Drug Safety
https://doi.org/10.1007/s40264-023-01279-3

ORIGINAL RESEARCH ARTICLE

Adverse Events to SARS-CoV-2 (COVID-19) Vaccines and Policy Considerations that Inform the Funding of Safety Surveillance in Low- and Middle-Income Countries: A Mixed Methods Study

Comfort K. Ogar[1,2] · Jonathan Quick[1,3] · Hannah N. Gilbert[1] · Rick A. Vreman[2] · Aukje K. Mantel-Teeuwisse[2] · Jean Claude Mugunga[1,4]

Accepted: 6 February 2023

Abstract

Introduction/Objective Rapid global approval of coronavirus disease 2019 (COVID-19) vaccines and concurrent introduction in high-income countries and low- and middle-income countries (LMIC) highlights the importance of equitable safety surveillance of adverse events following immunization (AEFIs). We profiled AEFIs to COVID-19 vaccines, explored reporting differences between Africa and the rest of the world (RoW), and analyzed policy considerations that inform strengthening of safety surveillance in LMICs.

Methods Using a convergent mixed-methods design we compared the rate and profile of COVID-19 vaccines' AEFIs reported to VigiBase by Africa versus the RoW, and interviewed policymakers to elicit considerations that inform the funding of safety surveillance in LMICs.

Results With 87,351 out of 14,671,586 AEFIs, Africa had the second-lowest crude number and a reporting rate of 180 adverse events (AEs) per million administered doses. Serious AEs (SAEs) were 27.0%. Death accounted for about 10.0% of SAEs. Significant differences were found in reporting by gender, age group, and SAEs between Africa and the RoW. AstraZeneca and Pfizer BioNTech vaccines were associated with a high absolute number of AEFIs for Africa and RoW; Sputnik V contributed a considerably high rate of AEs per 1 million administered doses. Funding decisions for safety surveillance in LMICs were not based on explicit policies but on country priorities, perceived utility of data, and practical implementation issues.

Conclusion African countries reported fewer AEFIs relative to the RoW. To enhance Africa's contribution to the global knowledge on COVID-19 vaccine safety, governments must explicitly consider safety monitoring as a priority, and funding organizations need to systematically and continuously support these programs.

Key Points

The African region reported fewer adverse events following immunization than the rest of the world.

There is no explicit policy by some donor organizations to fund safety monitoring in low- and middle-income countries.

Systematic and sustainable funding is needed for equitable safety monitoring.

✉ Comfort K. Ogar
kunacom@yahoo.com

[1] Department of Global Health and Social Medicine, Harvard Medical School, Boston, USA

[2] Utrecht Centre for Pharmaceutical Policy and Regulation, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[3] Duke Global Health Institute, Duke University School of Medicine, Durham, USA

[4] Partners In Health, Boston, USA

Published online: 22 February 2023

1 Introduction

There is low reporting of the adverse events (AEs) of pharmaceutical interventions (medicines and vaccines) in many countries across the world, particularly in low- and middle-income countries (LMICs) [1–3]. Monitoring the safety of pharmaceutical interventions will provide evidence to support the introduction of newer interventions and continued safe use of existing ones in LMICs and the rest of the world (RoW).

As of August 31, 2022, when the last update was made, 33 coronavirus disease 2019 (COVID-19) vaccines had been authorized for limited use or approved for full use around the globe [4]. By December 15, 2022, about 13.03 billion doses of COVID-19 vaccines had been administered globally [5]. Among the people in LMICs, 25.1% have received at least one dose of the vaccine within this period [6]. As of December 13, 2022, 34.1% of Africa's population has received at least one dose of a vaccine, with 27.8% being fully vaccinated [7].

The fast-tracked development of the COVID-19 vaccines and use of new technologies in their development have raised safety concerns [8, 9]. There have been reported cases of potentially serious but rare AEs such as thrombosis with thrombocytopenia syndrome (TTS), pericarditis, myocarditis, and Guillain-Barré syndrome (GBS) [10, 11]. Anaphylaxis and local and systemic reactions are other well-documented AEs with COVID-19 vaccines [12]. These reports were identified from high-income countries' (HICs') with robust safety surveillance infrastructures.

Historically, there was a delay of many years between introducing new vaccines in HICs and LMICs. This delay allowed for the proper characterization of the safety profile of such vaccines before introduction in LMICs [13]. More recently, the need to improve timely and equitable access to pharmaceutical products and vaccines in LMICs has led to the simultaneous introduction of such products in LMICs and HICs [13]. The infrastructure for post-introduction pharmacovigilance (PIPV) in many LMICs remains relatively weak [14], thus creating the need for donor/funding organizations to support the establishment of safety surveillance systems in LMICs to ensure equitable safety surveillance [15]. Not all LMICs can be funded for this, and priorities may need to be set. Thus, it is helpful to understand the policies and key considerations that inform which countries receive financial support to establish or strengthen existing systems. This work aims to profile the adverse events following immunization (AEFIs) with COVID-19 vaccines submitted to VigiBase—the World Health Organization's (WHO's) global database of individual case safety reports (ICSRs)—to explore the difference in reporting between Africa, with limited PIPV systems, and the RoW, and to understand the key considerations that inform the decisions made by donor organizations to strengthen safety surveillance systems in LMICs.

2 Methods

We undertook a convergent mixed-methods research [16], comprising quantitative analysis of AEFIs with COVID-19 vaccines reported to VigiBase and qualitative in-depth individual interviews of key policymakers from donor/funding organizations, to understand the policy considerations that inform the decision to support the establishment of safety surveillance systems in LMICs.

2.1 Quantitative Study Design, Setting, and Data Cleaning

We conducted secondary analysis of de-identified data on the AEs of COVID-19 vaccines reported to VigiBase from December 2020 to March 14, 2022. VigiBase is the WHO's global database of ICSRs and contains over 30 million ICSRs of suspected AEs of medicines and vaccines submitted by over 170 member countries of the WHO Program for International Drug Monitoring (PIDM) since 1968. The database is continuously updated with new reports from passive surveillance systems, active surveillance studies, or other safety surveillance systems implemented by participating countries [17, 18].

The data obtained from VigiBase were descriptively analyzed at the individual AE level and not at the level of ICSRs. The dataset contains information on the vaccines associated with the reported AEFI, age group, and the gender of those reporting the AEFIs. It also contains information on whether the event was serious or not, the reason for seriousness, and the event's outcome, among other variables. An AEFI is defined as "any untoward medical occurrence that follows immunization and does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease" [19]. The terms "adverse events" (AEs) and "adverse events following immunization" (AEFIs) are used interchangeably in this study. A serious adverse event (SAE) is "an adverse reaction that results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect" [19].

