

# Registration of essential medicines in Kenya, Tanzania and Uganda: a retrospective analysis

A Green<sup>1</sup>, R Lyus<sup>1</sup> , M Ocan<sup>2</sup>, AM Pollock<sup>1</sup>  and P Brhlikova<sup>1</sup> 

<sup>1</sup>Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne NE2 4AX, UK

<sup>2</sup>Department of Pharmacology and Therapeutics, Makerere University, Republic of Uganda, Kampala, PO Box 7062

**Corresponding author:** P Brhlikova. Email: [petra.sevcikova@newcastle.ac.uk](mailto:petra.sevcikova@newcastle.ac.uk)

## Abstract

**Objectives:** To audit national drug registers (NDRs) in Kenya, United Republic of Tanzania and Uganda with respect to national Essential Medicine Lists (EMLs) and to conduct an analysis of highly registered products including a sub-analysis of highly registered antimicrobial products.

**Design:** Retrospective analysis of registration of essential medicines and medicinal products on NDRs as of February 2018.

**Setting:** Not applicable.

**Participants:** None.

**Main outcome measures:** Registration status of essential medicines by country, essential medicine status of registered products by country and medicines with more than 50 registrations across all three countries.

**Results:** A high proportion of essential medicines are not registered: Kenya 28% (175/632), United Republic of Tanzania 50% (400/797) and Uganda 40% (266/663). Of registered products on the NDRs, more than half are not essential: Kenya 71% (4350/6151), United Republic of Tanzania 64% (2278/3590) and Uganda 58% (2268/3896). When the three NDRs were combined, there were 42 medicines with over 50 registered products, accounting for 30% (4153/13637) of products, many of which were non-essential.

**Conclusions:** Non-registration of essential medicines is a barrier to availability. Over-registration of medicines, particularly non-essential medicines, diverts regulatory resources towards registering non-priority and, sometimes, clinically sub-optimal medicines. The East African Community Medicines Registration Harmonization Project has the potential to improve access to key medicines if registration of essential medicines is prioritised and registration of non-essential medicines is restricted.

## Keywords

Clinical, medicines regulation, non-clinical, pharmacology and therapeutics, public health

Received: 27th September 2022; accepted: 25th April 2023

## Introduction

Access to essential medicines is fundamental to the human right to health and is enshrined in UN sustainable development goal 3.8 as ‘... access to safe, effective, quality, and affordable essential medicines’.<sup>1,2</sup> The World Health Organization (WHO) Model List of Essential Medicines, revised biannually since 1977, guides the development of national Essential Medicine Lists (EMLs) in 137 countries to promote access to appropriate medicines and to address the priority healthcare needs of populations.<sup>3</sup>

Although WHO & Health Action International surveys found that selected essential medicines are more available than non-essential medicines,<sup>4,5</sup> low- and middle-income countries (LMICs) struggle to ensure access to a broader set of essential medicines as specified by their national EMLs.<sup>6</sup> Access to quality-assured antimicrobials is a particular problem in LMICs.<sup>7,8</sup>

National drug registers (NDRs), or national registers of authorised medicines, are government lists containing information on medicines authorised in the relevant country. Registration in relation to the availability of essential medicines is an under-researched area. Previous analysis of medicine registration in Uganda has shown that only half (51%) of medicines listed as essential had a product registered with the National Regulatory Authority (NRA).<sup>9</sup> A more recent study including all medicines listed as essential in Pakistan found that 26% lacked registration status with anti-Parkinson’s medicines and antidotes particularly affected.<sup>10</sup> Alongside the under-registration of essential medicines, there may be over-registration of non-essential medicines. A recent analysis found that 64.3%, 53.2% and 51.1% of antimicrobials registered in Kenya, United Republic of Tanzania and Uganda, respectively, were non-essential.<sup>11</sup>

There is no published research into the optimal number of registered products for each International Nonproprietary Name (INN) to ensure availability. The WHO recommends at least three products registered by different manufacturers per medicine to ensure a stable supply.<sup>7</sup> Similarly, in response to drug shortages and unprecedented price increases for drugs with just one or two different manufacturers in the United States, it has been proposed that the United States Federal Drug Authority should prioritise market applications for generics with three or fewer products registered.<sup>12</sup> Other literature focuses on price reduction rather than availability: studies show initial reductions in generic-to-brand price ratios with more generic entrants; however, the impact of additional generic entrants was negligible after three to six entrants.<sup>13–15</sup>

Both under-registration of essential medicines and over-registration of medicines, particularly non-essential medicines, are highly problematic. The former for the non-availability of critical medicines to meet public health needs and the latter for diverting regulatory resources to non-priority, and in some cases, inferior and/or irrational treatments. Over-registration of non-essential antimicrobials is particularly concerning as these do not appear in national Standard Treatment Guidelines. This may lead to inappropriate use, which drives antimicrobial resistance.

