

1 **Title: Drug utilization patterns in the global context: a systematic review**

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37 **Funding:** No funding was involved in the preparation of this systematic review or in the decision to submit it
38 for publication.

39 **Key Words:** Prescribing indicators, Patient-care indicators, Facility-specific indicators, World Bank regions,
40 Income level, Rational drug use.

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1 **Highlights**

2 This systematic review found that:

- 3 • Average number of drugs per prescription met optimal levels for all World Bank regions
4 except Latin America and the Caribbean.
- 5 • Improvement needed in percentage of antibiotics prescribed per prescription in all regions
6 of the world.
- 7 • There is no country where the percentage of drugs prescribed by generic name is at optimal
8 levels.
- 9 • Average consultation time of physicians was below the optimal value (≥ 10 minutes) except
10 for Europe and Latin America.
- 11 • The percentage of drugs dispensed and availability of essential drugs was close to optimal
12 except in Europe and Latin America.

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ABSTRACT

Objectives: Standard drug use indicators have been developed by the World Health Organization/International Network for Rational Use of Drugs (WHO/INRUD). The objective of this systematic review was to evaluate, and report the current status of drug use within health systems in different regions of the world.

Design: Systematic review of the literature following PRISMA guidelines.

Methods: The INRUD bibliography, WHO archives, Google Scholar, Medline, PubMed, SpringerLink, ScienceDirect and Management Sciences for Health (MSH) resource databases were searched between 1985 and 2015 for studies containing 12 WHO/INRUD core drug use indicators. Secondary data sources were also searched.

Results: Four hundred and sixty three studies were retrieved and 398 were excluded as they did not provide relevant information or fulfill the selection criteria. Sixty articles met the criteria and were selected for final review. With respect to prescribing indicators, studies of “drug use” showed mixed patterns across geographic regions. Overall trends in “patient-care” and “facility-specific” indicators were similar across most of the World Bank regions.

1 However, based on the Index of Rational Drug Use (IRDU) values, East Asia and the Pacific
2 region demonstrated relatively better drug use practices compared with other regions.

3 **Conclusions:** This systematic review revealed that the drug use practices in all regions of the
4 world are suboptimal. A regulated, multi-disciplinary, national body with adequate funding
5 provided by governments throughout the world is a basic requirement for coordination of
6 activities and services, in-order to improve the rational use of drugs at a local level.

7 **Keywords:** Prescribing indicators, Patient-care indicators, Facility-specific indicators, World
8 Bank regions, Income level, Rational drug use.

1 **INTRODUCTION**

2 Medicines are the single most common therapeutic intervention and a crucial component
3 of medical care for any healthcare system [1]. According to the World Bank, in developing
4 countries, 20–50% of the health care expenditures are spent on drugs and other medical products
5 [2]. The appropriate use of drugs is essential for optimizing individual patient health and the
6 population health of any nation [3]. In 1985, the World Health Organization (WHO) organized a
7 conference to promote the rational use of drugs [4]. Since then, efforts have been augmented to
8 improve drug use, particularly in under-developed as well as developing countries [5]. According
9 to the WHO, the rational use of drugs requires that patients receive drugs appropriate to their health
10 problems, in optimal doses for correct duration at minimum cost to individuals and the nations’
11 health system [2, 6, 7]. There are numerous factors that influence rational prescribing for example;
12 the medical state of patients, beliefs, values and prescribing behaviour of physicians, the working
13 environment within the health system, the drug supply system, legislation, and information
14 available about the drugs [8-12].

15 Irrational prescribing of drugs by doctors and suboptimal drug use by patients is a global
16 problem. Studies have shown that worldwide over 50% of all drugs are prescribed or sold
17 incorrectly, and 50% of patients do not use drugs optimally [2]. Inappropriate prescribing practices
18 and irrational use of drugs can result in unsafe and ineffective treatment resulting in morbidity and
19 mortality and harm and distress to patients Increases in out-of-pocket expenses for patients and a
20 general waste of resources also occurs [2, 13]. In low and middle income countries, these problems
21 are exacerbated by restrained economic resources and lack of regulated drug policies [14].
22 According to published studies, poly-pharmacy, inappropriate antibiotic use, overuse of injectable
23 drugs, use of prescription drugs inconsistent with clinical guidelines, and less than optimal self-

1 medication are the major reasons for irrational drug use [2]. The increase in resistance due to the
2 overuse of antibiotics is a considerable problem of irrational drug use [2, 15]. Irrational drug use
3 has also been reported to reduce patients' confidence in their own health care systems [2].