Data on administered doses of COVID-19 vaccines were obtained from the published literature to estimate reporting rates for each WHO region. Where no data on administered doses were readily available in the public domain as far as

we were aware, the administered doses were extrapolated using available population data for the region and available data on doses administered per 100 persons (see electronic supplementary material [ESM]# 1 for data sources). Similarly, data from the WHO AFRO region on administered doses of COVID-19 vaccines received by vaccine type were used in combination with the total number of administered doses to estimate the administered doses for each vaccine and to facilitate the calculation of reporting rate by vaccine type for the region. Similar calculations were not done for other regions due to the non-availability of such data for some regions. Data were analyzed using STATA/BE 17.0 to provide descriptive statistics on demographic characteristics. Prior to data analysis, observations that were coded as either "unknown," "other," or "not applicable" were omitted from variables such as gender, age group, outcome, seriousness, and reporting type to ensure consistency across analyzed data. Observations where the vaccine name could not be definitively established were also omitted. Care was taken to ensure that the observations were omitted from only the relevant variables and not dropped from the entire dataset; hence, some totals may not always add up. The frequency of AEFIs was calculated by vaccine type, age group, and gender. Reporting AE rate per 1 million administered doses by vaccine type was not calculated for the RoW due to the non-availability of data on vaccine distribution/administration for some regions. The frequency of AEFIs by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) and the preferred term were assessed and reported as percentages. MedDRA® is a standardized medical terminology used for coding AEs in clinical trials and pharmacovigilance. Chi-square test was used to detect any differences in the proportion of reported AEFIs between Africa and the RoW for key parameters.

2.2 Qualitative Study Design

2.2.1 Study Population/Sampling Approach

Key policymakers from some donor/funding or global organizations that support safety surveillance of COVID-19 vaccines in LMICs at the time of the study were invited to participate in the virtual interview. We used purposeful sampling to identify interview participants to ensure the inclusion of persons who are key policy/decision-makers or those leading implementation of safety surveillance activities within the organizations. This sampling strategy allowed us to select participants based on information richness, as we sampled for individuals who would be information-rich cases, capable of providing us with rich data to help answer the research question. The first author compiled a list of 18 potential participants and their email addresses, with support from a key informant from one of the funding/implementing organizations. A request for an in-depth interview and an informed consent form were sent via email to all persons on the list.

2.2.2 Data Collection

Single, in-depth individual interviews were conducted with 12 key policymakers. Interviews were conducted with the aid of a semi-structured interview guide (see ESM# 2) that covered the following topics: (1) involvement in the safety surveillance of vaccines; (2) institutional policies that inform funding for safety surveillance; (3) criteria for selecting LMICs to be funded; and (4) key challenges and benefits associated with safety surveillance in LMICs. The interview guide allowed the interviewer to ask probing questions to gain greater insights into the interviewee's thoughts and experiences. The first author conducted in-depth interviews in English, and they lasted approximately 45–90 mins. Interviews were conducted virtually via Zoom at a time chosen by the participant and were video and audio recorded with written informed consent from participants.

2.2.3 Data Analysis

Data analysis was done using an inductive, thematic, content analysis approach to develop categories [20]. Following a complete review of the dataset, a subset of transcripts was open-coded to identify a draft codebook that represented interviewees' experiences with funding and or implementing safety surveillance for vaccines. The codebook was piloted and reviewed with members of the study team and finalized. All transcripts were coded using Dedoose® qualitative data management software [21].

The coded data were reviewed inductively to identify thematic content, which resulted in a set of draft categories. Final category and subtheme development involved an iterative process of reviewing the draft categories, coded data, and revisiting the interview scripts as necessary to provide additional depth and detail.

Finally, the quantitative and qualitative results were integrated using a joint display technique [22] to show where data from the quantitative review and qualitative interview converged or overlapped. See ESM# 3 for an illustration of the convergent mixed-methods approach used for the study.

3 Results

3.1 Profile of AEs with COVID-19 Vaccines

A total of 2,353,018 ICSRs containing 14,671,586 AEs of COVID-19 vaccines were contained in VigiBase as of March

2022. There were multiple AEs reported within ICSRs, with an average of six AEs per ICSR. The African region contributed the second-lowest number of overall reported AEs both in absolute numbers 87,351 (0.6%) as well as overall estimated reporting rates (180 per estimated million doses administered); see Table 1. AEs from the spontaneous (or passive) reporting system accounted for 96.7% of the reported AEs from Africa, whereas 3.3% were from studies. For RoW, these percentages were 95.0% and 5.0%, respectively. Africa's total contribution of AEs from studies was 2890 (0.4%) compared to 725,414 (99.6%) from the RoW (Table 2).

Overall, and for the RoW, reported AEs for females (73.6%) were higher than for males (26.4%). Within Africa, reporting between females and males was well balanced, with 53.2% reporting from females and 46.8% from males. Persons aged 18–44 years in both Africa and RoW had the highest number of AEs, at 63.4% and 46.7% of total reported AEs, respectively.

SAEs accounted for 12.2% of AEs reported from Africa compared to 27.1% for the RoW. Death was reported in 728 (10.1%) of SAEs from Africa as the reason for seriousness, compared to 211,546 (9.6%) for the RoW. Regarding outcome, 61.4% of the AEs reported from the African region had resolved at the time of reporting, similar to 58.2% of the AEs from the RoW.

3.2 Distribution of AEs by Vaccine Type and SOC

For the RoW, the Cormirnaty/Pfizer BioNTech vaccine, with 47.8%, had the highest percentage of reported AEs in absolute terms, followed by Vaxzevria/AstraZeneca, with 24.7%. For the African region, Vaxzevria/AstraZeneca had the highest, at 71.0%, followed by Cormirnaty/Pfizer BioNTech vaccine, at 12.3% (Table 3). For AE reporting rate per 1 million doses administered by identifiable vaccine type, AstraZeneca had the highest AE rate, at 701, closely followed by Sputnik V with 623 AEs per 1 million doses administered (Table 4). These rates are much higher than the overall rates of 180 per million doses for the overall reports (Table 1) and 178 per 1 million doses for identifiable vaccine types (Table 4) within the region. Similarly, the African region had a relatively large percentage of AEs reported for the Sputnik V vaccine (20.3% of all reported AEs for this vaccine).

For both Africa and the RoW, general disorders and administration site disorders were the most frequently associated SOC, at 34.7% and 26.5%, respectively. This was followed by nervous system disorders and musculoskeletal and connective tissue disorders (Africa 20.3%/RoW 13.7% and Africa 11.5%/RoW 11.2%, respectively). Headache (11.4%) was the most frequently reported AE for Africa, followed by pyrexia (8.6%) and injection site pain (7.5%), while chills (5.0%), headache (4.6%), and dizziness (4.3%) were the top three AEs for the RoW (Table 3).

3.3 Demographics of Interview Participants

A total of 12 key policymakers who accepted to be interviewed and consented were interviewed. Nine of the interviewees were male. Eight of them resided in the USA, two in Switzerland, and one each in Malaysia and South Africa.