The objectives of this study were: (1) to audit registered products on NDRs in Kenya, United Republic of Tanzania and Uganda and compare with national EMLs to establish a proxy measure of availability of essential medicines; and (2) to conduct a sub-analysis of highly registered products including a sub-analysis of highly registered antimicrobial products.

## Methods

### Countries and data sources

*The essential medicines lists.* Essential medicines lists were downloaded: the 2016 list for Kenya and Uganda and the 2017 list for United Republic of Tanzania.<sup>16,17,18</sup> Non-pharmacological products, such as antiseptic solutions, dialysis solutions and medical devices, were excluded. After exclusions, there were 632, 663 and 797 medicines in Kenya, Uganda and United Republic of Tanzania, respectively. The following information on medicines from the essential medicines lists was extracted: generic name of the medicine; strength; and dosage form.

*The NDRs.* Kenya, Uganda and United Republic of Tanzania, accessed on 26 February 2018, listed 6151, 3896 and 3590 products, respectively.<sup>19–21</sup> Non-medicinal and veterinary products were excluded. Medicines were collated and named consistently where spellings or names varied (e.g. Co-Amoxiclav vs. Amoxicillin and Clavulanic Acid).

### Data extraction

All medicines from the EMLs and NDRs were extracted including the name (as INN or combination of INNs), strength and dosage form and entered into a database. Two analyses were undertaken comparing the ‘registration’ status of essential medicines; and the ‘essential medicine’ status of all registered products.

These databases were analysed by two independent researchers and any discrepancies were resolved by a third researcher. Due to many inconsistencies in the formatting of strength and dosage form, visual comparison and manual changes were undertaken.

*Coding medicines on the EML for registration status.* Each essential medicine was searched for in the corresponding national drug registry. The registration status of each essential medicine was determined by applying to one of the following categories:

- If a product matched the description (name, strength and dosage form) of the essential medicine, then this essential medicine was considered ‘registered’. If the registered product’s strength was exactly half the essential medicine specifications, then the essential medicine was also considered ‘registered’ as taking two doses is clinically practical.
- If no registered products were found for an essential medicine, then this was considered ‘unregistered’ and labelled as ‘no products with INN’.
- If a medicine’s name (INN) was present within the drug registry but the strength or dosage form did not match essential medicine specifications, then this was considered ‘unregistered’ and further labelled as ‘non-EML specification’.
- If a medicine’s name (INN) was present within the drug registry but lacked information regarding strength or dosage form, then the medicine was considered ‘unregistered’ and further labelled as having ‘incomplete information’.

#### *Coding products on the NDRs for essential medicine status.*

Each product in the national drug registries was compared to the corresponding EML. If the product matched name, strength and dosage form, it was considered an ‘essential medicine’:

- If the product failed to meet any of the EML specifications, it was considered a ‘non-essential medicine’. If the registered product’s strength was exactly half the essential medicine specifications, then the registered product was also considered ‘essential’ as taking two doses is clinically practical.

#### *Analysis*

A series of analyses were performed to assess the registration status of essential medicines, the essential medicine status of all products on NDRs, and the essential medicine status and therapeutic class of medicines with more than 50 registered products across the three countries.

#### *Registration of essential medicines.*

- The overall number and proportion of essential medicines registered were calculated for each country and across all three countries.
- Essential medicines were categorised by therapeutic class, as determined by the EML for each country. The proportion of medicines registered and unregistered for each class was calculated.
- Essential medicines were grouped according to their unique INN and matched against products on the NDR to give a number of registered products per essential medicine by unique INN.
- Registered essential medicines by unique INN were then grouped by the number of registered products for each country: 1–2, 3–6, 7–15 or >15.

