**Prescribing Indicators at Primary Health Care Centers within the WHO African Region: A systematic analysis (1995-2015).**

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**ABSTRACT**

**Background**
Rational medicine use is essential to optimize quality of healthcare delivery and resource utilization.

**Objective**
To conduct a systematic review of changes in prescribing patterns in the WHO African region and comparison with WHO indicators in two time periods 1995-2005 and 2006-2015.

**Methods**
Systematic searches were conducted in PubMed, Scopus, Web of science, Africa-Wide Nipad, Africa Journals Online (AJOL), Google scholar and INRUD Bibliography databases to identify primary studies reporting prescribing indicators in Africa. This was supplemented by a manual search of retrieved references. We assessed the quality of studies using a 14-point scoring system modified from the Downs and Black checklist with inclusions of recommendations in the WHO guidelines.

**Results**
Forty-three studies conducted in eleven African countries were included in the overall analysis. These studies presented prescribing indicators based on a total 141,323 patient encounters across 572 primary care facilities. The results of prescribing indicators were determined as follows; average number of medicines prescribed per patient encounter = 3.1 (IQR 2.3- 4.8), percentage of medicines prescribed by generic name =68.0% (IQR 55.4-80.3), Percentage of encounters with antibiotic prescribed =46.75% (IQR 33.7-62.8), percentage of encounters with injection prescribed =25.0% (IQR 18.7-39.5) and the percentage of medicines prescribed from essential medicines list =88% (IQR 76.3-94.1). Prescribing indicators were generally worse in private compared with public facilities. Analysis of prescribing across two time points 1995-2005 and 2006-2015 showed no consistent trends.

**Conclusions**
Prescribing indicators for the African region deviate significantly from the WHO reference targets. Increased collaborative efforts are urgently needed to improve medicine prescribing practices in Africa with the aim of enhancing the optimal utilization of scarce resources and averting negative health consequences

**Keywords:** prescribing indicators, drug use indicators, pharmacoepidemiology, prescribing evaluation, medicine utilization studies, systematic reviews; Africa.

**BACKGROUND**

According to the World Health Organization (WHO), more than half of all medicines are inappropriately prescribed, dispensed or sold with such practices deemed to be most prevalent in healthcare settings in the developing world where mechanisms for routine monitoring of medicines use are still in early stages of development [1-4]. In developing and low middle income countries, pharmaceuticals account for a high proportion of household and overall healthcare expenditure [5]. Improvements in the way in which medicines are used is important in reducing morbidity and mortality, building public confidence and reinforcing the credibility of any healthcare system as well as saving scarce resources [6-8]. The "wise List" in Stockholm, Sweden for instance, is an example of an improvement in medicine use with an essential medicines list (EML) with high adherence to just 200 medicines to improve physician familiarity with quality medicines and reduce costs in a high income country that could provide valuable lessons for developing countries seeking to optimize resource utilization [9].

Since the late eighties, the WHO together with the International Network for Rational Use of Drugs (INRUD) have been advocating proper documentation of medicines use and have developed core drug use indicators in three related areas of prescribing practices, patient care and facility specific factors [10]. The drug use indicators are regarded as objective measures that can be extended to describe medicines usage in any health facility, country or an entire region.

The core drug use indicators include five prescribing indicators which are meant to detail particular prescribing characteristics related to poly-pharmacy, antibiotic use, injection use, generic prescribing and adherence to the essential medicines list (EML) [10, 11]. Even though an international standard of the prescribing indicators has not been empirically determined, the WHO has recommended reference values for each of the indicators (**see Table 1**) [12, 13]. In 1993, the WHO published the guideline "How to investigate drug use at health facilities: selected drug use indicators" aimed at outlining methods for the collection and presentation of information on medicines use in primary health care (PHC) centers [10]. Subsequently, the WHO has been publishing information on global medicines usage as part of its World Medicines Situation reports [1, 4]. A more detailed fact book focusing mainly on medicines use at PHCs in developing and transitional countries was also published in 2009 [14]. The broadest review on medicines usage was published in 2013; this incorporates data from 900 studies covering facilities at various level of care in 104 countries between 1990 and 2009 [15]. For the African region, the review reported the average number of medicines per patient encounter to be 2.6, percentage of encounters with antibiotics prescribed as 45.9%, percentage of encounters resulting in prescription of injection as 28.4%, percentage of medicines prescribed from EML to be 89.0% and percentage of medicines prescribed in generic name as 65.1% [15]. Despite not meeting the WHO targets, the estimates show relatively frequent prescribing from EML and of generic products. The high percentage of antibiotic and injection prescriptions has been attributed to disease burden, weak health systems and patients' preferences. A trend analysis showed 'little progress over time' [15].

The WHO African Region is one of the six regions of the WHO and consists of 47 member states with over 927 million inhabitants in 2013 [16]. The region faces one of the greatest disease burden compared to all other WHO regions. In 2013, the region's life expectancy at birth was 58 years, the lowest among all the WHO regions and 10 years below that of Southeast Asia (68 years), the region with the second lowest life expectancy [16]. According to the 2013 Global burden of disease estimates, while their relative burdens have seen some decline, communicable, newborn, nutritional, and maternal causes such as diarrheal diseases, lower respiratory infections, and protein-energy malnutrition still remain the top drivers of health loss in most African countries [17]. Yet, significant epidemiological transition characterized by a growing burden of non-communicable diseases (NCDs) is happening creating a case of an explosive "double disease burden" [18]. For instance, a recent systematic review demonstrated consistent increase in prevalence of hypertension in Africa from 19.7% in 1990 to 27.4% in 2000 and 30.8% in 2010 [19]. Aside its enormous disease burden, resources for improving health delivery in Africa remain scarce. In 2013, the region's average total health expenditure per capita (PPP int. $) was 222, the lowest among all WHO regions and extremely low when compared to Europe (2,214) and Americas (3,873) [16]. Moreover, available health system structures within the region suffer many deficits that hinder effective healthcare delivery. For instance, in the period 2007-2013, the physician to population ratio (per 10,000 population) was 2.7; this was far lower than the global average of 13.9 [16]. According to Motie, financial and human resource challenges have hindered many

healthcare systems within the African region from evolving to meet the emerging healthcare demands [20]. The increasing emergence of non-communicable diseases is likely to further exacerbate these trends.