3.4 Categories and Subthemes

Our qualitative findings revealed that many funding organizations do not have an explicit policy that informs the decision to fund LMICs for safety surveillance. Such decisions were often influenced by considerations about country priorities, the utility of the evidence generated, the perceived value added to global health by safety systems, and practical implementation issues. The main findings are summarized into three main categories and subthemes. A joint display table (Table 5) illustrates where findings from the quantitative study overlap with themes identified in the qualitative

Table 1 Distribution of overall adverse events and estimated adverse events per 1 million administered doses by World Health Organization (WHO) region

WHO region	Overall adverse events reported in dataset (as of March 14, 2022)	Doses administered (as of April 28, 2022)	Adverse events per 1 million doses
Africa	87,351	484,809,996	180
Americas	5,994,887	1,803,251,031	3324
Eastern Mediterranean	314,618	699,762,251[a]	450
Europe	7,081,924	1,556,921,620	4549
Southeast Asia	57,835	2,820,443,340	21
Western Pacific	1,134,971	4,171,260,000[a]	272
Global total	14,671,586	11,477,767,378	1278

[a]Doses extrapolated using assumptions in electronic supplementary material (ESM) # 1

Table 2 Comparison of key parameters between adverse events (AEs) from the African region and the rest of the world (RoW)

Parameter	Total, *n* (%)	Reported AEs within Africa vs RoW		Reported AEs between Africa and RoW	
		Africa, *n* (%)	RoW, *n* (%)	Africa, %	RoW, %
Reporting type ($n = 14{,}618{,}444$) $P < 0.001$					
Spontaneous reporting	13,890,140 (95.0)	84,013 (96.7)	13,806,127 (95.0)	0.6	99.4
Report from studies	728,304 (5.0)	2890 (3.3)	725,414 (5.0)	0.4	99.6
Total[a]		86,903 (0.6)	14,531,541 (99.4)		
Gender ($n = 14{,}523{,}111$) $P < 0.001$					
Male	3,836,029 (26.4)	40,358 (46.8)	3,795,671 (26.3)	1.1	99.0
Female	10,687,082 (73.6)	45,868 (53.2)	10,641,214 (73.7)	0.4	99.6
Total		86,226 (0.6)	14,436,885 (99.4)		
Age group ($n = 13{,}172{,}391$) $P < 0.001$					
0–27 days	1526 (0.0)	142 (0.2)	1384 (0.0)	9.3	90.7
28 days–23 months	7086 (0.1)	268 (0.3)	6818 (0.1)	3.8	96.2
2–11 years	5588 (0.0)	196 (0.3)	5392 (0.0)	3.5	96.5
12–17 years	176,773 (1.3)	82 (0.1)	176,691 (1.4)	0.0	100.0
18–44 years	6,165,552 (46.8)	49,522 (63.4)	6,115,940 (46.7)	0.8	99.2
45–64 years	4,634,543 (35.2)	22,086 (28.3)	4,612,457 (35.2)	0.5	99.5
65–74 years	1,323,148 (10.0)	4018 (5.2)	1,319,130 (10.1)	0.3	99.7
≥ 75 years	858,265 (6.5)	1760 (2.3)	856,505 (6.5)	0.2	99.8
		78,074 (0.6)	13,094,317 (99.4)		
Serious ($n = 14{,}658{,}954$) $P < 0.001$					
No	10,701,325 (73.0)	76,723 (87.8)	10,624,602 (72.9)	0.7	99.3
Yes	3,957,629 (27.0)	10,628 (12.2)	3,947,001 (27.1)	0.3	99.7
Total		87,351 (0.6)	14,571,603 (99.4)		
Seriousness ($n = 2{,}217{,}855$) $P < 0.001$					
Death	212,274 (9.6)	728 (10.1)	211,546 (9.6)	0.3	99.7
Life threatening	351,713 (15.9)	1671 (23.2)	350,042 (15.8)	0.5	99.5
Caused/prolonged hospital stay	1,151,809 (51.9)	2222 (30.9)	1,149,587 (52.0)	0.2	99.8
Disability/incapacitation	500,161 (22.6)	2561 (35.6)	497,600 (22.5)	0.5	99.5
Congenital anomaly/birth defect	1898 (0.1)	8 (0.1)	1890 (0.1)	0.4	99.6
Total		7190 (0.3)	2,210,665 (99.7)		
Outcome ($n = 9{,}254{,}309$) $P < 0.001$					
Recovered/resolved	5,390,192 (58.3)	49,561 (61.4)	5,340,631 (58.2)	0.8	99.2
Recovering/resolving	1,745,259 (18.9)	18,098 (22.4)	1,727,161 (18.8)	1.0	99.0
Not recovered/not resolved	1,978,864 (21.4)	11,732 (14.5)	1,967,132 (21.4)	0.6	99.4
Recovered/resolved with sequelae	87,276 (1.0)	616 (0.8)	88,660 (1.0)	0.7	99.3
Fatal	50,718 (0.6)	699 (0.9)	50,019 (0.6)	1.5	98.5
Total		80,706 (0.9)	9,173,603 (99.1)		
Fatal outcome ($n = 9{,}254{,}309$) $P < 0.001$					
Yes	50,718 (0.6)	699 (0.9)	50,019 (0.6)	1.5	98.5
No	9,203,591 (99.5)	80,007 (99.1)	9,123,584 (99.5)	0.8	99.2
Total		80,706 (0.9)	9,173,603 (99.1)		

[a]Total numbers do not always add up due to missing values

Table 3 Distribution of reported adverse events (AEs) by vaccine type and most frequently associated system organ class (SOC) after omitting missing variables and vaccines with unclassifiable names