#### *Essential medicine status of registered products.*

- The number and proportion of registered products that have essential medicine status were calculated for each country and across the three countries.

*Medicines with more than 50 registered products across all three countries.* In the absence of a marker of excessive registration in the literature, we took a pragmatic approach that was feasible and manageable based on the data. Looking at the medicines by individual country would have resulted in too many products and a detailed sub-analysis would not have been possible.

- The three NDRs were combined and medicines with more than 50 registered products were extracted.

- Medicines with more than 50 products across all three countries were grouped and analysed according to whether they were antimicrobials or non-antimicrobials. Non-antimicrobials were grouped into therapeutic classes. For each medicine, the number and proportion of products that were considered essential and non-essential by each national EML were calculated. Examples of medicines with excessive registration of products are discussed.

#### *Sub-analysis of antimicrobials.*

- The WHO Model List of Essential Medicines uses the AWaRe classification for antibiotics, that is, access, watch and reserve, to provide further guidance on appropriate use of antibiotics in the context of antimicrobial resistance.<sup>22</sup> Access antibiotics have activity against common susceptible bacteria and show lower resistance potential than antibiotics in other groups.<sup>22</sup> They are recommended as first- or second-line treatments, and access to these antibiotics should be ensured.<sup>22</sup> Watch antibiotics have higher resistance potential, while reserve antibiotics are the last-resort options that should be reserved for treatment of infections caused by multidrug-resistant bacteria.<sup>22</sup>
- Antimicrobials were further analysed using the WHO AWaRe System for antibiotics.

## **Results**

### *Registration status of essential medicines*

In Kenya, United Republic of Tanzania and Uganda, 28% (175/632), 50% (400/797) and 40% (266/663) of essential medicines, respectively, had no registered products (Table 1). Grouping registered essential medicines by unique INN identified 242, 207 and 233 medicines in Kenya, United Republic of Tanzania and Uganda, respectively. A significant proportion of those registered essential medicines had only 1–2 registered products: 38% (91/242) Kenya, 45% (93/207) United Republic of Tanzania and 36% (84/233) Uganda. In Kenya, United Republic of Tanzania and Uganda, 12% (29/242), 9% (18/207) and 10% (25/233) of registered essential medicines, respectively, had more than 15 registered products (Table 1).

Table 2 shows that the extent of registration of essential medicines varied substantially across therapeutic classes and between countries. Highlighted examples in Table 2 show 25%–49%, 50%–74% and >75% non-registration in blue, yellow and red, respectively. There is under-registration of anti-Parkinsonism medicines: 80% (4/5) in Kenya and United Republic of Tanzania and 100% (1/1) in

**Table 1.** The number and proportion of essential medicines with and without registered products and reasons for non-registration of essential medicines in Kenya, United Republic of Tanzania and Uganda.

	Kenya	United Republic of Tanzania	Uganda
Total number of EML medicines (n)	632	797	663
Registered essential medicine	457 (72%)	397 (50%)	397 (60%)
Non-registered essential medicine	175 (28%)	400 (50%)	266 (40%)
No products with the same specific INN	90	197	170
Non-EML specification	80	149	77
Incomplete Information – not known	5	54	19
Total number of EML medicines by unique INN (n)	242	207	233
1–2 products	91 (38%)	93 (45%)	84 (36%)
3–6 products	71 (29%)	55 (27%)	69 (30%)
7–15 products	51 (21%)	41 (20%)	55 (24%)
> 15 products	29 (12%)	18 (9%)	25 (10%)

EML, Essential Medicine List; INN: International Nonproprietary Name.

**Table 2.** Number and proportion of essential medicines without a registered product by therapeutic class in Kenya, United Republic of Tanzania and Uganda.

