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Familiarity, Knowledge and Practices of Healthcare Professionals Regarding the Pharmacovigilance of Biological Medicines in Lusaka, Zambia: A Multi-Facility Cross-Sectional Study

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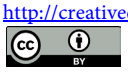
Abstract

Background: Pharmacovigilance of biological medicines is crucial because it ensures that medicines meet the World Health Organization (WHO) standards. In Zambia, there is little information on healthcare professionals' familiarity, knowledge and practices on the pharmacovigilance of biological and biosimilar medicines. Therefore, this study investigated the familiarity, knowledge, and practices related to the pharmacovigilance (PV) of biological and biosimilar medicines at selected hospitals in Lusaka, Zambia. **Methods**: The study was an analytical questionnaire-based cross-sectional study conducted among healthcare professionals (HCPs) at the Adult hospital, Cancer Diseases hospital, Paediatrics hospital and Women and New Born Hospital in Lusaka. Data were collected over four weeks in May and June 2021 and subsequently analysed using IBM SPSS version 21. The statistical significance was set at a 95% confidence interval. **Results**: Of 245 participants, only 115 (48.9%) of the HCPs were familiar with biological medicines to a basic understanding. Regarding the term biosimilars, most of the HCPs (40.9%) never heard of this word. The mean score for knowledge regarding the PV consid-



erations of biological medicines was 4.1 out of 8 questions. Most HCPs used non-proprietary names (44.2%) when prescribing, dispensing, or administering biological medicines. Additionally, more than half (57.3%) of HCPs did not record batch numbers when dispensing or administering biological medicines. **Conclusion**: Healthcare professionals were more familiar with the term biological medicines than biosimilars. Healthcare professionals generally scored poorly when their knowledge regarding the PV considerations of biological medicines was assessed. Thus, there is a need to provide adequate training and continuous professional development among healthcare professionals on the pharmacovigilance of biological and biosimilar medicines.

Keywords

Pharmacovigilance, Biological Medicines, Biosimilars, Brand, Batch, Zambia

1. Introduction

Biological medicines (BMs), defined as molecules derived from a biological source, do not have Adverse Drug Reactions (ADRs) properly quantified premarketing [1]. Furthermore, unlike small-molecule drugs, translation of preclinical data into clinical data is limited [2]. BMs are more immunogenic than small molecule drugs and have complex manufacturing processes [2], such that changes to a manufacturing process can result in differences between batches, which in some cases affects the benefit-risk balance of the medicines [3]. Another factor that may affect the safety of BMs is storage conditions; these molecules are quite sensitive such that even small changes to storage conditions may result in physical alterations, with consequent changes in their safety profile [4].

Biosimilars, similar to originator biological products in terms of quality, safety and efficacy, are manufactured by different companies using different manufacturing processes from each other and from the originator, which results in some structural differences between manufacturers. Despite this, originator BMs and biosimilars share the same international non-proprietary names (INN) [5]. Due to differences between biologicals produced by different manufacturers, agencies have adopted naming conventions for identification purposes. For example, the European Medicines Agency (EMA) uses INN, brand name, and manufacturer [6], while the Food and Drug Administration (FDA) guidelines require that each originator BM, related biological product, and biosimilar medicine bear a non-proprietary name in combination with a distinguishing suffix consisting of four lowercase letters that lack any meaning [7]. Furthermore, as some manufacturing changes [8] or distribution issues may affect the product's quality and subsequently its safety [9], robust pharmacovigilance (PV) systems should not only identify which biological medicine or biosimilar is affected but also which batches are affected [7].

The expiry of originator biological medicines patents has allowed develop-

ing countries such as Zambia to use more affordable biosimilars, several of which are currently registered with the Zambia Medicines Regulatory Authority (ZAMRA) [10]. As a member of the Southern African Development Community region, Zambia has aimed to harmonise PV of BMs with other countries in the region whilst ensuring they meet World Health Organization (WHO) global standards [4]. Some considerations highlighted by WHO are the mechanisms of traceability in case of adverse events, storage requirements of biologicals, manufacturing variability with consequent differences between batches and manufacturing companies, and immunogenicity [11].

Healthcare professionals (HCPs) must know that changes to the manufacturing process of BMs can result in immune reactions. They must possess the knowledge and understand biosimilar medicines and their PV [12]. This is important because poor knowledge of biological and biosimilar medicines can alter the confidence in the safety and efficacy of these products [13], as well as prescription [12]. Studies conducted elsewhere have revealed that HCPs are unfamiliar with originator biological and biosimilar medicines despite having them in their practice [14] [15] [16].

Healthcare professionals extract information to include in an ADR report from patient medical records (PMRs) [17]. For biological medicines, this means that brand names (or another identifier) and batch numbers must be used during the prescribing, dispensing, and administration, to be included in the ADR report for their PV to be effective. Studies conducted in other countries have shown that ADR reports have been made for these products, but in such a way that the responsible product, its batch number and manufacturer, cannot be traced [5] [15]. If this practice continues, the prescription of harmful originator biotherapeutic products and biosimilar medicines will continue.

Since the licensing of biological medicines in Zambia, there have been no studies to determine the familiarity of HCPs with biological and biosimilar medicines, knowledge of the factors (manufacturing process changes, immunogenicity, and storage) that alter the safety of biologicals, as well as the details required for proper identification of biologicals in reporting adverse events. Some biologicals currently used in Zambia are hospital administered, and some biosimilars are marketed by different marketing authorisation holders [10]. Currently, it is also unknown how these medicines are recorded during prescribing, dispensing, and administering to patients and if brand names or batch numbers are included in ADR reports.