Most health systems in Africa do not have established mechanisms for routine system-wide medicine monitoring and utilization. Moreover reviews of specifically designed studies are deemed to be out of date after three to five years or even less (Whitlock et al) [21]. This paper presents a systematic review to summarize available information on prescribing indicators for the WHO African region over the last two decades (1995-2015). Our aim was to critically appraise the quality of studies on prescribing practices in the Africa region and to compare the results of studies on prescribing indicators at PHCs in the African region against WHO recommended reference values. We also wished to understand whether there are observable differences in prescribing at private and public facilities in the WHO African region. To this end, we defined public to represent all fully government owned or quasi-governmental facilities. Private was defined to cover for-profit and mission health facilities.

## METHODS

### *WHO prescribing indicators*

The prescribing indicators measure the performance of healthcare providers in five key areas related to the appropriate use of medicines (**Table 1**) [10]. The derivation of these indicators for any health facility (s) is based on an analysis of patient clinical encounters. A patient encounter is recognized to represent "the duration of interaction between patient and health provider. Ideally, this encounter includes a number of components: history taking, diagnosis process: Selection of non-pharmacological or pharmacological treatment, prescription (and perhaps dispensing) of treatment; and explanations about treatment and its adverse effects, follow-up, and prevention." [22]. The encounters may be analyzed retrospectively using data from medical history records or can be analyzed prospectively as patients arrive during the period of data collection [10]. It is important to highlight that the determination of the core prescribing indicators does not require information on patients' signs and symptoms as they provide general prescribing tendencies (non-disease specific). The various prescribing indicators are meant to elucidate peculiar prescribing characteristics relating to polypharmacy, level of antibiotic and injection use and adherence to guidelines relating to generic and EML prescribing [23].

**Table 1:** WHO prescribing indicators and recommended reference values [12, 13].

### *Studies Retrieval Process*

We conducted a structured review of the literature in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[24]. Comprehensive searches were conducted in PubMed, Scopus, Web of science, Africa-Wide Nipad, Africa Journals Online (AJOL), Google scholar and INRUD Bibliography databases. The main key words used were "primary health care, primary health services, community health centres, community-based healthcare, health facilities, primary healthcare settings' AND "prescribing indicators, prescribing patterns, drug use indicators, drug utilization patterns, prescribing evaluation, prescribing statistics, rational prescribing, rational use of medicines, health facility indicators" AND "Africa , Sub-Saharan Africa , WHO African Region". The main limits used were 'humans' and 'English'. Additionally, we searched references of published reviews and selected papers for additional publications.

### *Inclusion and Exclusion of studies*

We included only observational studies published in English in peer-reviewed Journals between 1st January 1995 and 31st December 2015, which reported at least one WHO/INRUD core prescribing indicator or where these indicators were derivable from results/data presented. A study must have specified the total number of patient encounters involved for it to be accepted into the review. Furthermore, to eliminate potential bias, the review included only studies in which the sample of patient encounters were attained through a random sampling technique [25]. For studies with duplicate publications, the version published first or one with complete dataset was selected. In the case of interventional studies, we included only pre (baseline) values. Although, most hospital facilities provide secondary level care, in certain instances, outpatient departments

provide primary care services. Hence, where full description of this has been provided, studies conducted in such settings were included.

***Critical appraisal of studies***

Each Study's quality was assessed using a 14-point scoring system modified from the Downs and Black checklist with inclusions of recommendations in the WHO guidelines **(Box 1**) [10, 26]. We awarded a one point value if study satisfied each criteria. If study did not meet criteria, it was awarded a zero. As studies may not assess all the five indicators (e.g. a study may not measure antibiotic use), the criteria were applied in relation to the indicator (s) assessed. In view of this, the quality grading was expressed as a percentage. Irrespective of the number of criteria applied, a study is considered as 'high quality' if it scores ≥70% of the total tally scores based on the applicable criteria. A score of 69-51% was regarded as 'moderate quality' and a score of ≤50% was graded as 'low quality'.

**Box 1:** Studies' critical appraisal checklist**.**

***Statistical analysis***

Due to the wide heterogeneity of studies, a formal meta-analysis was not conducted. We therefore adopted a more descriptive approach as employed in previous reviews [14, 15]. For each WHO/INRUD prescribing indicator, we determined the median as well as the 25$^{th}$ and 75$^{th}$ percentiles [14]. We did not determine the mean values across studies as this would be unduly influenced by outliers [27]. For each prescribing indicator, study results were not weighted by sample size to avoid the undue influence of larger sample-sized studies [14]. In this case, the approach we adopted was to treat each study as a single data point with equal weight, without regard to sample size and variance. All computations were done electronically using Microsoft Excel 2015® and results of prescribing indicators were compared to the WHO's recommended reference values and with previous reported values [12-15]. Statistical estimates of the difference between the results of prescribing indicators obtained for private and public PHCs as well as between different publication periods was not conducted since variance would have been greatly underestimated in such circumstances [14]. Sub-analysis was also conducted across different facility ownerships (private vs public) as well as across the studies publication periods 1995-2005 and 2006-2015.