Class of essential medicine	Kenya			United Republic of Tanzania			Uganda		
	Total	Not registered (%)		Total	Not registered (%)		Total	Not registered (%)	
Anaesthetics	21	3	(14)	48	33	(69)	32	17	(53)
Anti-allergics and medicines used in anaphylaxis	8	0	(0)	14	1	(7)	9	0	(0)
Antidotes and other substances used in poisoning	19	14	(74)	10	9	(90)	17	12	(71)
Anti-epileptics/ anticonvulsants	18	5	(28)	17	7	(41)	14	5	(36)
Anti-infective medicines	160	33	21	185	55	30	162	45	28
Anti-migraine medicines	5	0	0	8	2	25	9	4	44
Anti-neoplastic and immunosuppressive medicines	85	22	26	64	39	61	53	31	58
Anti-Parkinsonism medicines	5	4	80	5	4	80	1	1	100
Cardiovascular medicines	38	9	24	55	23	42	39	11	28
Dermatological medicines (topical)	23	4	17	29	11	38	21	10	48

(continued)

**Table 2.** Continued

Class of essential medicine	Kenya			United Republic of Tanzania			Uganda		
	Total	Not registered (%)		Total	Not registered (%)		Total	Not registered (%)	
Diuretics	10	2	20	7	3	43	5	0	0
Ear, nose and throat medicines	7	3	43	10	4	40	15	3	20
Gastrointestinal medicines	19	2	11	34	19	56	26	5	19
Hormones, other endocrine medicines and contraceptives	33	7	21	70	31	44	39	17	44
Immunologicals and vaccines	20	2	10	20	19	95	22	13	59
Medicines acting on the respiratory tract	10	1	10	13	6	46	12	4	33
Medicines affecting the blood	24	16	67	21	15	71	11	6	55
Medicines for diseases of joints	7	2	29				5	3	60
Medicines for mental and behavioural disorders	21	12	57	35	17	49	33	11	33
Medicines for neurosurgical use							3	3	100
Medicines for pain and palliative care	36	9	25	45	19	42	34	7	21
Muscle relaxants (peripherally acting) and cholinesterase inhibitors	6	1	17	1	1	100	8	3	38
Ophthalmological preparations	16	5	31	68	38	56	39	19	49
Oxytocics and anti-oxytocics	7	2	29	8	1	13	4	1	25
Solutions correcting water, electrolyte and acid–base disturbances	13	1	8	17	9	53	12	6	50
Specific medicines for neonatal care	7	4	57				4	1	25
Vitamins and minerals	9	5	56	21	18	86	12	8	67

Blue, yellow and red highlighting shows 25%–49%, 50%–74% and >75% non-registration, respectively.

Uganda of essential anti-Parkinsonism medicines lack registration. There is also under-registration of antidotes and other substances used in poisoning: 70%–90% of essential medicines in this class do not have a registered product across the three countries.

### Audit of NDRs

**Essential medicine status.** Essential medicine products accounted for only 29% (1801/6161) of all registered products in Kenya, 37% (1312/3590) in United Republic of Tanzania and 42% (1628/3896) in

Uganda (Table 3). There are 13,637 registered products across the three countries in total.

**Medicines with over 50 registered products.** When the three NDRs were combined, there were 42 medicines with over 50 registered products. A list of these medicines and their corresponding number of registered products is displayed in Appendix 1. These 42 medicines accounted for 30% (4153/13637) of all registered products across the region.

**Antimicrobials with over 50 registered products by WHO AWaRe classification and essential medicine status.** There were 21 antimicrobial medicines with over 50 registered products each, representing a total of 2310 products. Of these, six were classified as Access and eight as Watch antibiotics under AWaRe classification, one was an antibiotic combination (ampicillin and cloxacillin) explicitly not recommended by the WHO and six were non-antibiotics (Table 4).

The essential medicine status of highly registered antimicrobial products ranged from 11% to 86% (Table 4). Of the 2310 antimicrobial products, 1719 were antibiotic and 591 were non-antibiotic products such as antimalarials, antifungals and antiparasitics. A total of 792 of 1719 (46%) antibiotics were essential medicines. A total of 381 of 591 (64%) non-antibiotic antimicrobials were essential medicines. When subdivided by WHO AWaRe classification, 44% (311/707) of Access antibiotics were essential and 50% (470/939) of Watch antibiotics were essential. No Reserve antibiotics had over 50 products.

**Examples of products of concern.** Combined Ampicillin and Cloxacillin is not recommended by the WHO but is considered an essential medicine in the United Republic of Tanzania. Between the three countries, there were 73 registered products. Despite essential medicine status in the United Republic of Tanzania, only 46% (11/24) of registered Ampicillin with Cloxacillin products met EML specifications.