This study investigated the familiarity, knowledge, and practices of HCPs regarding the PV of BMs at University Teaching Hospitals in Lusaka, Zambia.

2. Methods

2.1. Study Design, Setting and Population

The study was an analytical cross-sectional study conducted among pharmacists, pharmacy technologists, doctors, and nurses from the Adult hospital, Cancer diseases hospital, Paediatrics hospital and Women and New Born Hospital in

Lusaka, Zambia. A questionnaire (see **Appendix**) that was used in a similar study in Ireland [5], was adopted and modified to be used in the current study. Experts from academia, regulatory affairs, and hospital pharmacists did face and content validation of the questionnaire. The questionnaire was used to collect data on the sociodemographic characteristics of participants, 10 questions on ADR reporting, 2 questions on the familiarity with biological medicines, 8 questions on pharmacovigilance considerations of biological medicines, and 6 questions on practices regarding biological medicines among the participants. 2 questions were also asked on the familiarity with biosimilar medicines. Permission to conduct the study was sought from each hospital's administration, after which heads of departments distributed the questionnaires to HCPs who were willing to participate. The study was conducted over 4 weeks in May and June 2021. Excluded HCPs were those who did not give consent to participate in the study and those who were not available at the time of data collection.

2.2. Sample Size Calculation

The sample size was determined using Cochran's formula [18], adjusted for finite populations [19], and then for an 8.6% non-response rate (based on a non-response rate from a previous study [20], which was conducted in the same hospitals), giving a final sample size of 355. Due to the different numbers of HCPs from each hospital, disproportionate stratified sampling was used to obtain a representative sample of a profession from each hospital.

2.3. Data Analysis

Data were analysed using IBM SPSS version 21. Chi-squared test for independence was used to make comparisons between categorical variables. Participants' knowledge of the PV considerations of BMs was assessed by adding up correct items in that section of the questionnaire. The same was done for the knowledge of the conditions for reporting ADRs. A correct answer was given a score of 1 whilst an incorrect answer or "I don't know" was given a score of 0. Knowledge was considered "good" if scores were above 50%, whilst a score below 50% was considered poor. Kruskal Wallis H test was used to compare mean knowledge scores with demographics (profession, years of practice and area of practice). Mann-Whitney U test was used to confirm where the differences lay. A 5% significance level was applied through all testing, and a Bonferroni correction was applied when multiple group comparisons were made.

3. Results

A total of 245 responses were received following the distribution of 355 questionnaires, giving a total response rate of 69%. Seventy-six questionnaires were distributed to doctors (50 responded, 66%), 199 to nurses (132 responded, 66%) 51 pharmacists (43 responded, 84%), and 29 pharmacy technologists (20 responded, 69%). Ten questionnaires were excluded for analysis because the respondents were non-prescribing doctors, did not indicate their profession, or did

not indicate which hospital they practised at.

3.1. Demographics

Most respondents (40%) were from the Adult hospital, and most had been in practice for less than 5 years. The demographics of the HCPs are summarised in Table 1.

3.2. Familiarity with Biological Medicines and Biosimilars

Most HCPs were familiar with BMs and had a basic understanding (n = 115, 48.9%), whilst 96 (40.9%) had never heard of the term biosimilars (Table 2).

3.3. Knowledge of the Pharmacovigilance of Biological Medicines

Knowledge of the pharmacovigilance considerations of biological medicines

The mean knowledge score of the PV considerations of BMs for all HCPs was found to be 4.1 (SD 1.9). Mean knowledge scores varied by HCP (Table 3), as shown in Table 4.

Familiarity with the term "biological medicine" was associated with mean knowledge of the PV considerations of BMs (p = 0.001, Kruskal Wallis H test). Those who were very familiar had significantly higher scores (mean 4.9, SD 1.5), than those who had never heard of the term (mean 3.2, SD 1.9) (p < 0.001, Mann-Whitney U). Knowledge scores of those who were familiar with the term "biological medicine" were also significantly higher (mean 4.3, SD 1.6) than those who had never heard of the term (p = 0.002, Mann-Whitney U).

Table 1. Healthcare professional demographics.

	Doctor	Nurse	Pharmacist	Pharmacy technologist	Total
Group size	48 (20.4%)	128 (54.5%)	41 (17.4%)	18 (7.7%)	235
Area of Practice n (%)					
Adult hospital	19 (39.6)	39 (30.5)	22 (53.7)	14 (77.8)	94 (40.0)
Cancer Diseases Hospital	2 (4.2)	26 (20.3)	5 (12.2)	3 (16.7)	36 (15.3)
Paediatrics Hospital	10 (20.8)	27 (21.1)	6 (14.6)	1 (5.6)	44 (18.7)
Women and Newborn Hospital	17 (35.4)	36 (28.1)	8 (19.5)	0 (0)	61 (26.0)
Years in practice n (%)					
<5	17 (35.4)	54 (42.2)	17 (41.5)	9 (50.0)	97 (41.3)
5 - 9	13 (27.1)	38 (29.7)	12 (29.3)	9 (50.0)	72 (30.6)
10 - 19	10 (20.8)	17 (13.3)	9 (22)	0 (0)	36 (15.3)
20 - 30	5 (10.4)	9 (7.0)	2 (4.9)	0 (0)	16 (6.8)
>30	3 (6.2)	10 (7.8)	1 (2.4)	0 (0)	14 (6.0)

Table 2. Familiarity with biological and biosimilar medicines.