## RESULTS

***Studies identification and retrieval***

**Figure 1** outlines the schematic flow of the studies identification and inclusion process. A total of 4,208 articles were identified by literature search. After the exclusion of duplicates and irrelevant studies based on titles and abstracts, 44 articles were retrieved for detailed full-text analysis. Out of the 44 studies, 41 met the inclusion criteria for addition to the review. Two (2) additional studies were identified through the reference screening bringing the total number of studies included in the review to forty-three (43) [7, 8, 22, 28-67]. The 43 studies included in this review (**Table 2**) collectively reported WHO/INRUD prescribing indicators based on overall analysis of 141,323 patient encounters across 572 PHCs. The PHCs included 359 (62.8%) public and 213 (37.2%) private facilities. We were unable to separate 'mission-based' and 'business/for-profit' in the private facilities category as studies gave a limited description of their actitivies. About 65.1% (n=28) of studies were published in the period 2006-2015 whereas 34.9% (n=15) were published in the years 1995-2005. The 43 studies included in this review were conducted in 11 countries representing 23.4% (11/47) of countries in the region under study. The 11 countries included Ghana (4), Nigeria (11), Tanzania (6), Kenya (1), Gambia (1), Zambia (1), Zimbabwe (2), South Africa (6), Ethiopia (7), Burkina Faso (2) and Botswana (2). Figure 1-Schematic flow diagram of studies search and retrieval process. Table 2-Descriptive characteristics of included studies.

**Figure 1: Schematic flow diagram of studies search and retrieval process.**

**Table 2: Descriptive characteristics of included studies.**

***Quality of studies***

Overall, using the quality assessment criteria outlined, 51% of studies were graded as of high quality whereas 42% and 7% were graded as of medium and low quality respectively. The major factors that affected quality grades of studies included smaller sample size, lack of adherence to WHO guidelines (especially counting and classification of medications) and poor reporting of study information. Around one-third (32.6%) of studies included in the review involved patient encounters <600 and were deemed to be small per recommendations outlined in the WHO guidelines [10]. This is an important consideration as studies with larger sample size are more likely to present representative/generalizable results.

The studies collected data either prospectively (using current patients as they present for consultation) or retrospectively (using past medical records). In 27 studies, data on prescribing were collected retrospectively, in 14 studies this was done prospectively while another 2 studies used a mix approach of collecting prescribing information both prospectively and retrospectively. The fact that majority of studies adopted a retrospective approach is quite understandable as such data are easier to collect. Nonetheless, retrospective analysis introduces some bias if certain information is excluded owing to poor record keeping. In the study by Babalola et al [8] in Nigeria for instance, records of 40 patients were excluded from the analysis because they had incomplete data while in the case of Massele et al [50] in Tanzania, the patient registers of three consecutive years were abandoned for another register because they had incomplete data. It is possible that the excluded information may have presented different prescribing characteristics than those reported in the studies. Also most retrospective analyses rely on prescription sheets and hence may exclude patients who are not prescribed medicines. This is likely to lead to overestimation of variables such as average number of medicines per patient, injection prescribing rate and antibiotic prescribing rate although EML and generic prescribing rates are unlikely to be affected. While studies that adopted a prospective approach may minimize the loss of data and deal with other limitations of retrospective assessments, they also introduce an observer bias (Hawthorne effect) as it is difficult to blind the health facility staff. In Nsimba et al [55] study in Tanzania for instance, all health staff were briefed on the study prior to prospective data collection. Prescribers may modify their behaviour if they know they are been investigated and as such, results derived this way may also not be representative of typical prescribing behaviour [10]. In the two studies that adopted dual prospective and retrospective analysis, no significant difference in results were observed in the two approaches thereby affirming to a large extent the validity of their findings [40, 56].

It is recommended that prescribing indicators are analysed over an extended period (Ideally ≥1year) to minimized the impact of seasonal variations in morbidity patterns, peculiarities in staffing and inconsistencies in medicines supply which can all impact on the patterns of medicines prescribing [10, 39]. However, across studies reviewed, the period over which prescribing data were collected varied widely from as short as 1 day to as long as 24 months. Nineteen studies reported data collection period less than 1 year and these are likely to be prone to seasonal variations in prescribing and may not necessarily represent usual trends.

***Average number of medicines prescribed per patient encounter***

Information on the number of medicines prescribed per patient encounter on average was obtained from 40 studies covering a total patient encounter of 138,671. Among these studies, the median number of medicines prescribed per patient encounter was 3.1 (IQR 2.3- 4.8) (**Table 3**). The average number of medicines prescribed per patient encounter was higher for public 2.6 (IQR 2.2-4.7) than private 2.5 (IQR 2.3-3.2) centres. The reported average medicines prescribed per patient was higher for studies published in the period 2006-2015 (3.5; IQR 2.2-5.6) than the period 1995-2005 (2.4; IQR 2.3-4.0).

***Percentage of medicines prescribed by generic name***

Generic prescribing rate was reported in 33 studies covering a total of 121,797 patient encounters. Among these studies, the generic prescribing rate was 68.0% (IQR 55.4-80.3). Public PHCs reported a higher percentage (68.9%; IQR 57.6-84.5) of medicines prescribed generically than private centres (61.3%; IQR 47.7-75.7). Generic prescribing rate for studies published in the period 2006-2015 (70.4%; IQR 60.7-81.1) was higher than for studies published in the period 1995-2005 (64.2%; IQR 51.9-77.9).

***Percentage of encounters with antibiotic prescribed***
Data on antibiotic prescribing rate was also retrieved from 34 studies comprising of a total of 120,422 patient encounters. The overall proportion of encounters resulting in the use of antibiotics was 46.8% (IQR 33.7-62.8). Public PHCs reported lower antibiotic prescribing rate (45.0%; IQR 30.13-60.2) compared to private facilities (51.3%; IQR 37.5-66.6). Higher antibiotic prescribing rate was recorded among studies published in the period 2006-2015 (49.0%; IQR 37.8-63.1) than for those published in the period 1995-2005 (43.1%, IQR 33.7-61.7).