There were between 75 and 119 registered products for Amoxicillin and Clavulanic acid, also known

as Co-Amoxiclav, in each country. Of these, 77% were not essential as they were of non-EML strength, or dosage form. Similarly, there were between 27 and 85 products for Cefuroxime, a Watch antibiotic, and only 11% of these were essential, as it is not listed on either Kenya's or United Republic of Tanzania's EML.

**Non-antimicrobials.** There were 21 unique non-antimicrobial medicines with over 50 registered products each, representing a total of 1868 products (Table 5). For 13 of these medicines, the overwhelming majority of registered products in at least one country (>75%, highlighted in red) did not meet EML specifications. Across the combined registers, the essential status of products for each medicine varied from 0% to 95%.

Diclofenac is the most frequently registered non-antimicrobial, with 219 products registered across the three countries. Kenya's EML does not include Diclofenac as essential, and yet 85 products have been registered.

Pregabalin, an analgesic, is not on any country's EML; yet, there are 77 registered products across the region. Telmisartan, an anti-hypertensive, and rosuvastatin, a statin, are not listed as essential medicines in any country but both medicines have 65 unique registered products each across the three countries.

## Discussion

### *Lack of registration of essential medicines as a barrier to availability*

EMLs are a crucial tool for ensuring access to appropriate medicines. However, a high proportion of essential medicines are not registered (28% in Kenya, 50% in United Republic of Tanzania and 40% in Uganda). Moreover, a significant proportion of those that are registered have less than three products: 38%, 45% and 36% of essential medicines (by unique INN) for Kenya, United Republic of Tanzania and Uganda, respectively. Given that the WHO recommends at least three different manufacturers per medicine to ensure a stable supply,

**Table 3.** The proportion of registered products which are essential medicines in Kenya, United Republic of Tanzania and Uganda.

	Kenya	United Republic of Tanzania	Uganda
Total number of registered products, n	6151	3590	3896
Essential medicines, n (%)	1801 (29)	1312 (37)	1628 (42)
Non-essential medicines, n (%)	4350 (71)	2278 (63)	2268 (58)

**Table 4.** Highly registered<sup>a</sup> antimicrobial medicines by AWaRe category and essential medicine status in Kenya, United Republic of Tanzania and Uganda.

Medicine	Kenya				United Republic of Tanzania				Uganda						
	EM	%	Non-EM	%	EM	%	Non-EM	%	EM	%	Non-EM	%			
	Σ		Σ		Σ		Σ		Σ		Σ				
<b>AWaRe category</b>															
<b>Access</b>															
Amoxicillin and Clavulanic acid	27	23	92	77	119	17	23	58	77	75	21	23	69	77	90
Amoxicillin	41	66	21	34	62	26	49	27	51	53	19	50	19	50	38
Metronidazole	14	47	16	53	30	16	70	7	30	23	21	62	13	38	34
Sulfamethoxazole and Trimethoprim <sup>b</sup>	22	65	12	35	34	15	75	5	25	20	0	0	10	100	10
Chloramphenicol	0	0	16	100	16	13	59	9	41	22	19	83	4	17	23
Clarithromycin <sup>b</sup>	30	83	6	17	36	10	83	2	17	12	0	0	10	100	10
Azithromycin	30	37	51	63	81	29	97	1	3	30	31	50	31	50	62
Cefuroxime <sup>b</sup>	0	0	85	100	85	0	0	27	100	27	17	39	27	61	44
Ciprofloxacin	12	21	46	79	58	38	88	5	12	43	44	94	3	6	47
Ceftriaxone	39	75	13	25	52	43	91	4	9	47	38	93	3	7	41
Levofloxacin	31	55	25	45	56	3	20	12	80	15	11	33	22	67	33
Cefixime	29	53	26	47	55	5	45	6	55	11	14	44	18	56	32
Erythromycin <sup>b</sup>	0	0	35	100	35	18	86	3	14	21	6	46	7	54	13
Moxifloxacin	14	67	7	33	21	9	60	6	40	15	9	60	6	40	15
Ampicillin and Cloxacillin <sup>b</sup>	0	0	24	100	24	11	46	13	54	24	0	0	25	100	25
<b>Not recommended</b>															
<b>Non-antibiotic</b>															
Clotrimazole	34	67	17	33	51	26	68	12	32	38	29	85	5	15	34
Albendazole	25	39	39	61	64	26	96	1	4	27	19	68	9	32	28
Fluconazole	29	52	27	48	56	25	89	3	11	28	17	68	8	32	25
Artemether and Lumefantrine	29	78	8	22	37	20	53	18	47	38	17	53	15	47	32
Aciclovir	17	46	20	54	37	17	94	1	6	18	10	42	14	58	24
Quinine	12	71	5	29	17	10	71	4	29	14	19	83	4	17	23

EM: essential medicines; non-EM: non-essential medicines; Σ: total (n). Highlighted examples show that 25%–49%, 50%–74% and >75% of products do not meet EML specifications in blue, yellow and red, respectively.