	Never heard of the term	Heard of the term-can't define it	Familiar - has a basic understanding	Very familiar - has a complete understanding	Total
Familiarity with the term biological medicine n (%)					
Doctor	5 (10.4)	16 (33.3)	21 (43.8)	6 (12.5)	48 (100)
Nurse	29 (22.7)	28 (21.9)	61 (47.7)	10 (7.8)	128 (100)
Pharmacist	2 (4.9)	7 (17.1)	23 (56.1)	9 (22.0)	41 (100)
Pharmacy technologist	0 (0)	3 (16.7)	10 (55.6)	5 (27.8)	18 (100)
Overall	**36 (15.3)**	**54 (23.0)**	**115 (48.9)**	**30 (12.8)**	**235 (100)**
Familiarity with the term biosimilar medicine n (%)					
Doctor	15 (31.2)	12 (25.0)	17 (35.4)	4 (8.3)	48 (100)
Nurse	63 (49.2)	25 (19.5)	38 (29.7)	2 (1.6)	128 (100)
Pharmacist	12 (29.3)	5 (12.2)	16 (39.0)	8 (19.5)	41 (100)
Pharmacy technologist	6 (33.3)	6 (33.3)	6 (33.3)	0 (0)	18 (100)
Overall	**96 (40.9)**	**48 (20.4)**	**77 (32.8)**	**14 (6.0)**	**235 (100)**

Table 3. Mean knowledge scores of the PV considerations of biological medicines.

Mean Knowledge of PV considerations of biological medicines (out of 8 questions)		
	Mean	SD
Doctor	5.0[a]	1.8
Nurse	3.4	1.7
Pharmacist	5.2[a]	1.6
Pharmacy technologist	4.7[b]	1.4
Overall	**4.1**	**1.9**

Knowledge levels were compared using the Mann-Whitney U test. A Bonferroni correction was applied. [a]Doctors and pharmacists had higher mean knowledge scores than nurses ($p < 0.001$ in both cases); [b]Pharmacy technologists had higher mean knowledge scores than nurses ($p = 0.002$).

Table 4. Knowledge of the pharmacovigilance considerations of biological medicines.

	N	% correct	% incorrect	% don't know
Biosimilars are the same as generic medicines (Correct answer = "No")				
Overall	235	40.0	20.9	39.1
Doctor	48	41.7	31.2	27.1
Nurse	128	28.1	20.3	51.6
Pharmacist	41	70.7	9.8	19.5
Pharmacy technologist	18	50.0	22.2	27.8

Continued

In an adverse drug reaction report, it is better to identify a biological medicine by its non-proprietary name instead of its brand name (Correct answer = "No")				
Overall	235	26.0	56.2	17.9
Doctor	48	37.5	54.2	8.3
Nurse	128	17.2	56.2	26.6
Pharmacist	41	41.5	56.1	2.4
Pharmacy technologist	18	22.2	61.1	16.7
In general, biological medicines pose a greater risk of immunogenicity than non-biological (chemical) medicines (Correct answer = "Yes")				
Overall	235	40.0	19.6	40.4
Doctor	48	62.5	16.7	20.8
Nurse	128	30.5	18.8	50.8
Pharmacist	41	53.7	24.4	22.0
Pharmacy technologist	18	16.7	22.2	61.1
Different batches of the same biological medicine are always identical (Correct answer = "No")				
Overall	235	53.2	17.0	29.8
Doctor	48	72.9	4.2	22.9
Nurse	128	43.8	13.3	43.0
Pharmacist	41	61.0	31.7	7.3
Pharmacy technologist	18	50.0	44.4	5.6
Rare adverse drug reactions resulting from changes to the manufacturing process of a biological medicine can always be predicted (Correct answer = "No")				
Overall	235	49.8	24.7	25.5
Doctor	48	64.6	14.6	20.8
Nurse	128	38.3	27.3	34.4
Pharmacist	41	63.4	31.7	4.9
Pharmacy technologist	18	61.1	16.7	22.2
It is more important to include batch numbers in adverse drug reaction reports for non-biological medicines than it is for biological medicines (Correct answer = "No")				
Overall	235	37.0	42.6	20.4
Doctor	48	35.4	47.9	16.7
Nurse	128	26.6	45.3	28.1
Pharmacist	41	53.7	36.6	9.8
Pharmacy technologist	18	77.8	22.0	0
Keeping a biological medicine outside its recommended storage conditions may introduce or alter immunogenicity (Correct answer = "Yes")				
Overall	235	81.3	7.2	11.5
Doctor	48	93.8	0	6.2

Continued

Nurse	128	72.7	10.9	16.4
Pharmacist	41	87.8	7.3	4.9
Pharmacy technologist	18	94.4	5.6	0
Adverse drug reactions associated with a patient changing between different brands of biological medicine should be reported (Correct answer = "Yes")				
Overall	235	85.5	6.0	8.5
Doctor	48	87.5	6.2	6.2
Nurse	128	80.5	6.2	13.3
Pharmacist	41	92.7	7.3	0.0
Pharmacy technologist	18	100.0	0.0	0.0

Familiarity with the term "biosimilar medicine" was associated with mean knowledge of the PV considerations of BMs ($p < 0.001$, Kruskal Wallis H test). HCPs who were very familiar with the term biosimilar medicine had significantly higher scores (mean 5.4, SD 1.3) than those who had never heard of the term (mean 3.6 SD 1.8), ($p < 0.001$, Mann-Whitney U test). Those who were familiar also had significantly higher scores (mean 4.6, SD 1.7) than those who had never heard of the term ($p < 0.001$, Mann-Whitney U test).