***Percentage of encounters with injection prescribed***
Injection prescribing rate was retrieved from 32 studies consisting of a total 40,096 patient encounters. The overall proportion of encounters resulting in the prescription of an injection was 25.0% (IQR 18.7-39.5). The proportion of encounters at public PHCs which resulted in the prescription of an injection was determined as 25.6% (IQR 14.1-44.8) while that of private facilities was 29.0% (IQR 19.0-39.5). Injection prescribing rate was higher across studies published in the period 2006-2015 (25.0%; IQR 17.1-41.4) compared to studies published in the period 1995-2005 (24.8%; IQR 18.7-37.4).

***Percentage of medicines prescribed from an essential medicines list or formulary***
A total of 27 studies involving a combined number of 101,077 medicines prescribed presented rate of use of EML. The overall proportion of medicines prescribed from an EML was determined as 88% (IQR 76.3-94.1). Higher proportion of prescriptions from public centres (89.9, IQR 82.9-95.6) adhered to the use of EML than private centres (84.0%; IQR 69.8-91.9). EML use rate was higher among studies published in the period 2006-2015 (88.9%; IQR 70.8-94.0) than for the studies published within 1995-2005 (87.1%; IQR 84.9-92.0).

**Table 3:** Summary of Prescribing Indicators at PHCs within the WHO African Region**.**

## DISCUSSION

***Average number of medicines per patient encounter***
Our review showed a high number of medicines (3.1) prescribed per patient encounter. This value is higher than that reported by the WHO factbook for the African region (2.6) and that for the European (2.5), Southeast Asia (2.5) and the Americas (1.8) regions [14]. The WHO analysis was however based on a larger number of studies as the review was not limited to studies published in peer-reviewed journals, but included those reported in NGOs and Ministry of health reports and from other grey literature. On the other hand, although the WHO factbook and other reports have generally reported higher number of medicines prescribed per patient in private compared to public facilities we found the reverse with slightly higher number of medicines per patient in public (2.6) than private (2.5).

A generally high number of medicines prescribed per patient exceeding WHO reference value may point to polypharmacy as an increasing problem in Africa. Many parts of the region are experiencing a changing epidemiological transition creating a double disease burden of both communicable and NCDs [68] and there is evidence that poly-pharmacy becomes more prominent when health personnel need to treat multiple diseases simultaneously [69, 70] . Additionally, demographic shifts in most parts of Africa is resulting in an increasing elderly population who are likely to suffer significant co-morbidities and need for multiple medications [71, 72]. In countries like Ghana, Kenya, Nigeria and Tanzania the population aged 60 and over is projected to increase by around 147%, 144% and 80%, respectively between 2005 and 2030 [73]. Such patterns may partly account for the observed higher number of medicines prescribed per patient in the period 2006-2015 (3.5) as compared to the period 1995-2005 (2.4). Nonetheless, a number of studies reviewed reported very high levels of symptomatic management of cases [44, 50], and this may have contributed to the overall high number of medicines prescribed per patient.

Excessive use of multiple medicines per patient (poly-pharmacy) is likely to result in increased risk of adverse drug interactions, dispensing errors and decreased patients' knowledge of the correct doses of

medications. In the study in Nigeria by Uzochukwu et al [67], the percentage of patients remembering their dosing schedules decreased significantly as the number of medicines increased whereas Kapp *et al* [45] reported a direct correlation between the number of medicines prescribed and the occurrence of adverse events in South Africa. The occurrence of adverse events emanating from poly-pharmacy can create a cycle of health demands and costs as new treatments may be required [74].

***Percentage of medicines prescribed by generic name Generics***

The generic prescribing rate attained in this study (68.0%) was lower than that recommended by the WHO (100%). This result however portrays a better generic prescribing rate than reported by the WHO factbook for the African region (60%) albeit based on smaller number of studies. However, the results appear lower when compared to values reported for the WHO's Western Pacific region (78%), although higher than generic prescribing rates reported for the Eastern Mediterranean (27.7%) and Southeast Asian regions (48.9%) [14]. The lower generic prescribing rate observed in private than public centres is consistent with trends reported by the factbook and in other WHO reports [1, 14, 15].

The overall improved generic prescribing rate as documented by higher generic prescribing for the period 2006-2015 compared to the period 1995-2005 may be due to the increasing availability of standard medicines as generics. For instance, over 45 top brand medications are expected to have patent expired between 2011 and 2020 and thus likely to make generic versions readily available [75]. Once availability improves, lower cost becomes an incentive that could drive generic prescription. As an example; higher rates of generic prescribing [for proton pump inhibitors (PPIs) and statins] were seen in South Africa in 2010/2011 among patients enrolled into medical aid schemes receiving discounted medications [76]. In Netherlands, similar trends have been observed where about threefold increase in statins utilization was observed between 2000 and 2010 despite a 58% decrease in reimbursed expenditure mainly as a result of multiple supply and demand measures, including a preferential pricing policy [77]. Moreover, in recent years, considerable education and studies demonstrating no difference in outcomes between originators and generics across a wide range of products and classes including antipsychotics, anti-infectives and cardiovascular medicines have been undertaken and these may have contributed to the increase in generic prescribing [78-81].

The lower generic prescribing rates observed for private facilities may be due to the fact that prescribers in the private sector may perceive generic medicines as not financially rewarding as patients typically purchase medicines from same facilities and there may be a financial incentive to prescribe most expensive products [22]. Moreover, the prescribing of innovator (expensive) brands in the private sector may be due to prescriber's quest to satisfy the expectations of their clients (often the - well -to do) who may falsely perceive the issuance of expensive (innovator) medicines as constituting 'quality care'. Persistent prescription of branded (innovator) medicines is likely to result in increased treatment costs. In a study by Nwolisa *et al* at outpatient centres in Nigeria, the difference in cost between same drugs prescribed in brand names as against generic names were between 41.7% and 60% [71]. Nicolosi and Gray investigated the cost impact of generic and proprietary prescribing among chronic disease patients in South Africa and their findings indicated that of "all generic medicines identified 67.5% were more than 40% cheaper, per defined daily dose (DDD) per month, than the branded version" [72]. An analysis of facility-based medicines price data from 17 countries by Cameron and Laing [82], found that an average of 9-89% could be saved by switching from originator brands to lowest-price generic equivalents. To further improve generic prescribing diverse approaches may be adopted including addressing fears related to generics, thorough education of prescribers (beginning when they are in school or training) or in some instance the adoption of a compulsory INN prescribing policy [83, 84].