<sup>a</sup>Highly registered = >50 registered products across all three NDRs.

<sup>b</sup>Medicine absent from at least one EML but present on at least one EML.

Table 5. Highly registered<sup>a</sup> non-antimicrobial medicines by essential medicine status in Kenya, United Republic of Tanzania and Uganda.

Indication	Medicine	Kenya			United Republic of Tanzania			Uganda								
		EM %	Non-EM %	Σ	EM %	Non-EM %	Σ	EM %	Non-EM %	Σ						
Analgesia	Diclofenac <sup>b</sup>	0	85	100	85	45	83	9	17	54	47	59	33	41	80	
	Paracetamol	29	53	26	47	55	31	67	15	33	46	35	52	32	48	67
	Tramadol <sup>a</sup>	0	0	38	100	38	14	70	6	30	20	29	94	2	6	31
	Ibuprofen	22	48	24	52	46	7	41	10	59	17	12	50	12	50	24
	Pregabalin <sup>c</sup>	0	0	39	100	39	0	0	27	100	27	0	0	11	100	11
Cardio-vascular	Amlodipine	22	43	29	57	51	26	96	1	4	27	32	100	0	0	32
	Atorvastatin <sup>b</sup>	43	74	15	26	58	0	0	19	100	19	31	100	0	0	31
	Sildenafil <sup>b</sup>	0	0	37	100	37	12	57	9	43	21	0	0	17	100	17
	Telmisartan <sup>c</sup>	0	0	27	100	27	0	0	24	100	24	0	0	14	100	14
	Rosuvastatin <sup>c</sup>	0	0	40	100	40	0	0	12	100	12	0	0	13	100	13
	Atenolol <sup>b</sup>	0	0	22	100	22	8	44	10	56	18	8	47	9	53	17
	Losartan	22	92	2	8	24	12	67	6	33	18	13	87	2	13	15
Anti-diabetic	Metformin	31	53	27	47	58	12	35	22	65	34	23	58	17	43	40
	Glimepiride <sup>b</sup>	0	0	28	100	28	20	87	3	13	23	9	60	6	40	15
Proton pump inhibitors	Esomeprazole <sup>b</sup>	0	0	57	100	57	10	71	4	29	14	0	0	13	100	13
	Omeprazole	26	87	4	13	30	19	83	4	17	23	18	100	0	0	18
Respiratory	Montelukast <sup>b</sup>	32	97	1	3	33	0	0	30	100	30	0	0	23	100	23
	Cetirizine	32	89	4	11	36	11	100	0	0	11	14	58	10	42	24
	Salbutamol	5	23	17	77	22	15	71	6	29	21	10	50	10	50	20
	Betamethasone	13	81	3	19	16	9	45	11	55	20	16	100	0	0	16
Steroidal	Hydrocortisone	25	96	1	4	26	3	25	9	75	12	24	86	4	14	28

EM: essential medicines; non-EM: non-essential medicines; Σ: total (n). Highlighted examples show that 25%–49%, 50%–74% and >75% of products do not meet EML specifications in blue, yellow and red, respectively.

<sup>a</sup>Highly registered = >50 registered products across all three NDRs.

<sup>b</sup>Medicine absent from at least one EML but present on at least one EML.