Area of practice was associated with knowledge regarding PV considerations of BMs ($p = 0.005$, Kruskal-Wallis H test). Those practicing at Adult hospital had higher knowledge (mean = 4.5, SD 1.8) than those practicing at Paediatrics hospital (mean = 3.7, SD 1.9) ($p = 0.003$, Mann-Whitney U), and Cancer Diseases Hospital (mean = 3.7, SD 1.7) ($p = 0.006$, Mann-Whitney U).

There was no association between knowledge of the PV considerations of BMs and years of practice ($p = 0.497$, Kruskal-Wallis H test).

3.4. Knowledge of ADR Reporting

Most HCPs knew that ADRs could be reported to the Zambia Medicines Regulatory Authority (ZAMRA) (n = 160, 68.1%). Most HCPs (n = 126, 53.6%) knew about reporting ADRs using hard-copy ADR report forms, while only 39 (16.6%) knew about the Med Safety app. Most HCPs (n = 168, 71.5%) had never reported an ADR before (Table 5).

A Chi-square test for independence revealed that those who had practised for over 10 years were more likely to have reported an ADR at least once ($p < 0.001$).

3.5. Knowledge of ADR Reporting Conditions

The mean knowledge scores relating to ADR reporting were calculated based on 7 questions regarding ADR reporting (Table 6). The mean score for all HCPs was 4.4 (SD 1.5) (Table 7).

HCPs who had reported ADRs at least 3 times had higher knowledge scores of ADR reporting conditions (mean = 5.6, SD 1.3) than those who had never reported

Table 5. Knowledge of reporting to ZAMRA, reporting methods and experience.

	Doctor	Nurse	Pharmacist	Pharmacy technologist	Total
Knowledge of reporting ADRs to ZAMRA before survey n (%)					
Yes	33 (68.8)	73 (57)	39 (95.1)[a]	15 (83.3)	160 (68.1)
No	15 (31.2)	55 (43)	2 (4.9)	3 (16.7)	75 (31.9)
Reporting via Hardcopy ADR report forms n (%)					
Yes	29 (60.4)	39 (30.5)	40 (97.6)	18 (100.0)	126 (53.6)
No	19 (39.6)	89 (69.5)	1 (2.4)	0 (0.0)	109 (46.4)
Reporting via The Med Safety app n (%)					
Yes	7 (14.6)	9 (7)	18 (43.9)	5 (27.8)	39 (16.6)
No	41 (85.4)	119 (93)	23 (56.1)	13 (72.2)	196 (83.4)
Reporting via the ZAMRA website n (%)					
Yes	14 (29.2)	27 (21.1)	30 (73.2)	11 (61.1)	82 (34.9)
No	34 (70.8)	101 (78.9)	11 (26.8	7 (38.9)	153 (65.1)
Have you ever reported an ADR n (%)					
No	32 (66.7)	103 (80.5)	17 (41.5)	16 (88.9)	168 (71.5)
Yes (1 time)	5 (10.4)	17 (13.3)	7 (17.1)[b]	1 (5.6)	30 (12.8)
Yes (2 times)	2 (4.2)	3 (2.3)	4 (9.8)[b]	0 (0)	9 (3.8)
Yes (≥3 times)	9 (18.8)	5 (3.9)	13 (31.7)[b]	1 (5.6)	28 (11.9)

Knowledge levels of reporting to ZAMRA and ADR reporting experience compared using the Chi-square test for independence. A Bonferroni correction was applied. [a]Pharmacists knowledge of reporting ADRs to ZAMRA was significantly higher than that of doctors and nurses ($p = 0.002$ and $p < 0.001$, respectively); [b]Pharmacists had significantly higher experience (1 time, 2 times, ≥3 times) in reporting ADRs compared to nurses and pharmacy technologists ($p < 0.001$ and $p = 0.001$ respectively).

Table 6. Knowledge of ADR reporting conditions.

	N	% correct	% incorrect	% don't know
Do you have adequate knowledge on how to report an adverse drug reaction? (Yes)				
Overall	235	37.9	51.1	11.1
Doctor	48	31.2	56.2	12.5
Nurse	128	25.0	62.5	12.5
Pharmacist	41	73.2	19.5	7.3
Pharmacy technologist	18	66.7	27.8	5.6
Healthcare professionals should report serious ADRs even if uncertain that the medicine caused the event (Correct answer = "Yes")				
Overall	235	77.4	12.3	10.2
Doctor	48	77.1	14.6	8.3
Nurse	128	76.6	10.9	12.5