Parameter	Name	Total, *n* (%)	Reported AEs within Africa vs RoW		Reported AEs between Africa and RoW	
			Africa, *n* (%)	RoW, *n* (%)	Africa, %	RoW, %
Vaccine type[a] (*n* = 14,601,398)	Vaxzevria/AstraZeneca	3,643,320 (25.0)	61,133 (71.0)	3,582,187 (24.7)	1.7	98.3
	Cormirnaty/Pfizer BioNTech	6,955,029 (47.6)	10,662 (12.3)	6,944,367 (47.8)	0.2	99.8
	Janssen COVID-19 vaccine	611,274 (4.2)	7027 (8.1)	604,247 (4.2)	1.2	98.9
	Covilo/Sinopharm	183,199 (1.3)	2770 (3.2)	180,447 (1.3)	1.6	98.4
	Sputnik V	11,922 (0.1)	2416 (2.8)	9506 (0.1)	20.3	79.7
	CoronaVac/Sinovac	135,713 (0.9)	1405 (1.6)	134,308 (0.9)	1.0	99.0
	SPIKEVAX (Moderna)	3,060,923 (21.0)	1078 (1.3)	3,059,845 (21.1)	0.0	99.9
	Total	14,601,398	86,491 (0.6)	14,514,907 (99.4)		
Reported AEs[b]	Headache	682,719 (4.7)	9959 (11.4)	672,760 (4.6)		
	Pyrexia	555,905 (3.8)	7499 (8.6)	548,406 (3.8)		
	Injection site pain	450,538 (3.1)	6568 (7.5)	443,970 (3.0)		
	Dizziness	632,349 (4.3)	4872 (5.6)	627,477 (4.3)		
	Chills	735,626 (5.0)	3132 (3.6)	732,494 (5.0)		
	Total	14,671,586	87,351	14,584,235		
SOC[b]	General disorders and administration site disorder	3,444,547	26,373 (34.65)	3,418,174 (26.5)	0.8	99.2
	Nervous system disorders	1,776,763	15,476 (20.3)	1,761,287 (13.7)	0.9	99.1
	Musculoskeletal and connective tissue disorder	1,453,500	8762 (11.5)	1,44,738 (11.2)	0.6	99.4
	Injury, poisoning	954, 865	4230 (5.6)	950,635 (7.4)		
	Gastrointestinal disorders	800,300	4193 (5.5)	796,107 (6.2)		

COVID coronavirus disease 2019, *RoW* rest of the world

[a]Frequency calculated for only vaccines with identifiable/verifiable names

[b]Only the 5 most frequently reported AEs and SOC associated with AEs are presented

Table 4 Estimated adverse events (AEs) per 1 million doses by vaccine type for the World Health Organization (WHO) AFRO Region

Vaccine type	Reported AEs		Vaccines distributed in Africa as of April 20, 2022		Reported AEs per 1 million doses
	Number[a]	%	Number[b]	%	
Vaxzevria/AstraZeneca	61,133	70.7	87,265,799	18	701
Sputnik V	2416	2.8	3,878,480	1	623
Cormirnaty/Pfizer BioNTech	10,662	12.3	87,265,799	18	122
Janssen COVID-19 vaccine	7027	8.1	106,658,199	22	66
Covilo/Sinopharm	2770	3.2	72,721,499	15	38
CoronaVac/Sinovac	1405	1.6	33,936,700	7	41
SPIKEVAX (Moderna)	1078	1.3	29,088,600	6	37
Other	NA	NA	63,025,299	13	NA
Total	86,491		484,809,996		178

COVID coronavirus disease 2019, *NA* data not available

[a]Frequency calculated for only vaccines with identifiable/verifiable names, as shown in Table 2

[b]Estimated using the total number of administered vaccines and percentage of vaccine types administered in Africa using data as of April 28, 2022, from the WHO AFRO dashboard [4]

Table 5 Joint display of convergent data from quantitative and qualitative findings

Category	Evidence	Supporting quantitative data	Interpretation
(Not) prioritizing safety monitoring	'I was on the phone with the Minister of Health for [city name] trying to get them to do vaccine safety assessment because they were using the Russian Sputnik COVID vaccine, and no one knows that much about that. And his response was "God I've got enough problems I don't want to find any vaccine safety issue, I'll currently keep up what I'm doing.'" KI-11	A relatively large share of AEs reported for Sputnik V and Sinopharm vaccines originated from Africa (26.7% and 5.1%, respectively) despite having relatively lower (1% and 15%, respectively) numbers of vaccines distributed within the region	Africa may be receiving vaccines with limited information on their safety. Robust surveillance systems are needed to generate the data needed for their continued and safe use within the region
	"I think that many programs see vaccine safety surveillance as a threat because they don't come, there's a reluctance to look for things that they are uncomfortable to have to react to. And maybe they aren't fully prepared to react to them." KI-05	African countries received an estimated 4.2% (485/11,560 million doses) of vaccines distributed and contributed 0.6% of the vaccine safety data in VigiBase	A perceived inability to effectively respond to AEs may contribute to a reluctance to detect and report them
Perceived utility of the safety surveillance system	"Sometimes the systems are different—the way that you report and collect data are different… Things like sore arms, you might get a little fever the day after. We call those reactivity to the vaccine; it's not really a complication, it's one of the responses that you get because your immune system is reacting to the vaccine, so you may get fever and stuff. What countries have more difficulty capturing are the serious adverse events..." KI-06	Statistically significant difference between Africa and RoW in AEs from the different reporting systems ($P < 0.001$). Systemic and local reactions (headache, pyrexia, injection site pain, dizziness and chills) were the most frequently reported reactions for Africa and RoW	The perception that spontaneous reporting systems are useful but tended to capture mainly non-serious and well-documented events. More robust systems are needed for effective safety surveillance in LMICs
	"You have certain uniqueness in certain populations. For instance, you have certain populations where it's an aging population. You [may] find that there are actually a cluster of deaths occurring in those aging populations, or in younger populations, or maybe in a population with particular characteristics." KI-19	Statistically significant differences between Africa and RoW in the number of AEs reported by gender and age group ($P < 0.001$)	There may be population-specific differences between Africa and RoW that need to be understood. Robust studies are needed to detect if such differences really exist

Table 5 (continued)

Category	Evidence	Supporting quantitative data	Interpretation
Robust systems that contribute to global knowledge on safety	"Ultimately you need countries that have the capacity to identify people who have serious medical problems and then figure out what their medical history is. For example, figure out that medical history involves getting a vaccine in the previous few weeks." KI-09	12.6% of reports from Africa are SAEs vs 87.4% for non-SAEs. For the RoW, it was 26.1% SAEs vs 74% non-SAEs	Reporting systems in Africa capture fewer SAEs and so do not seem to be contributing to the global knowledge on COVID-19 vaccines to their full potential.
	"The other kinds of studies are surveillance projects like the hospital sentinel sites surveillance. Those will feed more into the global understanding of the vaccines because if you can successfully link the hospitalization data to the immunization data you may actually find more of these unusual things. But you will also be able to understand better the actual rate which these things happen because, you have a denominator that you can understand a bit better and so hopefully you'll understand more at what frequency do these things occur and that sort of information is going to be really important for the global community. I mean understanding if there's a difference in using these vaccines in Africa compared to Western Europe. They may behave differently—some of these adverse events may not occur with the same frequency everywhere and so understanding that will be really important." KI-06	About 5% (143/2890) of reports from studies in Africa were SAEs compared to 12% (90,690/725,414) for RoW with more robust data collection systems. Statistically significant differences between number of SAEs and SAEs with a fatal outcome reported from Africa vs RoW ($P < 0.001$)	Few safety studies are undertaken in Africa, and these studies record few SAEs

AE adverse event, *COVID-19* coronavirus disease 2019, *KI* key informant, *LMICs* low-and middle-income countries, *RoW* rest of the world, *SAE* serious adverse event

study; additional qualitative evidence is provided in the table to further support the themes described below.