<sup>c</sup>Medicines absent from all EMLs.



registration of less than three products is insufficient. Under-registration of essential medicines is likely to be a barrier to availability, although it is important to note that there are other legal routes to availability of medicines, such as special import licences, that are often used by non-governmental organisations.<sup>9</sup>

We found that 80%–100% of anti-Parkinsonism medicines, 71%–90% of antidotes and anti-poisoning medicines, 0%–43% of diuretics, 28%–41% of anti-epileptics, 21%–44% of hormonal and endocrine medicines and 21%–30% of anti-infectives were unregistered. A similar distribution of unregistered medicines was recently found for Pakistan, with 26% of essential medicines lacking a registered product overall.<sup>10</sup>

A recent multi-country study of LMICs, including United Republic of Tanzania and Uganda, on the challenges of registering essential medicines for maternal, newborn and child health highlighted that a lack of legal provisions for regulatory decisions made by the WHO and other regulatory authorities, a lack of competent staff and funding within NRAs and, in the context of the low-cost/low-profit markets for many essential medicines, lengthy and onerous registration processes are important barriers to registration of essential medicines.<sup>23</sup> Additionally, the authors found that the procedures for prioritising medicines for registration do not consider the risk associated with only having a single supplier of an essential medicine.<sup>23</sup> A survey exploring the perspectives of pharmaceutical companies in South Africa reported registration costs, inspection fees and country-specific inspection requirements as reasons for not exporting medicines to other African countries.<sup>24</sup> Other studies have concluded that regulatory fees do not hinder access to medicines.<sup>25,26</sup>

Over-registration of medicines, particularly non-essential medicines, is an inefficient use of scarce regulatory resources. Most registered products on the NDRs in Kenya, United Republic of Tanzania and Uganda are not essential: 71%, 63% and 58%, respectively. There is a lack of research into the optimal number of registered products for each INN to ensure availability, above which further registrations offer no additional benefit. In Kenya, United Republic of Tanzania and Uganda, respectively, 21%, 20% and 24% of registered essential medicines (by unique INN) had 7–15 registered products and 12%, 9% and 10% had over 15 registered products. Based on limited literature focussing on competitive pricing, these groups may represent over-registered medicines.<sup>13–15</sup> Additionally, there were 42 medicines with more than 50 registered products across all three NDRs. These accounted for 30% (4153/13637) of all registered products across the region. This illustrates

that a disproportionate amount of regulatory capacity has been consumed by applications for a small number of highly registered medicines.

A South African study found that some generic medicine companies submit several applications for the same medicine under different trade names and that a high percentage of registered generics are not marketed.<sup>27</sup> The current study does not look at manufacturers or consumption data, so it may be that many of these registered products are not making it onto the market. Further research is required to address these gaps.

Regulators do not have a mandate to prioritise essential medicines over non-essential products. This study highlights the need for policies to prioritise or ‘fast-track’ the registration of essential medicines over non-essential medicines, further prioritise essential medicines with less than three registered products and deprioritise medicines that are already highly registered.

### *Clinical implications of unavailability of essential medicines and over-registration of non-essential medicines*

**Antimicrobials.** Of the 21 most highly registered antibiotics, accounting for 2310 products, only 792 (46%) were essential. Non-essential antibiotics do not appear in national Standard Treatment Guidelines, which is likely to lead to the inappropriate use. Inappropriate use drives antimicrobial resistance. The registration of large numbers of non-essential Watch antibiotics is particularly concerning for antimicrobial resistance. High registration suggests high market potential and sales for these medicines.

**Pain.** Diclofenac, a non-steroidal anti-inflammatory drug (NSAID), an analgesic, has been removed from the WHO model EML due to significant cardiovascular risks and because safer alternatives are available. Despite this, Diclofenac remains on the national EML of almost 90% of countries globally and forms one-third of the market for NSAID use in low-, middle- and high-income countries despite being a high-risk NSAID.<sup>28</sup> This study found 219 Diclofenac products registered for use across the three countries; of these, 127 (58%) do not meet EML specifications. Pregabalin, an analgesic, is on none of the national EMLs but has 77 registered products across the region. The high number of registered products for these medicines suggests a substantial market.

**Cardiovascular disease and diabetes.** Metformin is an essential medicine and has 132 products registered across all three countries. However, 101 (77%) of these are not essential, due to being inappropriate doses or combined with other medicines. Gliclazide is regarded as an essential medicine by both the United Republic of Tanzania and Kenya and yet is not registered at an appropriate dose in either country. Glipizide is considered essential in the United Republic of Tanzania; yet, there are no registered products. Rosuvastatin is not on any of the national EMLs or the WHO model EML because of its inferior benefits and increased risks compared to other statins. Despite this, there are 65 products of rosuvastatin registered across all three countries.