Continued

Pharmacist	41	87.8	9.8	2.4
Pharmacy technologist	18	61.1	22.2	16.7
Healthcare professionals should report serious ADRs even if they do not have all the details of the event (Correct answer = "Yes")				
Overall	235	55.7	33.2	11.1
Doctor	48	45.8	43.8	10.4
Nurse	128	58.6	28.1	13.3
Pharmacist	41	58.5	36.6	4.9
Pharmacy technologist	18	55.6	33.3	11.1
All serious ADRs are known before the medicine is marketed (Correct answer = "No")				
Overall	235	51.5	38.3	10.2
Doctor	48	62.5	31.2	6.2
Nurse	128	35.9	48.4	15.6
Pharmacist	41	75.6	22.0	2.4
Pharmacy technologist	18	77.8	22.2	0
One case reported by a healthcare professional does not contribute much to knowledge on medicine risks (Correct answer = "No")				
Overall	235	70.6	20.0	9.4
Doctor	48	83.3	14.6	2.1
Nurse	128	60.2	26.6	13.3
Pharmacist	41	85.4	9.8	4.9
Pharmacy technologist	18	77.8	11.1	11.1
Patients can report adverse drug reactions independent of a healthcare professional (Correct answer = "Yes")				
Overall	235	60.0	24.3	15.7
Doctor	48	52.1	22.9	25.0
Nurse	128	61.7	21.9	16.4
Pharmacist	41	68.3	31.7	0
Pharmacy technologist	18	50.0	27.8	22.2
Healthcare professionals should report ADRs associated with overdose, misuse or error (Correct answer = "Yes")				
Overall	235	86.8	9.4	3.8
Doctor	48	81.2	14.6	4.2
Nurse	128	87.5	7.8	4.7
Pharmacist	41	87.8	9.8	2.4
Pharmacy technologist	18	94.4	5.6	0

Table 7. Mean knowledge scores of ADR reporting by profession.

Mean Knowledge of ADR reporting conditions (out of 7 question items)		
	Mean	**SD**
Doctor	4.3	1.6
Nurse	4.1	1.4
Pharmacist	5.3[a]	1.3
Pharmacy technologist	4.8	1.7
Overall	**4.4**	**1.5**

Mean ADR knowledge levels compared using the Mann-Whitney U test. A Bonferroni correction was applied. [a]Pharmacists had significantly higher mean knowledge scores compared to doctors and nurses ($p = 0.003$ and $p < 0.001$ respectively).

an ADR (mean = 4.2, SD 1.5), and those who had reported an ADR only once (mean = 4.3, SD 1.4). A statistically significant association existed between knowledge of ADR reporting conditions and the number of times HCPs had reported an ADR ($p < 0.001$, Kruskal Wallis H test). A Mann-Whitney U test showed that the mean knowledge of ADR reporting conditions of HCPs who had reported an ADR at least 3 times was higher than those who never reported ($p < 0.001$) and those who had reported only once ($p = 0.001$).

There was no relationship between years of practice and knowledge of ADR reporting conditions ($p = 0.792$, Kruskal Wallis H test) and area of practice and knowledge of ADR reporting ($p = 0.139$, Kruskal-Wallis H test).

3.6. The Practice of Biological Medicine Pharmacovigilance

Most HCPs indicated that BMs were prescribed, dispensed or administered in their practice (n = 199, 84.7%). However, 3.8% (n = 9) said they were not used, while 11.5% (n = 27) did not know. Of the HCPs who indicated that they used BMs in their practice, only 9% (n = 18) had ever reported an ADR caused by them (Table 8).

Most HCPs (n = 88, 44.2%) used non-proprietary names in prescribing, dispensing, or administering BMs, and 114 (57.3%) did not record batch numbers during dispensing/administering of BMs (Table 8).

When asked to rank the value of brand names and batch numbers when prescribing, dispensing and administering BMs to patients, HCPs thought using batch numbers was more valuable than using brand names. However, HCPs regarded the recording of batch numbers when dispensing and administering BMs as more difficult than brand name recording (Table 9).

There was a difference in the value and ease of use placed on brand names and batch number recording among HCPs (Table 10).

There was no statistically significant association between the value HCPs placed on the use of brand names when prescribing, dispensing, or administering BMs with their knowledge of the use of brand names or non-proprietary names when reporting an ADR caused by a BM ($p = 0.714$, Kruskal Wallis). There

Table 8. Brand name and batch number recording practices.

	Doctors	Nurses	Pharmacist	Pharmacy technologist	All HCPs
Have you ever reported an ADR caused by biological medicines n (%)					
Yes	6 (14.3)	7 (6.8)	5 (13.5)	0 (0)	18 (9)
No	35 (83.3)	95 (92.2)	32 (86.5)	16 (94.1)	178 (89.4)
I don't know	1 (2.4)	1 (1.0)	0 (0)	1 (5.9)	3 (1.5)
Overall	42 (100)	103 (100)	37 (100)	17 (100)	199 (100)
How are biological medicines recorded when prescribing/dispensing/administering n (%)					
Brand name	5 (11.9)	14 (13.6)	6 (16.2)	2 (11.8)	27 (13.6)
Non-proprietary name	18 (42.9)	47 (45.6)	17 (45.9)	6 (35.3)	88 (44.2)
Both brand and non-proprietary names	18 (42.9)	30 (29.1)	14 (37.8)	9 (52.9)	71 (35.7)
I don't know	1 (2.4)	9 (8.7)	0 (0)	0 (0)	10 (5.0)
Varies by medicine	0 (0)	3 (2.9)	0 (0)	0 (0)	3 (1.5)
Overall	42 (100)	103 (100)	37 (100)	17 (100)	199 (100)
Are batch numbers recorded when dispensing/administering biological medicine n (%)					
Yes	10 (23.8)	17 (16.5)	7 (18.9)	3 (17.6)	37 (18.6)
No	17 (40.5)	55 (53.4)	29 (78.4)	13 (76.5)	114 (57.3)
I don't know	15 (35.7)	31 (30.1)	1 (2.7)	1 (5.9)	48 (24.1)
Overall	42 (100)	103 (100)	37 (100)	17 (100)	199 (100)

Table 9. Value and ease of use of brand names and batch numbers in clinical practice.

	n	Mean score	Standard Deviation
Worthless (1) - Valuable (7)			
Brand name recording	199	5.9	1.6
Batch number recording	199	6.1	1.6
Easy (1) - Difficult (7)			
Brand name recording	199	3.8	2.0
Batch number recording	199	5.2	1.6

Table 10. HCP value and ease of use with brand name and batch number recording.