3.4.1 Category 1: (Not) Prioritizing Safety Surveillance as a Key Component of Health System Strengthening

Prioritizing coverage over safety Participants expressed the view that many LMICs placed more emphasis on rates of overall vaccine coverage and did not perceive safety as a priority. Thus, the majority of funds available for health system strengthening (HSS) are dedicated to the procurement of syringes and needles, cold chain equipment, supply chain logistics, and staff training that directly support vaccine coverage. A minuscule amount of the funds available for HSS is used to support safety surveillance.

> The vast majority of the health system strengthening funding is geared towards trying to address issues around making sure that children get vaccinated, or in GAVI jargon "coverage." (Key Informant-05, male policymaker)

Playing the Ostrich Although safety monitoring is acknowledged as part of HSS, many countries are reluctant to prioritize safety because they fear that safety data will draw attention to vaccine safety issues. Participants opined that decision-makers sometimes prefer to avoid setting up safety monitoring systems and instead "play the ostrich," believing that if they do not look for AEs, they will not find any, and consequently all will be well, and they will have peace.

> The problem is that some health ministers want to stick their head in the sand and if there's a problem, they don't want to know about it. The problem is that with social media, the problem will surface anyway and they won't have any idea how to evaluate it. (Key Informant-07, male policymaker)

Adequate Handling of Data on AEs Participants noted that for countries to prioritize safety, there must be capacity within the country to handle safety issues. They advocated for strong collaborations between regulators and key stakeholders, and highlighted the importance of effective communication and feedback mechanisms. Participants emphasized the importance of relevant committees to undertake benefit–risk evaluation of safety signals, suggesting that in the absence of these committees, safety surveillance would remain a low priority in many LMICs.

> Regulators also have to be responsive. In the sense that once they get the information, what do they do with the information? Once they have analyzed, if there is any finding …, do they also give feedback to the healthcare workers to say yes, we've seen this information, this is what we are getting? Because there has to be a two-way sort of feedback mechanism where those that are providing information also know that their time is not wasted. (Key Informant-12. female Policymaker)

3.4.2 Category 2: Perceived Utility of the Safety Surveillance System

Generate evidence for decision-making at the local level Participants explained that many LMICs lack systems to collect locally generated data. As a result, in-country, population-level decisions are based on data generated from HICs where the systems and infrastructure for generating such data are available.

> One of the biggest challenges from the [organization name] perspective right now is the fact that we are making decisions for low- and middle-income countries based on data available in high income countries which I personally think is not correct. (Key Informant-11, male policymaker)

Interviews highlighted the potential of using data generated in LMICs to understand major disease patterns (morbidities and mortalities), as well as access to care in those settings. Such data are useful for benefit–risk analysis and can be leveraged to answer specific questions that may be relevant for the introduction or continued use of certain products in particular populations or geographic locations of interest. Localized safety surveillance systems can generate data to support course-correcting measures for public health programs and inform appropriate regulatory decisions. Participants shared experiences where local safety surveillance systems preemptively identified problems that could have derailed mass vaccination campaigns. Sometimes, these problems may not be related to an inherent characteristic of the vaccine product but to its handling and administration. One participant shared this example:

> For example, in the episode in [Country X] where somebody used pancuronium [a muscle relaxant] as a diluent for a vaccine. What they discovered is that the vials looked very similar, same color, pattern and everything. (Key Informant-03, male policymaker)

Improving public/global health and equity Interviewees expressed the view that implementing safety monitoring should be an integral part of an effective global immunization strategy that seeks to achieve equity in global vaccine coverage and safety. They support safety surveillance systems as a vital component of the "complete package" that should accompany the introduction of any vaccine, with the expectation that safety surveillance is central to improving global health security and disease elimination/eradication.

> I think it's part of the package. I mean we would not be doing our job correctly if we were to offer countries vaccines and that was it and I mean we didn't help them to set up the monitoring mechanisms and the distribution mechanisms and so on. And so vaccine safety and adverse effect reporting is a necessary part of that. (Key Informant-03, male policymaker)

A standard part of introducing a new intervention such as a vaccine is having a risk management plan that identifies potential risks and puts mitigation measures in place before any harm occurs. Participants indicated that, similar to the practice in HICs, having effective safety monitoring systems in LMICs will help to institutionalize risk management planning in parts of the world where it is not implemented as an early warning system.

> It's a shame when you have a product that is accompanied for example with the risk management plan in a high-income country; but it can be used in the absence of risk management elsewhere, to me that is a disparity that I think we understand that there is a need to reduce those inequities and disparities in how products are managed in order to either reduce risk or mitigate risk. (Key Informant-09, male policymaker)

Building robust systems that contribute to global knowledge on vaccine safety Respondents noted that many safety surveillance systems in LMICs rely on spontaneous reporting systems, which in many cases are still rudimentary. These systems are limited because they mainly identify more common, expected, and well-documented AEs. Strengthening spontaneous reporting systems remains a key objective for funders:

> For the spontaneous reporting, we sort of want all countries to have that. So, I think even when we're doing active surveillance strengthening, we want to make sure that some of that, some of that work is translating over to strengthening the passive system. (Key Informant-02, female policymaker)

Participants also noted that more robust surveillance systems that can identify rare, unexpected AEs are needed to improve LMICs' contribution to actual vaccine–AEFI associations, which can increase local and global knowledge of vaccine safety.

> If you have background rates of events and you can monitor that and do observed versus expected, so you know 10,000 people were vaccinated, you'd expect one event. If you saw 10, then you'd be concerned. But you can also use those cases to do more formal studies such as case control studies and case cohort studies and self-control studies. Basically, epidemiologic studies that allow you to see whether the association is real. (Key Informant-07, male policymaker).

3.4.3 Category 3: Practical Implementation Issues

Enabling and supportive political and bureaucratic environment within a country Participants indicated that politically stable countries with enabling governance and supportive bureaucratic systems make it easier for funding organizations to establish safety surveillance systems. Preexisting positive relationships fostered through ongoing projects were key considerations for funding organizations. Funders/implementers tended to avoid collaborations with countries that were perceived as having uncooperative bureaucracies, because they feared approval delays and political instability.

> We've been wary of countries that are, you know, having a lot of political instability because of that buy-in issue and just the logistics of doing work in that setting. (Key Informant-02, female policymaker)

Product availability/product pipeline Participants noted that sometimes the decision to fund specific LMICs to establish active safety surveillance or to strengthen existing passive surveillance systems depends on where new vaccines or those in the pipeline will become available. According to an interviewee:

> We put together a safety working group and one of the things they did was to look at the global health pipeline of when these new products are coming, like you know when are they coming, which of these products have let's say safety questions attached to them that you need more information on and then which countries are they going to… (Key Informant-01, male policymaker)

Existing capacity (technical and infrastructural) within a country The existing capacity to support safety surveillance within a country was identified by interviewees as a key consideration to support the establishment of a safety surveillance system. These capacities include basic infrastructure and a trained and experienced workforce.

