncommon (≥ 1/1000 to < 1/100) [20]. Among the very common side effects listed on the PI, fatigue was not identified as a signal by the IC but was identified by the ROR in dataset A.

Regarding the BNT162b2 vaccine, we identified signals of disproportionate reporting for dyspnoea, chest pain, and rash (Table 10). Rash is listed in the PI as uncommon (≥ 1/1000 to < 1/100) whilst dyspnoea and chest pain are absent [22]. Myocarditis/pericarditis has been shown to be associated with BNT162b2. Chest pain is a commonly reported symptom of myocarditis/pericarditis [23] and presented as a signal in relation to the BNT162b2 vaccine. It is possible that some cases of chest pain could be undiagnosed mildly symptomatic cases of myocarditis/pericarditis; however, this cannot be assumed. Dataset A analyses did not detect signals for side effects that were listed as very common or common in the BNT162b2 PI. Disproportionality analysis is highly

dependent on the data used as the background rate. Given that background rates were calculated from a vaccines database, AEs that are common for several vaccines will not be detected. This is a likely explanation as to why side effects common to both BNT162b2 and Ad26.COV2.S vaccines were not detected for both vaccines.

Dataset C was used to ascertain whether there was masking. In total, 7416 additional non-COVID AEFI were added which created a more stable background rate. If masking is present, we would expect signals to become stronger or new signals to emerge. For Ad26.COV2.S, three new signals emerged for fatigue, pain and injection site swelling. All side effects categorized as 'very common' on the PI were identified by dataset C, and all but one classified as 'common'—injection site erythema—were identified. For BNT162b2, two signals emerged for fatigue and dizziness; both of which are listed in the vaccine PI as very common ($\geq$ 1/10) and uncommon ($\geq$ 1/1000 to < 1/100), respectively. For BNT162b2, rash appeared as a signal in dataset A and no longer presented as a signal in dataset C. The disproportionately large number of reports related to COVID-19 vaccines compared with other vaccines in dataset A has the potential to either mask existing signals or result in the generation of false associations. Stabilisation of the background rate is primarily driven by our need to elicit masking and to ensure that all safety signals are identified. However, this stabilisation of the background rate has the potential to identify false associations, which this signal of rash may be.

4.3 Signals of Disproportionate Reporting of AESI

Of the nine AESI evaluated in this study, Guillain–Barré syndrome, thrombosis with thrombocytopenia, venous thromboembolism, and myocarditis/pericarditis are all included in the PI. Myocarditis/pericarditis presented as a signal of disproportionate reporting in relation to BNT162b2. In dataset C, signals were elicited for DVT and DIC. The significance of this in relation to the BNT162b2 vaccine is not well documented. We did not detect signals in our dataset for any coagulopathies in relation to Ad26.COV2.S, shown to be associated with adenovirus-vectored vaccines [24]. Given the rarity of such events, and limitations associated with a symptom-based database for AESI detection, not detecting signals for some AESI is not surprising.

4.4 System and Database Limitations

In our study, we observed incomplete sharing of data between NDoH-EPI and SAHPRA databases (Fig. 1). Owing to incomplete data sharing and different data sources, not all data in the NDoH-EPI database contribute to VigiBase. Therefore, signals of disproportionate reporting regarding COVID-19 vaccines in the NDoH-EPI database may differ from those calculated from the SAHPRA database.

Other limitations regarding the use of SRS databases include the distribution of types of AEFI/AESI reported among different age, sex and ethnic groups. Prior to the pandemic, AEFI reported to NDoH-EPI were predominantly those that occurred among EPI program recipients. The nature and range of AEFI/AESI reported amongst persons 12 years and under differs from those seen in adults. The addition of non-COVID adult vaccination (non-EPI) AEFI to the augmented database was an attempt to reduce the impact of this issue.

A comprehensive evaluation of the South African AEFI surveillance system, involving both qualitative and quantitative analyses of numerous system attributes, identified broader areas in need of strengthening. The study identified that the system was heavily affected by under-resourcing, especially in more rural provinces. The study revealed that insufficient resourcing directly impacted reporting rates, investigation of suspected cases and causality assessment [25].

5 Conclusions

Limited research has been published on AEFI/AESI related to COVID-19 vaccines in Africa. This is likely owing to the limitations of national SRSs. As of 15 October 2023, AEFI reports from Africa only constituted 4% of global reports [26]. However, our study indicates that the South African surveillance system has the capacity for signal detection, and that signals that have emerged align with those reported globally. Suboptimal reporting rates, systems-based limitations and consequent methodological constraints around use of the database for signal detection have all been identified as areas for improvement.

There are several context-specific factors that may contribute to the underreporting of AEFI. These could include but are not limited to: insufficient awareness among members of the public and healthcare workers around the need to report AEFI/AESI, a lack of understanding of reportable AEFI, and fear or anger towards healthcare workers who inform a patient that a condition is an AEFI. Underlying issues need to be explored to determine context-specific areas in need of strengthening. Development of a single integrated database would streamline processes and create a satisfactory system for signal detection. Strengthening signal detection can assist in the development of a system for signal prioritization. The NISEC committee focuses on conducting causality assessment of serious/severe AEFI; a system of signal prioritization could assist the committee in systematically identifying potential risks and prioritizing

possible signals for causality assessment. To the best of our knowledge, this is the first pharmacovigilance study to emerge from a low- and middle-income (LMIC) post-COVID-19 that utilizes an SRS for signal detection and the first for South Africa. We have demonstrated the capability of the South African AEFI surveillance system to detect signals that align with those reported globally, despite evidence of underreporting. Signal detection is possible even within resource-limited settings. We propose further analyses to uncover evidence of masking and evaluation of system attributes to identify areas for system strengthening.

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Declarations

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

Consent to participate Not applicable

Consent for publication Consent was obtained from all co-authors, no other consent to publish was required

Data Availability Statement Data that support the findings in this manuscript are not openly available as they are sensitive patient-based data. Data can be made available from the corresponding author upon reasonable request

Author contributions All authors read and approved the final version of this manuscript. Chenoa Sankar—conceptualization, methodology, software, formal analysis, investigation, writing original draft, review and editing, and visualization; Stephen Evans—methodology, supervision, review and editing, and resources; Johanna Meyer, Hannah May Gunter, and Victoria Sekiti—review and editing, and resources; Kerrigan McCarthy—conceptualization, supervision, investigation, review and editing, and resources.

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