4 Essential Drugs List (EDL) promotes efficient and effective use of medicines. The choice
5 of essential drugs is complex and the needs of the population must be considered as part of the
6 selection process. This is specifically with respect to diagnosis, prophylaxis, treatment (therapy)
7 and rehabilitation using parameters of the risk-to-benefit ratio, quality and practical management,
8 cost effectiveness, and patient acceptance and compliance [8, 9, 16]. Approximately one-third of
9 the world's population does not have access to essential drugs [2] either because they are not
10 included in the EDL, or key drugs on the EDL are not available at the time of prescribing.

11 Previous studies have shown that drug use practices are less than optimal [16]. To better
12 understand pattern of drug use and to allow quantification and comparison through systematic
13 means, standardized drug use indicators have been developed by the World Health
14 Organization/International Network for Rational Use of Drugs (WHO/INRUD) [3]. To-date, these
15 standard drug use indicators have been successfully used in developing countries for performance
16 management and process improvement [3, 17, 18].

17 The purpose of this systematic review was to examine and report the current status of health
18 facilities in different regions of the world in terms of drug use based on WHO/INRUD core drug
19 use indicators [2] (see Table 1). A review article [19] and a fact book published by the WHO [20]
20 reports the results based on data available up to 2009. The contribution that this current systematic
21 review makes is in the detailed description of patient-care and facility-specific indicators and
22 presentation of evidence that results in greater generalizability of individual indicators within a

1 variety of World Bank regions. This paper also uses published indices [15, 21, 22] to compare the
2 rational use of drugs within different regions of the world. This systematic review provides useful
3 information for researchers, administrators, policymakers and other important stakeholders to
4 evaluate existing patterns of drug utilization at global, national, regional and local levels.
5 Furthermore, this review informs the formulation of educational interventions, national drug
6 policies and National Essential Drugs Lists (NEDL), as well as hospital formularies, in-order to
7 improve prescribing patterns and the cost-effective use of drugs.

8 **< Insert Table 1 here >**

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1 **METHODS**

2 Published studies and scientific reports containing 12 WHO/INRUD core drug use
3 indicators were systematically identified for the period 1st January 1985 to 31st December 2015.
4 Studies from developed, developing and transitional countries that presented drug use data were
5 extracted. A systematic review ensured complete collection of literature. The PRISMA guidelines
6 [23] were followed [Appendix 1: PRISMA Checklist].

7 **Search strategy**

8 A systematic search strategy was implemented using WHO archives, Google Scholar,
9 Medline, PubMed, SpringerLink, ScienceDirect and Management Sciences for Health (MSH).
10 Search terminologies included: “Drug use indicators”, “WHO/INRUD”, “Prescribing indicators”,
11 “Patient-care indicators”, “Facility-specific indicators” and “Prescribing behavior” which were
12 used in diverse combinations with BOOLEAN and MeSH search methods. In addition, all studies
13 available in the conference proceedings of the Third International Conference for Improving Use
14 of Medicines (held in Turkey, 2011), were reviewed and included in the search for completeness
15 [24]. Appropriate secondary data sources were also sourced [19, 20, 25]. Initially, 463 studies were
16 identified and retrieved. Of these, 106 were duplicates that were excluded. From the remaining
17 357 articles, over half (169) were excluded based on having irrelevant titles and/or ambiguous
18 content. Subsequently, the full text of 188 articles was read and 123 studies were removed at this
19 point due to failure to provide relevant information. Constructive disagreement amongst the
20 research team regarding study eligibility was resolved through discussion and mutual agreement
21 within team meetings. Sixty five articles made the final selection (Figure 1) based on criteria
22 outlined in Table 2. Three reviewers SS, MRS and MAZ systematically searched the studies from

1 the INRUD bibliography, whilst two independent reviewers checked all studies to verify the
2 validity of screening processes. All authors agreed to include these final studies in the review.