> It really comes down to: Do they have sufficient number of qualified individuals to carry it out, Do they have sufficient resources for it? Do they have the enabling legislation for it? Do they have the tools? (Key Informant-09, male policymaker)

4 Discussion

Our quantitative study, which was mainly descriptive, found that countries in the African region reported relatively low numbers of AEs with COVID-19 vaccines compared to the RoW. About a quarter of all reported AEs in the dataset were serious, with hospitalization occurring in about 50% and death in 10% of the reports. Persons aged 18–44 years and females reported the greatest number of AEs for Africa and RoW, which can be expected given the relative size of this group. Well-documented local and systemic reactions including headache, pyrexia, injection site pain, dizziness, and chills were most frequently reported. General disorders and administrative site disorders, and nervous system disorders were the most affected SOCs. AstraZeneca and Pfizer BioNTech had the highest count of AEs in absolute terms for Africa and RoW, reflecting their widespread global use. In our qualitative studies, three main categories emerged from the insights shared by interview participants to explain how decisions to support LMICs to set up or strengthen existing surveillance systems are made. Many participants reflected that their organizations do not have an explicit policy for funding safety surveillance in LMICs. Such decisions tended to be based on how countries prioritize safety, the perceived utility/value of such safety surveillance systems, and the practical issues involved in setting up the systems.

The relatively low number of AEs with COVID-19 vaccines reported from the African region in our study is in line with other studies that have reported a lower reporting rate of AEs from Africa and other resource-limited settings [23, 24]. Historically, reporting of AEs in LMICs has always lagged behind reporting in HICs, where pharmacovigilance systems tend to be better established. A study showed that in 2015, the African and South-East Asian regions lagged behind most other regions in the number of reported AEFIs [25]. Until recently, safety surveillance in LMICs was considered a luxury as countries focused more on improving access to pharmaceutical interventions, including vaccines. However, support from many donor organizations towards improving access has also brought support for establishing safety surveillance systems in line with the practice in HICs [26].

Our analysis showed that overall, a considerable number of the reported AEs in the dataset were serious (27%) regardless of reporting source (passive or studies). A smaller percentage was reported for Africa. Close to 10% of the SAEs for Africa and the RoW indicated death as the reason for seriousness. Siddhartha et al. reported a lower frequency of 1% fatality for the SAEs in their analysis of AEs from VigiBase® in 2021 [27]. Within the first month of COVID-19 vaccination implementation, 9.2% ($n = 640$) of reports to the Vaccine Adverse Event Reporting System (VAERS) were SAEs, with 1.6% ($n = 113$) deaths [28]. Africa's contribution to the total SAEs in our data was less than 1%, with a statistically significant difference in reporting of SAEs and reporting by gender compared to the RoW. Given the morbidity and the economic and social burden imposed on individuals by SAEs [29, 30], monitoring systems that can pick up such reactions early and facilitate the implementation of preventive measures will be beneficial in Africa and other resource-constrained regions.

The AEs reported in this study are expected AEs that have been well documented from clinical trials and observational studies in HICs. In our study, systemic and local reactions, including headache, pyrexia, and injection site pain, were the top three most frequently reported AEs from the African region, while chills, headache, and dizziness were the top three in RoW. Gee et al. reported headache, fatigue, and dizziness as the most frequently reported symptoms in VAERs in the first month of vaccination with COVID-19 vaccines in the USA [28]. Other studies have reported similar findings [12, 31]. These findings reflect the views of some interviewees that post-introduction safety surveillance systems in many countries, including LMICs, detect mainly well-known and well-documented events. Reporting of known AEs is valuable because it contributes to evaluating the actual incidence of known AEs in the post-marketing phase, but the value of more robust and rigorous systems for safety surveillance in LMICs cannot be overemphasized. Fewer AEs were reported from studies conducted in Africa (3.3%) compared to the RoW (5.0%). This may reflect the limited infrastructure and funding available for more robust and rigorous hospital or sentinel site-based safety surveillance, which is more likely to identify serious and unexpected SAEs faster. Expanding the safety surveillance infrastructure for Africa will be a necessary step towards enhancing the region's active safety surveillance, promoting equitable safety monitoring, and contributing to global knowledge for protecting and promoting health.

Data from the African region showed that AstraZeneca, Pfizer BioNTech, and Janssen vaccines had higher absolute numbers of AEs. For the RoW, the order was Pfizer BioNTech, AstraZeneca, and Moderna. For the African region, AstraZeneca had the highest estimated rate of AEs per 1 million administered doses by vaccine type, followed by Sputnik V vaccine. Although Sputnik V constituted only about 1% of the vaccine doses administered within Africa as of April 28, 2022 [7], the high rate of reported AEs per 1 million doses relative to other vaccines administered in Africa is remarkable. This very high reporting rate for Sputnik V relative to other more widely distributed vaccines in Africa amplifies the concerns raised about the safety of vaccines from less established manufacturers [32] and the need for strong safety surveillance systems in Africa where

such vaccines are likely to be distributed. Reporting rates by vaccine type for Africa could not be compared with the RoW due to limited data on vaccine distribution for some regions. The reported event rates are crude reporting rates, which should be interpreted with caution in the absence of information on background rates of the events in the African population.

Participants in the qualitative study alluded that many funding organizations do not have an explicit policy that supports the decision to fund safety surveillance in LMICs. Such decisions tend to be influenced by several considerations including how recipient countries prioritize safety surveillance, the perceived utility of safety surveillance systems to generate data for local and global decision-making, and practical implementation issues such as existing capacity and the political environment within a country. Previous studies have shown that while safety surveillance (pharmacovigilance) activities were established early in developing countries following the thalidomide disaster of the early 1960s, many LMICs did not prioritize it for various reasons, including limited access to medicines, poor funding, limited technical capacity, and low awareness of its importance in healthcare [33–35]. In 2008, the support for the establishment or strengthening of safety surveillance in LMICs got a boost from The Roll Back Malaria partnership, which issued guidelines requiring the inclusion of pharmacovigilance in the Global Fund and other related proposals [36]. An analysis of 26 proposals submitted to the Global Fund after the guidelines were issued revealed that only 46% of proposals mentioned the establishment of pharmacovigilance systems. Subsequently, countries received guidelines and recommendations on how to include pharmacovigilance sections in their proposal for the Affordable Medicine Facility for malaria (AMFm) proposal from WHO and the Medicines for Malaria Venture (MMV) [36]. Several other funding organizations now provide various levels of support for safety surveillance in LMICs [37].