	N	**Mean score**	**Standard Deviation**
Brand name recording Worthless (1) - Valuable (7)			
Doctor	42	6.6[a]	0.9
Nurse	103	5.9	1.6
Pharmacist	37	5.1	2.1
Pharmacy technologist	17	6.3	1.4

Continued

Brand name recording Easy (1) - Difficult (7)			
Doctor	42	3.9	2.1
Nurse	103	3.8	1.9
Pharmacist	37	4.3	1.9
Pharmacy technologist	17	3.1	1.8
Batch number recording Worthless (1) - Valuable (7)			
Doctor	42	6.7[b]	0.8
Nurse	103	5.8	1.8
Pharmacist	37	6.0	1.8
Pharmacy technologist	17	6.8	0.6
Batch number recording Easy (1) - Difficult (7)			
Doctor	42	4.7	1.7
Nurse	103	5.0	1.6
Pharmacist	37	5.7[c]	1.5
Pharmacy technologist	17	5.9[d]	1.5

Value and ease of use of brand names and batch numbers among HCPs in PMRs compared using Mann Whitney U test. A Bonferroni correction was applied. [a]Doctors valued the use of brand names more than pharmacists ($p = 0.002$); [b]Doctors valued the use of batch numbers significantly more than nurses ($p = 0.004$); [c]Pharmacists regarded the recording of batch numbers when dispensing or administering biological medicines to patients as more difficult than doctors and nurses ($p < 0.001$ and $p = 0.006$ respectively); [d]Pharmacy technologists regarded the recording of batch numbers when dispensing medicines to patients as more difficult than doctors ($p = 0.001$).

was also no significant association between the value HCPs placed on the use of batch numbers when dispensing or administering BMs with their knowledge of the use of batch numbers in reporting ADRs associated with BMs ($p = 0.120$ Kruskal-Wallis H test).

There was no association between the use of brand or non-proprietary names when prescribing, dispensing or administering BMs and the value placed on their use in PMRs ($p = 0.238$, Kruskal-Wallis H test), and their ease of use ($p = 0.197$, Kruskal Wallis H test). There was also no association between the use of batch numbers when dispensing/administering BMs and the value placed on the use in PMRs ($p = 0.241$, Kruskal-Wallis H test), and their ease of use ($p = 0.06$, Kruskal Wallis).

4. Discussion

This study investigated the familiarity, knowledge, and practices of HCPs regarding the PV of BMs at selected hospitals in Lusaka, Zambia. Most HCPs were familiar with BMs (48.9%) but only to the point of having a basic understanding, while most HCPs (40.9%) had never heard of the term "biosimilar medicine".

Despite this, up to 84.7% of HCPs indicated that these medicines were prescribed, dispensed, and administered in their practice. This is similar to other studies conducted in Latin America [15], Malta [14], and Ireland [5], which showed that, despite being unfamiliar with biosimilars, many used them in their practice. HCPs must be educated about BMs that they prescribe, dispense, and administer to their patients as they have additional PV considerations from small molecule drugs.

The current study showed that those who were familiar (*i.e.*, had a basic or complete understanding) of the terms biological medicine and biosimilars had higher mean scores when their knowledge of PV considerations was assessed. Furthermore, many HCPs (74.1%) thought that using non-proprietary names in ADR reports of BMs was better than using the brand name, or did not know which was better to use. The lack of knowledge of the importance of the use of brand names in ADR reports of BMs can also influence their use in practice as the PMR serves as the source of information to include in the ADR report. HCPs were asked how BMs are named in PMRs when prescribing, dispensing, and administering, for which almost half (44.2%) indicated they use non-proprietary names. Currently, Zambia has many biosimilars registered for use [10]. If an ADR occurs, it would be difficult to identify the biosimilar that caused it. PV guidelines or legislation must be made specifically for BMs and biosimilars stating that the use of these drugs should be identified using some identifier (e.g., brand names) to enhance their PV. In Europe, legislation was passed in 2012 encouraging HCPs to use brand names in clinical practice [21].

When HCPs were asked about batch number recording when reporting an ADR, HCPs either did not know or thought it was more important to include them for non-BMs than BMs (63%). This inaccurate perception can potentially influence the practice of recording batch numbers in PMRs, since, just like brand name reporting, PMRs would be the source of information for the ADR report. When HCPs were asked whether batch numbers are generally recorded when dispensing or administering BMs to patients, 57.3% indicated that they are not. If an ADR occurred with the use of a BM, including the batch number in an ADR report would prove difficult, if not impossible for the reporter, if batch numbers are not routinely recorded in PMRs. Studies conducted in Latin America [15], Europe [22], and Australia [23], which aimed to determine the lack of inclusion of batch numbers in ADR reports, found that many prescribers did not have the information available at the time of reporting. A solution to this problem would be the education of HCPs on the importance of batch number inclusion in ADR reports and PMRs [17].

In the current study, when HCPs were asked to rank on a scale of 1 to 7 (with 1 representing easy and 7 representing difficult) the ease of recording batch numbers in PMRs, they gave an overall score of 5.2. This may mean that the lack of use of batch numbers when dispensing or administering BMs may also indicate additional barriers to recording them in clinical practice. HCPs in other

countries have expressed difficulty in recording batch numbers, some stating that electronic patient records do not have fields to include batch numbers [24], while others have stated that it is impractical to manually record batch numbers when dispensing and administering medicines [17]. This may also be the case at the selected hospitals where the study was conducted.