3 **<Insert Figure 1 here>**

4 **< Insert Table 2 here >**

5 **Data entry**

6 A purpose designed data extraction form was used for data entry. Each record described;
7 drug use patterns in countries based on classification by geographical and income level in World
8 Bank regions. A maximum of three studies per country were selected regardless of the number
9 available. Studies were selected which included all standard indicators (or a maximum number) of
10 the most recent ones. A careful literature search revealed that there are a good number of INRUD
11 indicator studies available from counties like China, India, and Ethiopia etc. Contrary to this, only
12 a few studies were available from European countries. Therefore, to maintain uniformity in the
13 data, the researchers developed a criterion that if more than three studies were available from a
14 single country, then a maximum of three of the most recent studies reporting the maximum number
15 of INRUD indicators would be included in the review.

16 All data was entered then rechecked before being exported into Statistical Package for
17 Social Sciences (SPSS v 21.0) and Microsoft Excel 2010 for analysis.

18 **Analysis**

19 Descriptive statistics were used to analyze the data. In this systematic review the primary
20 outcome measures were the 12 commonly reported WHO/INRUD indicators as outlined in Table

1 1. The optimal values for prescribing [13], patient-care and facility-specific indicators [15, 21]
2 were adopted from previous studies.

3 The median value for each indicator was calculated based on the total number of studies in
4 each geographic region according to the World Bank regional classification, as well as the income
5 level classification of the countries analyzed. To assess the rational use of drugs, summary indices
6 were calculated: Index of Rational Drug Prescribing (IRDP), Index of Rational Patient-Care Drug
7 Use (IRPCDU) and Index of Rational Facility-Specific Drug Use (IRFSDU). These indices were
8 developed by employing a validated mathematical model derived by Zhang and Zhi (1995) [26].
9 This is an established model for developing indices that has been well cited with respect to the
10 drug prescribing indicator literature in developing nations including China, Saudi Arabia, United
11 Arab Emirates, Egypt, Pakistan, Sierra Leone, Zambia and Ethiopia [15, 21, 27-32]. For the
12 calculation of indices (index of non-polypharmacy, index of rational antibiotic use and index of
13 safe injection drug use), the following formula was used;

$$14 \quad \text{Index} = \frac{\text{Optimal value}}{\text{Observed value}}$$

15 All other indices (index of generic name, index of EDL, consultation time index,
16 dispensing time index, index of drugs actually dispensed, index of labeling of drugs, index of
17 patients' knowledge, index of EDL availability and index of key drug availability in stock) were
18 calculated using the following formula;

$$19 \quad \text{Index} = \frac{\text{Observed value}}{\text{Optimal value}}$$

20 The maximum value for each of the indices was 1. The close the value to 1 the better the
21 performance for that indices. The Index of Rational Drug Use (IRDU) was calculated by summing
22 the IRDP, IRPCDU, and IRFSDU. The World Bank regions (geographic and income level) were

- 1 ranked based on the IRDU and the regions with the highest IRDU value were considered to be
- 2 performing the best and so; were ascribed a rank of 1.

1 **RESULTS**

2 **Core drug use indicators by World Bank regions**

3 Table 3 outlines studies of prescribing indicators by geographic origin. The majority of
4 studies were undertaken in Sub Saharan Africa, followed by South Asia, East Asia and the Pacific,
5 the Middle East and North African regions, respectively. Very few studies have been conducted
6 in Europe and Central Asia, or Latin America and the Caribbean regions.

7 Findings from this internationally focused systematic review suggest a mixed picture of
8 prescribing patterns across various geographic regions (Table 3). Studies from East Asia and the
9 Pacific region point towards positive performance in this region, with the highest percentage of
10 drugs prescribed from an EDL/formulary, and the highest percentage of generic prescribing.
11 Studies from Latin America and the Caribbean region had the lowest number of drugs per
12 prescription and the lowest number of antibiotics. The percentage of injections prescribed per
13 prescription was similar when comparing all the regions.