Interviewees noted that several practical issues, including the prevalent political and bureaucratic environment, available technical and infrastructural resources within countries, and the countries targeted for the introduction of new or planned interventions, influenced the decision about countries to support. The challenges with the implementation of pharmacovigilance in LMICs have been well documented [26, 33, 38]. It has been noted that it is only when regular and sustainable budget allocation is provided by the government that meaningful and long-term progress can be achieved, as seen in India and China [26]. Thus, it behooves governments in LMICs to prioritize not only vaccine coverage but also vaccine safety and to provide the enabling environment for robust safety surveillance to be carried out with government funding and with support from donor organizations.

4.1 Strengths and Limitations

A key strength of the study was drawing insights from key policymakers in the qualitative study. This allowed insights from qualitative evidence to explain some of the quantitative findings. Some of the key limitations of our study include the fact that most of the data were obtained from spontaneous reporting systems that rely on self-reporting, with the possibility of reporting bias resulting from heightened awareness about the safety of COVID-19 vaccines and uncertainty about the vaccines' contribution to the reported events. This may have led to overreporting and overestimation of the burden of AEs. Also, ICSRs submitted to VigiBase do not typically contain certain information that allows some analysis to be done, such as the cause of death for fatal cases. Secondly, some regions did not have information on the doses administered (denominator) to support rate calculations. We have extrapolated the vaccine doses administered in those regions. These rates need to be interpreted with caution because AEs from spontaneous reporting systems and other reporting sources were combined in the numerator data, and the background rates of the reported AEs are unknown. In addition, the distribution of the different vaccine types could not be obtained for all regions, making it difficult to calculate the relative contribution of each vaccine to the reported AEs in this work. Another limitation of the study is that countries in the different regions have varying types of approved vaccines, vaccine distribution, and submission of ICSRs to VigiBase; hence, the comparison between regions needs to be interpreted with caution. Finally, for the qualitative study, the voices and perspectives of the PIPV implementers in recipient countries were not captured to understand what challenges they may be facing with safety surveillance and their proposals on how best to handle such challenges. Interview participants were selected based on the need to provide information-rich insights from the funder's perspective, and we did not use a pre-selected theoretical framework to inform the wording and phrasing of the questions.

This study did not do a detailed review of the types and seriousness of the reported AEs by vaccine type. For Africa, there is a need to undertake such studies to fully understand the contribution of each vaccine to the profile of reported AEFIs.

5 Conclusion

Countries in Africa reported fewer AEFIs with COVID-19 vaccines in VigiBase relative to the RoW, with statistically significant differences in the reporting of key parameters, such as gender, age group, and serious reactions, that warrant further investigation. Funding organizations mostly do

not have systematic approaches for deciding where funding may be allocated. Such decisions were influenced by country priorities, the perceived value added by the evidence generated by such systems to local and global decision-making, a desire to achieve equity in global vaccine coverage and safety through an effective global immunization strategy, and practical implementation issues. African countries and other countries in LMICs need robust safety surveillance systems to generate good data to inform decisions. Continuous support from national governments and donor/funding organizations will enhance equitable safety monitoring and Africa's contribution to the global knowledge on COVID-19 vaccine safety in particular and the safety of other pharmaceutical interventions in general.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-023-01279-3.

Acknowledgements We wish to acknowledge the contribution of Patrick C. Souverein of Utrecht University, who helped with extracting the VigiBase data that was used for the quantitative study. We acknowledge all the key policymakers from the different organizations that provided their rich perspectives during the interview that informed the qualitative component of this work. We use this opportunity to honor a pharmacovigilance hero, Sten Olsson, who was instrumental in the establishment of a pharmacovigilance system in many countries in Africa. He was a member of the team that developed the protocol for this work. VigiBase, the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC), is the source of the information used for the quantitative component of this study. The information comes from a variety of sources, and the probability that the suspected adverse effect is drug related is therefore not the same in all cases. The information provided in this study does not represent the opinion of the UMC or the WHO.

Declarations

Funding Comfort K. Ogar received funds from Harvard University and the Ronda Stryker and William Johnston MMSc Fellowship in Global Health Delivery to undertake the research work as part of her master's thesis work. However, no funding support was received for the writing of the manuscript. The Global Health and Social Medicine (GHSM) department of Harvard Medical School (HMS) paid the fee for open access publication of this article.

Conflict of interest Comfort K. Ogar received funds from Harvard University and the Ronda Stryker and William Johnston MMSc Fellowship in Global Health Delivery to undertake the research work as part of her master's thesis work. No funding support was received for the writing of the manuscript. Jean Claude Mugunga, Hannah N. Gilbert, Jonathan Quick, Rick A. Vreman, and Aukje K. Mantel-Teeuwisse declare no conflict of interest.

Ethics approval The Harvard Institutional Review Board (IRB) determined that the quantitative study was not human subject research under 45 Code of Federal Regulations (CFR) 46.102(e), and additional IRB review was not required. The Nigerian Health Research and Ethics Committee (NHREC) also determined that the quantitative study meets the criteria for exemption under the National Code for Health Research Ethics and was exempt from the NHREC oversight. Because it involved secondary analyses of de-identified data, informed consent was not obtained. Similarly, the Harvard IRB determined that the qualitative study meets the criteria for exemption under the regulations found at 45 CFR 46.104(d) (2) and as such did not require further IRB review. The NHREC reviewed and approved the qualitative study and written informed consent with the following approval number NHREC/01/01/2007-03/08/2021.

Consent to participate The quantitative study was secondary analyses of de-identified data and did not require informed consent. All participants in the qualitative study provided written informed consent to participate prior to the interview.

Consent for publication Not applicable. No participant information is contained in the article, and therefore, consent for publication was not sought from participants.

Availability of data and materials The datasets generated during and/or analyzed during the current study are not publicly available due to confidentiality requirements for handling reports of adverse reactions but may be made available from the corresponding author on reasonable request upon approval from the Uppsala Monitoring Centre (UMC).

Code availability Not applicable.

Author contributions CKO conceived the study and developed the protocol for the study. JCM, HNG, RAV, and AKM-T reviewed the protocol. CKO analyzed the data and drafted the manuscript. JCM, HNG, JQ, RAV, and AKM-T reviewed and approved the data analysis and manuscript. All authors read and approved the final version.