Assessment of HCPs' knowledge of the other PV considerations of BMs generally showed poor knowledge. For example, 60% did not know or thought non-BMs pose a greater risk of immunogenicity than BMs, while almost half (46.8%) thought that different batches of BMs are always identical. These incorrect perceptions hamper the PV of BMs. Therefore, HCPs need to be educated regarding these considerations to enhance the PV of BMs.

Biologics and biosimilars must be transported and stored at highly regulated temperatures [25]. Notably, most HCPs (81.3%) recognised that storing BMs outside their recommended storage conditions may introduce or alter immunogenicity. Temperature fluctuations may increase the formation of protein aggregates and therefore affect the product quality [25].

To check whether HCPs knew under which conditions reporting an ADR was important, 7 questions were asked. Poor knowledge was demonstrated for some questions. For example, almost half (48.5%) did not know or thought that all serious ADRs were known before marketing, and 29.4% thought that one case did not contribute significantly to knowledge of medicinal risk. A study conducted among private healthcare facilities in Lusaka, Zambia also showed that only 42% of HCPs knew that serious ADRs can also be detected after the marketing of drugs [26]. A systematic review of 45 articles found that indifference (perceptions that one case does not contribute much to the knowledge of the risk of medicine) was a reason for the under-reporting of ADRs in 67% of the articles [27].

HCPs' perception of their knowledge of how to report ADRs was assessed. Less than half (37.9%) of HCPs indicated that they have adequate knowledge on how to report an ADR. This lack of knowledge seems to be a common theme in many PV studies [28] [29], including a study conducted among HCPs at the selected hospitals in Lusaka in 2014. In the study, only 22.2% of the HCPs had prior PV training [20]. One possible solution to tackle this lack of knowledge would be incorporating PV education into undergraduate training programs, as well as incorporation into continuous professional development activities.

Over half (53.6%) of HCPs knew they could report ADRs via hardcopy report forms. However, few knew that they could report ADRs via the Med Safety app (16.6%) and the ZAMRA website (34.9%). HCPs have previously cited the lack of ADR report forms as a reason for not reporting ADRs [30], including a 2014 study conducted at the selected hospitals in Lusaka [20]. As such, HCP education on other reporting methods could enhance ADR reporting.

The study presented some limitations; about 30% of HCPs did not respond to the survey questionnaire and therefore this may result in bias that may affect the

generalisation of the results.

5. Conclusion

Only 61.7% of HCPs were familiar with biological medicines; some understood the basics while others had a complete understanding. However, only 38.8% of HCPs were familiar with biosimilar medicines because they had a basic or complete understanding of them. HCPs generally did not score well when their knowledge regarding the PV considerations of biological medicines was assessed. Some HCPs did not know under what conditions they should report ADRs and some ADR reporting methods. Lastly, the practices of some HCPs at the selected hospitals did not enhance the pharmacovigilance of biological medicines.

Recommendation

Future research could look at the ZAMRA ADR database to determine the reporting of brand names and batch numbers in ADR reports of biological medicines.

Ethics Approval Statement

Ethical approval was granted by ERES Converge IRB and the National Health Research Ethics Board with reference numbers 2021-Mar-014 and NHRA00017/4/05/2021, respectively.

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Conflicts of Interest

All authors declare no conflict of interest.

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Appendix 1: Study Questionnaire

Throughout the questionnaire, tick only the single checkbox that applies under each question and/or sub-question

1) Are you a

☐ Consultant ☐ Senior Resident Medical Officer

☐ Junior Resident Medical Officer ☐ Pharmacist

☐ Pharmacy Technologist ☐ Nurse

☐ Other (please specify)……..

To Be Filled In By Medical Practitioners Only

2) How many years are you registered as a medical practitioner?

☐ <5 years ☐ 5 - 9 years

☐ 10 - 19 years ☐ 20 - 29 years

☐ >30 years

3) How many years have you been in practice?

☐ <5 years ☐ 5 - 9 years

☐ 10 - 19 years ☐ 20 - 29 years

☐ >30 years

4) Please indicate the therapeutic area in which you practice?

☐ Women and newborn hospital ☐ Adult hospital

☐ Paediatrics hospital ☐ Cancer Diseases Hospital

5) Do you ever prescribe medicines to patients under your care?

☐ Yes ☐ No

☐ Other (please specify)……..

To Be Filled In By Pharmacist/ Pharmacy Technologist Only

2) How many years have you been practising as a pharmacist/pharmacy technologist?

☐ <5 years ☐ 5 - 9 years

☐ 10 - 19 years ☐ 20 - 29 years

☐ >30 years

3) Please indicate the therapeutic area in which you practice?

☐ Women and newborn hospital ☐ Adult hospital

☐ Paediatrics hospital ☐ Cancer Diseases hospital

To Be Filled By Nurses Only

2) How many years has it been since you first entered practice?

☐ <5 years ☐ 5 - 9 years

☐ 10 - 19 years ☐ 20 - 29 years

☐ >30 years

3) Are you a (choose all that apply):

☐ Registered General Nurse ☐ Registered Public Health Nurse

☐ Other (please specify)……

4) Please indicate the therapeutic area in which you practice?