14 **< Insert Table 3 here >**

15 Table 4 shows the studies from different countries that measured patient-care and facility-
16 specific indicators in different settings by geographic location. Because of the smaller number of
17 studies, the data from Europe and Central Asia, and Latin America and Caribbean regions is
18 merged into one group.

19 This systematic review suggests that overall trends in patient-care and facility-specific
20 indicators were similar when comparing all regions of the world (Table 4). Low average
21 consultation times as well as dispensing times were observed in all regions of the world except for

1 Europe and Latin America, and South Asia. Studies from East Asia and the Pacific region reported
2 the highest percentage of drugs actually dispensed, the highest proportion of patients with correct
3 knowledge of drug doses, the highest percentage of EDL availability and the highest percentage
4 of key drugs in stock at the time of prescribing. Studies from South Asia reported the highest
5 percentage of adequate labeling.

6 **< Insert Table 4 here >**

7 **Core drug use indicators by World Bank income level regions**

8 Figures 2 and 3 present the overall results of the core drug use indicators by World Bank
9 income level regions. This systematic review indicates disparities in prescribing patterns across
10 regions [Additional file: WHO/INRUD indicators by World Bank income level]. Studies from
11 high income level countries report the lowest percentage of patients prescribed antibiotics and
12 injectable and the highest percentage of drugs prescribed from an EDL/formulary. The generic
13 prescribing rate per prescription was highest for the low income countries which also report the
14 lowest number of drugs per encounter.

15 **< Insert Figure 2 here >**

16 **< Insert Figure 3 here >**

17 With respect to patient-care indicators, studies from high income level countries showed
18 the highest average consultation and dispensing times, along with the greatest percentage of drugs
19 actually dispensed [Additional file: WHO/INRUD indicators by World Bank income level].
20 Studies from lower-middle and upper-middle income level countries report the highest percentage
21 of patients with knowledge of the correct doses and the highest percentage of adequate labeling,
22 respectively. Similarly, with reference to facility-specific indicators, low income level countries

1 had the highest percentage of EDL availability and the highest percentage of key drugs in stock
2 [Appendix 2: WHO/INRUD indicators by World Bank income level].

3 **Summary indices**

4 Table 5 summarizes the overall results of the core drug use indicators in terms of indices; IRDP,
5 IRPCDU, and IRFSDU.

6 **< Insert Table 5 here >**

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1 **DISCUSSION**

2 The irrational use of drugs exists all over the world and ultimately can lead to unwanted
3 effects in most patients [15]. In this systematic review, we identified current treatment practices in
4 different regions of the world using established indicators. This is expected to help prioritize
5 interventions for improving drug use practices, and the evaluation of the outcome of these
6 interventions. Our findings provide useful baseline information for future monitoring and
7 assessments of the rational use of drugs in the international context.

8 **Prescribing indicators**

9 The results of this review show that the average number of drugs per prescription was
10 above optimal levels for all World Bank classified regions except for Latin America and the
11 Caribbean. This is an important finding as poly-pharmacy leads to escalated risk of drug
12 interactions [92], prescribing errors [93], reduced compliance [35], possible adverse effects, and
13 wastage of drugs. This leads ultimately to increased hospital costs [94], as well as fiscal
14 implications for the health-care system. Evidence-based clinical guidelines such as prescribing
15 policies and standard treatment guidelines are crucial for promoting the rational use of drugs as
16 they help prescribers in making appropriate clinical decisions [2]. This study supports an increased
17 focus on this.