***Percentage of encounters with an antibiotic prescribed***

The percentage of encounters with antibiotics prescribed in this review was 46.8% which exceeds the reference value of <30% recommended by the WHO [12]. The antibiotic use rate in this study is however similar to that reported by the WHO (47%) [14]. However, it is lower when compared to estimates provided for the Eastern Mediterranean region (53.2%) but higher than that of the Americas (39.3%) and European (33.5%) regions [14]. A higher value for antibiotic use was reported for the private facilities (51.3%) than public facilities (45%) which does suppose that antibiotic prescribing may be more of a problem in the private than public sector-an observation consistent with WHO reported trends [1, 14].

The higher antibiotic prescribing rate reported for the 2006-2015 period than for the 1995-2005 period may point to a non-improving or potentially worsening problem of antibiotic use in Africa. The overall high levels of antibiotic prescribing may partly be accounted for by the extensively documented high burden of infectious diseases within the African region. For instance, in the studies included in the review by Massele *et al.* [50] in Tanzania, Enato *et al.* [41] in Nigeria and Bosu and Ofori-Adjei [39] in Ghana, 58%, 38.3%, and 22% of conditions presented at the PHCs respectively were attributable to infectious diseases (excluding malaria). These high levels of reported infections are likely to contribute to high level of antibiotic prescribing. Additionally, in many parts of Africa, HIV/AIDS remains endemic which although does not require the use of antibiotics can increase the prevalence of opportunistic bacterial infections necessitating the use of antibiotics [53].

Not all antibiotic prescribing and use is appropriate. In a number of studies, antibiotics were reported as been prescribed to treat diseases like malaria, diarrhoea and RTIs (mostly viral in origin) conditions which do not usually require antibiotic use [40, 56, 59]. At PHCs in many parts of Africa, microbiology laboratory facilities are often non-existent and as such prescribers may rely mainly on their clinical judgment. While empirical use of antibiotics based on clinical judgment other than laboratory confirmations is permitted in many instances such as otitis, apparent pneumonia and cellulitis, it is well recognized that consistent use of antimicrobials when infection or diagnosis has not been established or fully confirmed can lead to overprescribing [85]. While it is recommended good practice that medicines are written for specified diagnosis in one study conducted in Nigeria by Isah [44], over 50% of the patients' folders reviewed had no established diagnosis whereas another study conducted in Ethiopia by Desta *et al.* [40] reported that any compliant presented by patient was recorded as final diagnosis. One study investigated prescribing patterns across different health professionals and found higher level of antibiotic prescribing more prevalent in lower cadre staff like community nurses and health assistants than in medical doctors and pharmacists [8]. However across all the studies, higher antibiotic use were generally reported for mix of health workers (physicians, nurses, medical assistants etc.). Lack of in-service training was recognised as contributing to poor prescribing practices as demonstrated by one study in Ghana, in which the investigators reported that for the PHCs surveyed, none of the prescribers had received an in-service training in the preceding 5 years [39].

In addition to lack of adequate training, prevailing socio-cultural factors and demand are known to influence irrational antibiotics use [86]. These factors were reported by some studies to have influenced prescribing behaviours [40]. In private settings, prescribers are more likely to adhere to patient demand for antibiotics and injections for fear of losing out on customers and this may underline the higher antibiotic prescribing rate observed. Some studies found a correlation between patient overload and injection and antibiotic use [22, 64]. In many parts of Africa there are widespread reports of acute shortage of health staff, therefore in many instances, there is increased likelihood of personnel playing dual role of prescriber and dispenser. Such occurrences can be a breeding ground for irrational prescribing as no control mechanisms will be in place to check wrong, incorrect or poor prescribing. Dispensing prescribers are particularly worrying in the private-for-profit sector where there may be financial incentives for over-prescribing. For instance, Trap et al found that PHC dispensing doctors were more likely to prescribe antibiotics than non-dispensing doctors in Zimbabwe [22]. Prescribers may find it more convenient and time-saving to prescribe an antibiotic rather than educate a patient that his condition does not require an antibiotic as it will require more lengthy discussion [87]. In a study in Ghana by Polage et al. [88], ninety-eight percent of physicians stated that they rarely order or never order tests, because of time constraints.

Indiscriminate use of antibiotics backed by no diagnostic certainty can contribute to the development of drug resistance [85]. In one study included in this review, the researchers carried out further antibiotic sensitivity testing. Their findings indicated that, vaginal and endocervical isolates were always resistant to the commonly used antibiotics such as ampicillin and tetracycline but almost always sensitive to antibiotics like cefuroxime and gentamicin which were less frequently prescribed at the facilities [39]. The development of antibiotic drug resistance can cause significant morbidity and mortality as infectious disease rates remain high in the African region. High use of antibiotics is also costly and the development of resistance can further aggravate treatment cost by requiring the use of more powerful and expensive antibiotics which are likely to be unavailable in many parts of Africa. In the Bosu and Ofori-Adjei study in Ghana, antibiotics alone accounted for about 40% of treatment cost in patients in whom they were prescribed [39].