References

1. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96.
2. Suresh Bowalekar MK. Extent of Under Reporting of Adverse Drug Reactions (ADRs) in India: Evaluation using Logistic Regression Analysis (LRA) Model. J Clin Trials [Internet]. 2014. http://www.omicsgroup.org/journals/extent-of-under-reporting-of-adverse-drug-reactions-adrs-in-india-evaluation-using-logistic-regression-analysis-lra-model-2167-0870.1000155.php?aid=23793. Accessed 1 Aug 2021.
3. Tandon VR, Mahajan V, Khajuria V, Gillani Z. Under-reporting of adverse drug reactions: a challenge for pharmacovigilance in India. Indian J Pharmacol. 2015;47(1):65–71.
4. Zimmer C, Corum J, Wee SL. Coronavirus Vaccine Tracker. The New York Times [Internet]. 2022 Apr 21. https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html. Accessed 9 Feb 2021.
5. Holder J. Tracking Coronavirus Vaccinations Around the World. The New York Times [Internet]. 2022 Apr 28. https://www.nytim

es.com/interactive/2021/world/covid-vaccinations-tracker.html. Accessed 20 July 2021.
6. Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, et al. Coronavirus Pandemic (COVID-19). Our World Data [Internet]. 2022 Apr 28. https://ourworldindata.org/covid-vaccinations. Accessed 9 Oct 2021.
7. WHO AR. Africa COVID-19 Vaccination dashboard [Internet]. Africa COVID-19 Vaccination dashboard. 2022. https://app.powerbi.com/view?r=eyJrIjoiOTI0ZDlhZWEtMjUxMC00ZDhhLWFjOTYtYjZlMGYzOWI4NGIwIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9. Accessed 6 Apr 2022.
8. Li Y-D, Chi W-Y, Su J-H, Ferrall L, Hung C-F, Wu T-C. Coronavirus vaccine development: from SARS and MERS to COVID-19. J Biomed Sci. 2020;27(1):104.
9. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med. 2020;382(21):1969–73.
10. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA Vaccines. Circulation. 2021;144(6):471–84.
11. WHO. Updated recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 [Internet]. 2021. https://www.who.int/news/item/30-07-2021-updated-recommendations-for-use-of-the-chadox1-s-recombinant-vaccine-against-covid-19. Accessed 7 Aug 2021.
12. Wu Q, Dudley MZ, Chen X, Bai X, Dong K, Zhuang T, et al. Evaluation of the safety profile of COVID-19 vaccines: a rapid review. BMC Med. 2021;19(1):173.
13. Izurieta HS, Zuber P, Bonhoeffer J, Chen RT, Sankohg O, Laserson KF, et al. Roadmap for the international collaborative epidemiologic monitoring of safety and effectiveness of new high priority vaccines. Vaccine. 2013;31(35):3623–7.
14. Graham JE, Borda-Rodriguez A, Huzair F, Zinck E. Capacity for a global vaccine safety system: the perspective of national regulatory authorities. Vaccine. 2012;30(33):4953–9.
15. Amarasinghe A, Black S, Bonhoeffer J, Carvalho SMD, Dodoo A, Eskola J, et al. Effective vaccine safety systems in all countries: a challenge for more equitable access to immunization. Vaccine. 2013;31:B108–14.
16. Creswell JW, Clark VLP. Designing and conducting mixed methods research. London: SAGE; 2011.
17. Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic Facts | SpringerLink. Ther Innov Regul Sci. 2008;42:409–19.
18. Uppsala Monitoring Centre. About VigiBase [Internet]. 2022. https://who-umc.org/vigibase/. Accessed 6 Apr 2022.
19. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP)—Annex I—Definitions (Rev 4). 2017 Oct 9;EMA/876333/2011 Rev 4:33.
20. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;1(15):1277–88.
21. Home | Dedoose [Internet]. 2022. https://www.dedoose.com/. Accessed 6 Apr 2022.
22. Guetterman TC, Fetters MD, Creswell JW. Integrating quantitative and qualitative results in health science mixed methods research through joint displays. Ann Fam Med. 2015;13(6):554–61.
23. Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Olsson S, Sartori D, et al. Adverse drug reaction reporting in africa and a comparison of individual case safety report characteristics between africa and the rest of the world: analyses of spontaneous reports in VigiBase®. Drug Saf. 2016;39:335–45.
24. Jusot V, Chimimba F, Dzabala N, Menang O, Cole J, Gardiner G, et al. Enhancing pharmacovigilance in sub-Saharan Africa through training and mentoring: a GSK pilot initiative in Malawi. Drug Saf. 2020;43(6):583–93.
25. Lei J, Balakrishnan MR, Gidudu JF, Zuber PLF. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015. Vaccine. 2018;36(12):1577–82.
26. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. Expert Rev Clin Pharmacol. 2015;8(4):449–60.
27. Siddhartha D, Pankaj B, Sanchi S, Sanjeev M, Jaykaran C. Adverse events reported from the COVID-19 vaccines: a descriptive study based on the WHO database (VigiBaseR). J Appl Pharm Sci. 2021. https://doi.org/10.7324/JAPS.2021.110801.
28. Gee J, Marquez P, Su J, Calvert GM, Liu R, Myers T, et al. First month of COVID-19 vaccine safety monitoring—United States, December 14, 2020–January 13, 2021. Morb Mortal Wkly Rep. 2021;70(8):283–8.
29. Formica D, Sultana J, Cutroneo P, Lucchesi S, Angelica R, Crisafulli S, et al. The economic burden of preventable adverse drug reactions: a systematic review of observational studies. Expert Opin Drug Saf. 2018;17(7):681–95.
30. Goodman JC, Villarreal P, Jones B. The social cost of adverse medical events, and what we can do about it. Health Aff (Millwood). 2011;30(4):590–5.
31. Chen J, Cai Y, Chen Y, Williams AP, Gao Y, Zeng J. Nervous and muscular adverse events after COVID-19 vaccination: a systematic review and meta-analysis of clinical trials. Vaccines. 2021;9(8):939.
32. Pagliusi S, Jarrett S, Hayman B, Kreysa U, Prasad SD, Reers M, et al. Emerging manufacturers engagements in the COVID-19 vaccine research, development and supply. Vaccine. 2020;38(34):5418–23.
33. Isah AO, Pal SN, Olsson S, Dodoo A, Bencheikh RS. Specific features of medicines safety and pharmacovigilance in Africa. Ther Adv Drug Saf. 2012;3(1):25–34.
34. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries. Drug Saf. 2010;33(8):689.
35. Pirmohamed M, Atuah KN, Dodoo ANO, Winstanley P. Pharmacovigilance in developing countries. BMJ. 2007;335(7618):462.
36. Stergachis A, Bartlein RJ, Dodoo A, Nwokike J, Kachur SP. A situational analysis of pharmacovigilance plans in the Global Fund Malaria and US President's Malaria Initiative proposals. Malar J. 2010;9(1):148.
37. Nwokike J, Ludeman E, Thumm M. Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries [Internet]. Arlington, VA: Management Science for Health; 2013 Sep. p. 144. https://siapsprogram.org/publication/comparative-analysis-of-pharmacovigilance-systems-in-five-asian-countries/. Accessed 20 July 2022.
38. Shyam Bhaskaran, Preston C, Long R. Smart Safety Surveillance (3S): Proven Approach to Building Functional LMIC Pharmacovigilance Systems [Internet]. DIA Global Forum. 2021. https://globalforum.diaglobal.org/issue/december-2021/smart-safety-surveillance-3s-proven-approach-to-building-functional-lmic-pharmacovigilance-systems/. Accessed 29 July 2022.