18 The percentage of antibiotics prescribed per prescription in these studies suggests that
19 improvement is needed in all regions of the world. Misuse and over-prescribing of antibiotics is a
20 common global problem with potentially dire circumstances. One of the important manifestations
21 of irrational use of antibiotics is the higher probability of antibiotic resistance developing [15].
22 This review suggests that the percentage of encounters for which an injectable dosage form is

1 prescribed is optimal all over the globe, except in Sub Saharan Africa (Table 3). An excessive use
2 of injections when oral formulations are available is not cost-effective nor clinically inappropriate
3 [2] because patients are more likely to suffer from blood borne diseases such as Hepatitis C and
4 HIV [15] and there is no obvious increase in clinical benefit

5 This international review suggests that nowhere in the world is the percentage of drugs
6 prescribed by generic name, at optimal levels. This suggests that practice is not in accordance with
7 policy; the WHO guidelines for rational prescribing [92]. The situation is most alarming in the
8 Middle East and North Africa, as well as in high income level countries; although in high-income
9 countries it may be less of an issue with drug availability and affordability being potentially
10 greater. Non-generic prescribing practices suggests that there is room for reducing national
11 pharmaceutical expenditure; particularly in the developing world Interventions that reduce the
12 significant influence of originator brand pharmaceutical companies on medical prescribers should
13 be thought about. The main advantages of generic prescribing are lower treatment costs and the
14 avoidance of prescription and dispensing errors that may arise due to “look-alike” or “sound-alike”
15 brand names [95]. The WHO deems generic prescribing to be a safety measure for patients as the
16 process allows professionals to clearly depict the drug name and also allows easily accessible
17 information about the drug, and leads to less ambiguous communication among health care
18 providers [15].

19 Unlike with generic prescribing, the percentage of drugs prescribed from EDL/formulary
20 was seen to be almost optimal in most regions except Europe and Central Asia (Table 5). Drugs
21 included in EDL are older, tested in practice, low cost and have established clinical use [15].
22 Furthermore, a smaller number of drugs in EDL makes inventory management less complicated.

1 Similarly, there is less chance of medication errors by prescribers and pharmacists, because access
2 to the appropriate knowledge and information is available for a smaller number of drugs [2].

3 **Patient-care indicators**

4 This systematic review suggests that the average consultation time of the physicians for all
5 regions ranged from 2.3 to 7.3 minutes, which was below the optimal value ≥ 10 minutes except
6 for Europe and Latin America where it was 14.2 minutes (Table 4). According to the WHO, a
7 shorter consultation time is inadequate in-order to conduct a complete patient examination, that is;
8 to conduct proper history taking, complete physical examination, appropriate health education,
9 sound physician-patient interaction and to prescription of therapy [15]. The short consultation time
10 reported in all regions could be the result of a large number of patients to be examined per
11 physician. Similarly, the average dispensing time was also not optimal for all regions of the world
12 (Table 5). The short dispensing time is insufficient to provide complete information to patients
13 about dosage regimen, unwanted drug effects, precautions and checking for adequate labeling and
14 dispensing of drugs. The optimal dispensing time may relate to patient compliance through the
15 information provided and knowledge gained about drugs, which is a primary step in improving
16 patient care.

17 The percentage of drugs actually dispensed was close to the optimal index for most regions
18 except Europe and Latin America (Table 5). An inadequate drug supply will lead to the use of non-
19 essential drugs that will ultimately cause an increase in out-of-pocket expenses for patients. It will
20 have a negative impact on patients' health status, convenience and trust of the health care system
21 [2]. The WHO recommends that each dispensed drug should be adequately labeled including the
22 patient's name, dose of the drug and dosage regimen [3]. At the same time, patient knowledge

1 about the correct dosage is highly influential in promoting treatment adherence. The findings from
2 this systematic review reveal that drug labeling practices were sub-optimal throughout the world
3 (Table 5). Moreover, patients did not have the correct drug dosage knowledge. Omission of the
4 patient's name on the product label is a serious issue that has significant consequences including
5 drug misuse and abuse. Similarly, without satisfactory knowledge about the risks and benefits of
6 drugs and an understanding of proper dosage regimens, patients might not achieve expected
7 clinical results [2].

8 **Facility-specific indicators**

9 The percentage of availability of EDL/formulary listed drugs was close to the optimal index
10 for most regions except Europe and Latin America. However, the percentage of key drugs in stock
11 at the time of prescribing was found to be below the optimal index. Shortage of essential drugs is
12 disadvantageous as it leads to prescribing more costly drugs from the open market. According to
13 the WHO, physicians should be adherent to prescribing the drugs listed in the EDL/formulary. At
14 the same time, concerned authorities at a government level must ensure the availability of essential
15 drugs at health care facilities.