***Percentage of encounters with an injection prescribed***

The overall injection use rate determined in this study was 25.0% which exceeds the reference value (<20%) recommended by the WHO [12]. The WHO fact book reported an injection use rate of 27.5% which is a bit higher than that attained in this study [14]. The result also indicates a higher use of injectable medications when compared to results reported for Eastern Mediterranean (20.1%), European (17.2%) and West Pacific (23.2%) regions. In comparison, the study found higher use of injections at private facilities (29%) than at public centres (25.6%) which is also in accord with global trends reported by the WHO [1, 14]. The similar injection prescribing rate in the periods 2006-2015 and 1995-2005 may highlight a non-changing injection use behaviours among health personnel in the region.

Widespread injection prescribing was reported across all mix of health workers (doctors, nurses, medical assistants etc.). Patient preference, socio-cultural beliefs have been also noted to influence prescribing behaviours. In a study by Massele and Mwaluko in Tanzania, it was reported that some patients walked into the PHC facility with their own supply of injectable medicines, syringes and needles asking for them to be prescribed these medicines because they believed injections were more powerful in restoring and maintaining health than other formulations [89]. As indicated previously, patient influences are likely to be felt more in the private sector where there may be a financial implication if prescribers do not adhere to patient demands. As the administration of injections often requires supervision by skilled health care providers, the frequency of prescription of injectable medications is important [90]. Excessive and indiscriminate use of injections can increase the risk of spreading blood-borne diseases such as hepatitis B and even HIV/AIDS especially in a region where infections rates remain high. Moreover, overuse of injections sets up a cycle of repeated visits putting pressure on healthcare staff and driving costs.

***Percentage of medicines prescribed from an essential medicines list or formulary***

The overall EML prescribing adherence of 88.0% in this study is comparable to the 87.8% reported by the WHO albeit lower than the optimal recommended value (100%) [13]. The EML prescribing rate presented in this review is higher when compared to estimates reported for other regions like the European (55.1%), Americas (71.4%) and the South East Asia (81%) regions [14]. The results obtained indicate that adherence to EML when prescribing is better at public (93.5%) that private facilities (83.95%), a pattern consistent with what has been reported previously by the WHO [14, 15].

The general high EML prescribing rate may be due to wider adoption of the use of EML in many countries as well as expanding number of medicines on various EMLs [91]. Regardless, the non-optimal use of EML as reported in this study can be attributed to a myriad of factors such as ineffective distribution of EML, inadequate sensitization among health workers and a general lack of enforcement mechanisms. In separate studies by Bosu and Ofori-Adjei [39] and Odusanya and Oyediran [7] conducted in Ghana and Nigeria respectively, all the facilities studied lacked a copy of an EML. Moreover, some studies reported that the main source of information for prescribers were drug representatives [39, 49]. Such sources have been documented to be problematic as drug companies may over-represent the efficacy of their medicines, discredit the efficacy of competitor brands and likely to induce prescribers to prescribe outside established guidelines [92, 93]. The lower EML adherence observed in private practice may be due to the fact that in many countries in Africa, the private sector is encouraged but not obliged to prescribe from EML as may be the case for public centres [53].

***Limitations***

This systematic review has some limitations. Firstly, the identified studies were concentrated in a few (11 out of 47) countries in the studied region. While a lack of research into this area in parts of Africa may have contributed to this; it may have also been due to the inclusion of only articles published in English and also the exclusion of grey literature. Around one-third (32.6%) of studies included in the review involved patient encounters <600 and were deemed to be small per recommendations outlined in the WHO guidelines [10]. This review also took the assumption that the African region is homogenous although in reality, there may be differences in disease burden, health system challenges, socio-cultural and political climates across countries which all can affect how medicines are used. Majority of the studies (74%) also collected data retrospectively. We consider that retrospective analysis may result in the overestimation of poly-pharmacy

(average number of medicines), antibiotic utilization and injection use because patients who were not given a prescription are likely to be excluded [25]. In our analysis we stratified results by key sector (public and private) but did not control for differences in prescriber characteristics. Therefore, the apparent differences in the prescribing indicators between the two sectors may be due to multiple factors. We assessed prescribing indicators at two time points and this is unlikely to reveal much about prescribing trends. Importantly, this review reports indicator-based studies which are unable to ascertain whether the reported prescribed medicines were actually taken by the patients involved. Indicator-based studies while able to identify medicine use problem areas, do not answer the question of rationality or appropriateness of treatment which may require a different methodology and analysis [23]. It is also important to reiterate that while the WHO proposed reference values are important, these have not been empirically determined [25]. While our review has analysed data on studies published over the last two decades, it is possible that some studies covered in grey literature may have been missed.

**Conclusion**

The values obtained in this review deviate significantly from the WHO recommended reference values. While our review is based on limited studies, it does highlight that some improvements in prescribing practices are needed. The prescribing patterns observed are reflective of population factors as well as varied health system challenges on the African continent. Increased collaborative efforts are therefore required to improve medicine prescribing practices in the region. This is necessary not only to avert negative health consequences but also to afford the optimal utilization of scarce resources.

## DECLARATIONS

### Ethical Approval
An ethical approval was not required for this study as it did not report any individual data but relied on aggregate data from published studies already available in the public domain.

### Consent to publish
Not applicable

### Availability of data and materials
We declare that the data supporting the conclusions of this article are fully described within the article.

### Competing interests
The Authors declare no competing interests.

### Funding
None

### Authors' Contributions
RO conceived the study, undertook the literature review and appraisal, analysis and first draft. PB and AP contributed to the design of the study, supervised the study analysis and contributed to drafting of the manuscript. All authors read and approved the final content of this manuscript.