☐ Women and newborn hospital ☐ Adult hospital

☐ Paediatrics hospital ☐ Cancer Diseases hospital

Adverse Drug Reaction Reporting

Adverse Drug Reaction Reporting

An adverse drug reaction is a response to a medicine which is noxious and unintended. An adverse drug reaction can be reported directly to the Zambia Medicines Regulatory Authority (formerly Pharmaceutical Regulatory Authority) or the manufacturer of the medicine. An adverse drug reaction can be reported using hardcopy report forms, via email, online on the ZAMRA website, and using the Med Safety app.

1) Before this survey, did you know that an adverse drug reaction could be reported directly to the Zambia Medicines Regulatory Authority (ZAMRA)?

☐ Yes ☐ No

2) Before this survey, did you know that an adverse drug reaction could be reported using:

a) Hardcopy ADR report forms?

☐ Yes ☐ No

b) The Med Safety app?

☐ Yes ☐ No

c) The ZAMRA website?

☐ Yes ☐ No

3) Have you ever reported an adverse drug reaction?

☐ No (0 times) ☐ Yes (1 time)

☐ Yes (2 times) ☐ Yes (≥3 times)

Do you think that:

1) Do you have adequate knowledge on how to report an adverse drug reaction?

☐ Yes ☐ No ☐ I don't know

2) Healthcare professionals should report serious Adverse drug reactions even if uncertain that the medicine caused the event

☐ Yes ☐ No ☐ I don't know

3) Healthcare professionals should report serious adverse drug reactions even if they do not have all the details of the event (e.g. complete patient history, demographic data)

☐ Yes ☐ No ☐ I don't know

4) All serious adverse drug reactions are known before medicine is marketed

☐ Yes ☐ No ☐ I don't know

5) One case reported by a healthcare professional does not contribute much to knowledge on medicine risks

☐ Yes ☐ No ☐ I don't know

6) Patients can report adverse drug reactions independent of a healthcare professional

☐ Yes ☐ No ☐ I don't know

7) Healthcare professionals should report adverse drug reactions associated with overdose, misuse or error

☐ Yes ☐ No ☐ I don't know

Biological Medicines

Biological Medicines: Familiarity

1) How familiar are you with the term biological medicine?

☐ Never heard of the term ☐ Heard of the term - can't define it

☐ Familiar - I have got a basic understanding

☐ Very familiar - I have got a complete understanding

2) How familiar are you with the term biosimilar medicine?

☐ Never heard of the term ☐ Heard of the term - can't define it

☐ Familiar - I have got a basic understanding

☐ Very familiar - I have got a complete understanding

Biological medicines are produced from biological sources, such as animals, human blood, or the cells of a living organism. Examples of biological medicines include monoclonal antibodies (e.g.infliximab, trastuzumab, bevacizumab), insulins (wosulin, insugen), interferon alfa 2b, erythropoietins (wepox, vintor), vaccines and blood products. A biosimilar is a biological medicine which is highly similar to an original biological medicine.

1) Biosimilars are the same as generic medicines

☐ Yes ☐ No ☐ I don't know

2) In an adverse drug reaction report, it is better to identify a biological medicine by its non-proprietary name (e.g. insulin) instead of its brand name (e.g. Wosulin)

☐ Yes ☐ No ☐ I don't know

3) In general, biological medicines pose a greater risk of immunogenicity than non-biological (chemical) medicines

☐ Yes ☐ No ☐ I don't know

4) Different batches of the same biological medicine are always identical

☐ Yes ☐ No ☐ I don't know

5) Rare adverse drug reactions resulting from changes to the manufacturing process of a biological medicine can always be predicted

☐ Yes ☐ No ☐ I don't know

6) It is more important to include batch numbers in adverse drug reaction reports for non-biological medicines than it is for biological medicines

☐ Yes ☐ No ☐ I don't know

7) Keeping a biological medicine outside its recommended storage conditions may introduce or alter the immunogenicity

☐ Yes ☐ No ☐ I don't know

8) Adverse drug reactions associated with a patient changing between different brands of biological medicine should be reported

☐ Yes ☐ No ☐ I don't know

Biological Medicines: Practice

9) Are biological medicines prescribed/dispensed/administered in your practice?

☐ Yes ☐ No ☐ I don't know

10) Have you ever reported an adverse drug reaction caused by biological medicines?

☐ Yes ☐ No ☐ I don't know

11) In your practice how are the names of biological medicines that have been prescribed/dispensed/administered to patients generally recorded?

☐ Brand name (e.g. Wosulin) ☐ Non-proprietary name (e.g. insulin)

☐ Both brand name and non-proprietary name

☐ I don't know

☐ Varies by medicine (please specify)……

12) In your practice are the batch numbers of biological medicines that have been administered/ dispensed to patients generally recorded?

☐ Yes ☐ No ☐ I don't know

☐ Yes, but only for some medicines (please specify)……

Please mark your response to the following questions on each scale ranging from 1 to 7

13) Do you believe that recording the brand names of all biological medicines prescribed/administered/dispensed to patients is:

	1	2	3	4	5	6	7
Worthless (1) - Valuable (7)	☐	☐	☐	☐	☐	☐	☐
Easy (1) - Difficult (7)	☐	☐	☐	☐	☐	☐	☐

Any other comments……

……

14) Do you believe that recording batch numbers of **ALL** biological medicines administered/dispensed to patients are:

	1	2	3	4	5	6	7
Worthless (1) - Valuable (7)	☐	☐	☐	☐	☐	☐	☐
Easy (1) - Difficult (7)	☐	☐	☐	☐	☐	☐	☐

Any other comments……..……