16 **CONCLUSION AND RECOMMENDATIONS**

17 The results of this systematic review reveal that irrational drug use practices are occurring
18 in all regions according to World Bank classification. Irrational utilization of drugs may lead to
19 increased adverse effects, increased morbidity and mortality, greater wastage of resources and
20 higher out-of-pocket expenses for patients. Based on this review the authors recommend that
21 continuous education and training of physicians is needed to reinforce rational prescribing. This is
22 particularly with regards to antibiotics, injectable, generic medicines and prescribing from an EDL.

1 The patient-to-physician ratio should be decreased to allow for prolongation of consultation time,
2 which allows thorough history taking, comprehensive examination and sound therapeutic
3 relationships between patients and physicians. This should also be the case to ensure sound drug
4 dispensing and improvement of patient knowledge through increased duration of counselling
5 sessions. Availability of key drugs in stock should be improved to ensure timely and effective
6 treatment of health related problems.

7 For the effectiveness of given national program which focusses on the safe and rational use
8 of drugs, monitoring of drug use and utilization of collected data for the development,
9 implementation and evaluation of strategies is essential. The authors strongly believe that through
10 the implementation of the 12 core WHO interventions [2] the situation might improve, resulting
11 in more rational prescribing and optimal use of drugs. Future studies should look at the outcomes
12 of these intervention plans for continuous process improvement.

13 **Strengths**

14 This systematic review fills a significant gap in the literature and has the following main
15 strengths;

- 16 • Coverage of the recent studies on the topic under review.
- 17 • Detailed description of patient-care and facility-specific indicators which previous
18 reviews have not summarized. The results are presented such that greater generalizability
19 of individual indicators in different regions of the world is apparent.
- 20 • The authors have used the published WHO/INRUD indices to systematically compare the
21 rational use of drugs among different regions of the world.
- 22 • The findings from this review provide useful information for researchers, administrators,
23 policy-makers and other important stakeholders to evaluate existing patterns of drug
24 utilization at global, regional and national country level.

- 1 • This systematic review is expected to assist in the formulation of educational
2 interventions, drug policies and National Essential Drugs Lists (NEDL) as well as
3 hospital formularies to improve prescribing patterns and the cost-effective use of drugs
4 nationally and internationally.

5 **Limitations**

6 There are a few limitations to this review.

- 7 • Studies reporting the indicators for treatment of illness in populations under 5 years of age
8 were excluded.
- 9 • No interventions and their impacts have been summarized.
- 10 • Studies were not differentiated based on private and/or public sector involvement nor
11 prescriber type.
- 12 • A process of meta-analysis was not performed due to the heterogeneity of results in the
13 included studies.

14 **Authors' contribution**

15 MAT, MRS and MAZ are the primary authors who conceptualized the article. SS MRS
16 and MAZ screened all titles and abstracts and determined whether the studies met inclusion
17 criteria. MAT and ZUDB checked all studies to verify the validity of screening. MAT, ZUDB and
18 SS provided intellectual ideas included in the development and review of the article. MRS and
19 MAZ drafted the initial manuscript. MAT, ZUDB and SS undertook critical revisions of the
20 manuscript. All authors read and approved the final version of the manuscript.

21 **Acknowledgements**

22 **Funding:** None.

23 **Competing interests:** None declared.

24 **Ethical approval:** Not required.

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- 1 **Legends of the figures**
- 2 *Figure 1:* Schematic diagram explaining the assortment of studies/reports
- 3 *Figure 2:* Prescribing indicators by World Bank income level regions
- 4 *Figure 3:* Patient-care and facility-specific indicators by World Bank income level regions
- 5 **Captions of the tables**
- 6 *Table 1:* Core drug use indicators and their optimal values
- 7 *Table 2:* Inclusion and exclusion criteria
- 8 *Table 3:* Prescribing indicators by World Bank regions
- 9 *Table 4:* Patient-care and facility-specific indicators by World Bank regions
- 10 *Table 5:* Index of Rational Drug Use (IRDU) in selected countries