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### Abbreviation
WHO: World Health Organization
HIV: Human Immunodeficiency virus
AIDS: Acquired immune deficiency syndrome
PHC: Primary health care
EML: Essential medicines List
NCD: Non communicable disease
LRI: Lower respiratory infection
GDP: Gross domestic product
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RTI: Respiratory tract infections

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**Box 1: Critical Appraisal Checklist**

1. Objective of the study clearly described
2. Study design or data collection methods clearly stated
3. Participants representative of a general patient population (Ideally studies of prescribing indicators should involve a sample of general illness encounters representing a mix of health problems)
4. Adequate sample size (WHO recommends a minimum of 600 encounters)
5. Whether type of facility was specified (i.e. public or private)
6. Whether the number of facilities involved was specified
7. Patient age/gender and other characteristics reported
8. Whether study described how medicines were counted (WHO recommends that FDCs should be counted as one)
9. Whether study defined the medicines to be regarded as antibiotic according to the WHO/INRUD classification if antibiotic indicator was assessed (Only affects quality in terms of % antibiotics use).
10. Whether the reference essential medicines list (EML) used in the study was specified. Researchers may utilize the WHO model EML, facility EML or national EML as reference guide.
11. Whether study specified the medicines regarded as injections. Ideally, routine immunizations should not be counted as injections (Only affects quality in terms of % of injections use).
12. Whether the statistical method employed in analyzing the results of the study was appropriate and fully described.
13. Whether the study described how missing data was handled and if any confounders
14. Whether the study results were discussed appropriately. For instance, if conclusion (s) were relevant to the findings.

| WHO prescribing Indicator | Reference Value |
|---|---|
| Average number of medicines per encounter | <2 |
| Percentage of medicines prescribed by generic name | 100% |
| Percentage of encounters with an antibiotic prescribed | <30% |
| Percentage of encounters with an injection prescribed | <20% |
| Percentage of medicines prescribed from an essential medicines list or formulary | 100% |

**Table 1: WHO prescribing indicators and reference values [12, 13]**

**Table 2:** Descriptive characteristics of included studies

| No. | Author Details | Year of Publication | Country | Data collection method | Data collection duration | Mean age of patients | Type of facility (s) | No. of facilities | Setting | Prescriber type (s) | No. of patient encounters |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Abdella and Wabe [27]. | 2012 | Ethiopia | Retrospective | 1year | n.s | Public | 1 | Urban | Health Officers | 384 |
| 2. | Adisa et al [28]. | 2015 | Nigeria | Prospective | 3months | ≥15 | Public | 8 | Urban | n.s | 400 |
| 3. | Afriyie and Tetteh [29]. | 2013 | Ghana | Retrospective | 7months | n/s | Public | 1 | urban | Medical assistants, Doctors | 120 |
| 4. | Afriyie et al [30]. | 2015 | Ghana | Prospective | 6months | n/s | Public | 1 | Urban | Medical assistants, doctors | 3127 |
| 5. | Ahiabu et al [31]. | 2015 | Ghana | Retrospective | 1 year | n/s | Private & Public | 4 (public=1, private=3) | Urban | Doctors, medical assistants | 1600 |
| 6. | Angamo et al [32]. | 2011 | Ethiopia | Prospective | 6weeks | n/s | Public | 4 | Urban | n.s | 3058 |
| 7. | Babalola et al [5]. | 2011 | Nigeria | Retrospective | 1 year | 19.4 years | Public | 20 | n/s | Community health workers, physicians, health assistants, pharmacy technicians, nurses and Pharmacist | 560 |
| 8. | Ball et al [33] | 2000 | Zimbabwe | Prospective | n/s | n/s | Public | 1 | Urban | nurses | 31 |
| 9. | Bantie [34] | 2014 | Ethiopia | Prospective | n/s | n/s | Public | 6 | n/s | n.s | 600 |
| 10 | Bexell et al. [35] | 1996 | Zambia | Retrospective | 3months | n/s | Public | 8 | Urban | Clinical officers | 1167 |
| 11 | Boonstra et al.[36] | 2002 | Botswana | Prospective | n/s | 25.5 | Public | 30 | Rural & Urban | Registered nurse, Family nurse practitioner | 2994 |
| 12 | Boonstra et al.[37] | 2005 | Botswana | Prospective | n.s | <5 | Public | 30 | Rural & Urban | Nurses | 255 |
| 13 | Bosu and Ofori-Adjei [38] | 2000 | Ghana | Retrospective | 1 year | 15 years | Public | 6 | Rural | Doctors and medical assistants | 585 |
| 14 | Desta et al. [39] | 1997 | Ethiopia | Prospective & Retrospective | Prospective 1-2 days Retrospective-1yr | n/s | Public | 18 | n/s | n.s | 2,340 |
| 15 | Dippenar et al.[40] | 2006 | South Africa | Prospective | 2month | n/s | Public | 1 | Urban | Doctors, nurses | 1000 |
| 16 | Enato et al.[41] | 2012 | Nigeria | Retrospective | 6 months | n/s | Public | 1 | Rural | Doctors, nurses | 315 |
| 17 | Enato et al.[42] | 2013 | Nigeria | Retrospective | 1year | n/s | Public | 3 | Urban | Community health officers | 1440 |
| 18 | Isah.[43] | 2008 | Nigeria | Retrospective | 1 year | n/s | Private | 20 | Rural | n.s | 2,510 |
| 19 | Kapp et al.[44] | 2013 | South Africa | Retrospective | 3months | 41.0 years | Public | 4 | Urban | n.s | 400 |
| 20 | Katende-Kyenda et al. [45] | 2007 | South Africa | Retrospective | 1year | n.s | private | 9 | Urban | n.s | 83655 |
| 21 | Krause et al.[46] | 1999 | Burkina Faso | Prospective | 2months | n/s | Public | 9 | Rural | nurses | 313 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 22 | Massele and Nsimba. [47] | 1997 | Tanzania | Prospective | 20 days | n/s | Public & Private | 40 (public= 20, private=20) | Urban | n.s | 1,200 |
| 23 | Massele et al.[48] | 2001 | Tanzania | Retrospective | 14 months | n/s | Private | 20 | Rural & Urban | Doctors | 1,200 |
| 24 | Massele et al.[49] | 2007 | Tanzania | Retrospective | 1 year | n/s | Public & Private | 20 (public= 10, Private=10) | n/s | n.s | 2,000 |
| 25 | Massele et al.[50] | 2012 | Tanzania | prospective | 3months | n/s | Public & Private | 20 (public=10, private=10) | Urban | Clinical officers, and other paramedics | 2,000 |
| 26 | Meyer et al.[51] | 2001 | South Africa | retrospective | 1month | n/s | public | 22 | n/s | nurses | 1,287 |
| 27 | Mohlala et al.[52] | 2010 | South Africa | prospective | 5months | n/s | private | 36 | Rural & Urban | Doctors | 276 |
| 28 | Nsimba et al.[53] | 2004 | Tanzania | Retrospective | 1year | n/s | private | 10 | n/s | n.s | 600 |
| 29 | Nsimba.[54] | 2006 | Tanzania | Prospective | n/s | <5years | Public | 10 | n/s | n.s | 652 |
| 30 | Odusanya & Oyediran.[6] | 2000 | Nigeria | Retrospective | 6months | n/s | Public | 12 | n/s | Community health officers, Public health nurses | 650 |
| 31 | Olayemi et al.[55] | 2006 | Nigeria | Prospective & Retrospective | Prospective-2-3days Retrospective-n/s | n/s | Public | 20 | Rural & Urban | n.s | 1,560 |
| 32 | Oyeyemi & Ogunleye.[56] | 2013 | Nigeria | Retrospective | 1year | 34years | Public | 4 | Urban | Medical officer, community health officer, nurses and community health extension workers | 600 |
| 33 | Phillips-Howard et al.[57] | 2003 | Kenya | Retrospective | 1year | <5 | Public | 8 | Rural | n.s | 9,318 |
| 34 | Risk et al.[58] | 2013 | Gambia | Retrospective | 1 year | 1.71 | Public | 20 | Rural & Urban | n.s | 2,400 |
| 35 | Savadogo et al.[59] | 2014 | Burkina Faso | Prospective | 1month | <5 | Public | 2 | Urban | n.s | 376 |
| 36 | Shiferaw et al.[60] | 2010 | Ethiopia | Retrospective | 1 year | n/s | Public | 19 | n/s | n.s | 731 |
| 37 | Sisay and Mekonnen.[61] | 2012 | Ethiopia | Retrospective | 2years | n.s | Public | 2 | Urban | n.s | 424 |
| 38 | Suleman et al.[62] | 2013 | Nigeria | Retrospective | 3months | n/s | public | 10 | n/s | n.s | 222 |
| 39 | Tamuno.[63] | 2011 | Nigeria | Retrospective | 1year | n.s | Private | 10 | Urban | n.s | 998 |
| 40 | Trap et al.[22] | 2002 | Zimbabwe | Retrospective | <6 months | n/s | Private | 57 | urban | Doctors | 1,699 |
| 41 | Truter et al.[64] | 2010 | South Africa | Retrospective | 8weeks | n/s | Public | 1[m] | Rural | Supervised student trainees | 4026 |
| 42 | Tsega et al.[65] | 2012 | Ethiopia | Retrospective | 1 year | 25 years | Public & Private | 11 (public=3, private=8) | Rural & Urban | n.s | 600 |
| 43 | Uzochukwu et al.[66] | 2002 | Nigeria | Retrospective | n/s | n/s | Public | 33 | n/s | n.s | 1,650 |