**Neurological disorders.** Co-Careldopa is the gold-standard treatment for Parkinson's disease, while Biperiden and Pramipexole are other treatments named in national EMLs and Standard Treatment Guidelines. Despite this, no products were registered for these medicines in any of the three countries.

**Limitations.** EMLs and NDRs were accessed before March 2018. Inconsistencies in formatting within the registers may have produced inaccuracies within the central spreadsheet; however, we conducted multiple checks and corrections to minimise errors.

In the current study, we did not analyse manufacturers and there were no sales data available. It was not possible to analyse whether there were duplicate product registrations, i.e. the same product being registered separately in each country or the same manufacturer registering the same medicine under different trade names within a country.

The groups selected to demonstrate the number of registered products per unique INN (1–2, 3–6, 7–15, >15) were arbitrary although to the extent possible, based on the available literature. We believe they provide a useful indicator of the extent of registration of unique medicines.

**Recommendations.** Regional regulatory harmonisation through the EAC Medicines Regulatory Harmonization Programme offers the opportunity to strengthen regulatory capacity and reduce the regulatory burden on resources. The African Medicines Agency, formed in 2021, has described that its main objective is to 'enhance capacity to...' 'regulate medical products in order to improve access to quality, safe and efficacious medical products'.<sup>29</sup> The following recommendations may assist state parties to improve access to essential medicines.

Policies should be developed to prioritise the registration of essential medicines, particularly those with an insufficient number of registered products.

This would require continuous monitoring of NDRs and EMLs. Provisions should be included to restrict the over-registration of medicines, with a focus on non-essential medicines. Such measures could improve the availability of essential medicines and limit the diversion of regulatory resources towards registering non-priority and, in some cases, clinically sub-optimal medicines.

Future work should assess which products enter the market after registration by analysing data on manufacturers and sales. Further research is also required to examine the implications of registration of essential medicines and excessive registration of non-essential medicines for clinical practice and antimicrobial resistance.

## Declarations

**Competing Interests:** None declared.

**Funding:** None declared.

**Ethics approval:** Not applicable. All data were publicly available and no ethical approval was necessary.

**Guarantor:** PB.


**Contributorship:** All authors contributed to the formulation of the research question, data collection, data analysis and writing of the article.

**Acknowledgements:** We thank Anna Holmes, Lily Wray, Grace Hillsmith, Samaa Musa, Emma Rainey, Rob Slater, Christie Mellor, Sarah Matthews, Sam Whiteman, Dua Hashmi and Fiona Daghli for their assistance in extracting the data and Professor Richard Walker and Dr Colin Millard for earlier participation.

**Provenance:** Original research, not commissioned.

**ORCID iDs:** R Lyus  <https://orcid.org/0000-0002-3093-3704>

AM Pollock  <https://orcid.org/0000-0002-7388-3110>

P Brhlikova  <https://orcid.org/0000-0003-2085-0304>

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## Appendix

**Table 5.** List of unique INNs with more than 50 registered products across all three NDRs and number of registered products per medicine when all three NDRs are combined.

Medicine	Number of registered products (n)	Medicine (cont)	Number of registered products (n)
Amoxicillin and Clavulanic acid	284	Esomeprazole	84
Diclofenac	219	Aciclovir	79
Azithromycin	173	Pregabalin	77
Paracetamol	168	Sildenafil	75
Cefuroxime	156	Cetirizine	71
Amoxicillin	149	Omeprazole	71
Ciprofloxacin	148	Erythromycin	69
Ceftriaxone	140	Glimepiride	66
Metformin hydrochloride	132	Hydrocortisone	66
Clotrimazole	123	Rosuvastatin	65
Albendazole	119	Telmisartan	65
Fluconazole	109	Salbutamol	63
Atorvastatin	108	Sulfamethoxazole and trimethoprim	63
Artemether and Lumefantrine	107	Chloramphenicol	61
Levofloxacin	104	Ampicillin and Cloxacillin	60
Amlodipine	103	Clarithromycin	58
Cefixime	98	Atenolol	57
Tramadol	89	Losartan	57
Ibuprofen	87	Quinine	54
Metronidazole	87	Betamethasone	52
Montelukast	86	Moxifloxacin	51
Total			4153