n.s: not specified
m: mobile clinic

**Table 3:** Summary of prescribing indicators at PHCs within the WHO African region

| | Prescribing Indicators | | | | |
|---|---|---|---|---|---|
| | Average number of medicines prescribed per encounter ℓ | Percentage of medicines prescribed by generic name | Percentage of encounters€ with an antibiotic prescribed | Percentage of encounters€ with an injection prescribed | Percentage of medicines prescribed from an essential medicines list |
| **WHO reference values (10,11)** | **<2** | **100%** | **<30** | **<20** | **100%** |
| *Facility Type* | | | | | |
| All | 3.1 (IQR 2.3-4.8) n=138,671 | 68.0% (IQR 55.4-80.3) n=121,797 | 46.8% (IQR 33.7-62.8) n=120,422 | 25.0% (IQR 18.7-39.5) n=40,096 | 88.0% (IQR 76.3-94.1) n=33140 |
| Public℘ | 2.6 (IQR 2.2-4.7) n=44,596 | 68.9% (IQR 57.6-84.5) n=28046 | 45.0% (IQR 30.1-60.2) n=26,071 | 25.6% (IQR 14.1-4.8) n=28,400 | 89.9% (82.9-95.6) n=23,044 |
| Private℘ | 2.5 (IQR 2.3-3.2) n=92,475 | 61.3% (IQR 47.7-75.7) n=92,151 | 51.3% (IQR 37.5-66.6) n=92,751 | 29.0% (IQR 19.0-39.5) n=10,096 | 84.0% (IQR 69.8-91.9) n=8,496 |
| *Studies publication period* | | | | | |
| 1995-2005 | 2.4 (IQR 2.3-4.0) n=25,289 | 64.2% (IQR 51.9-77.9) n=13,949 | 43.1% (IQR 33.7-61.7) n=15,971 | 25.0% (IQR 17.1-41.4) n=14,549 | 87.1% (IQR 84.9-92.0) n=10,324 |
| 2006-2015 | 3.5 (IQR 2.2-5.6) n=113,382 | 70.4% (60.7-81.1) n=107848 | 49.0% (IQR 37.8-63.1) n=104,451 | 24.8% (IQR 18.7-37.4) n=25,547 | 88.9% (IQR 70.8-94.0) n=22,816 |

IQR=interquartile range n=total number of patient encounters used in analysis ℘=excludes Ahiabu et al.[32] which did not provide individual results for public and private facilities.