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Incidences of poor-quality pharmaceutical products in Nepal

Astha Neupane, Maheshwor Bastakoti, Sabita Tamang, Basant Giri*

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences

P. O. Box 23002, Kathmandu, Nepal

*Correspondence

Dr. Basant Giri

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences

PO BOX 23003, Kathmandu, Nepal

bgiri@kias.org.np

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ABSTRACT

Objectives: To evaluate the pattern of substandard and falsified pharmaceutical products in Nepal.

Setting: We analyzed drug recall notices from 2010 – 2020 by the department of drug administration (DDA), Nepal and systematically reviewed peer reviewed research articles.

Participants: A total of 72 drug recall notices issued from 2010 to 2020 by DDA were included. Only four research papers that reported original drug quality data from Nepal were included.

Results: A total of 346 pharmaceutical products were recalled during the reported period. The number of recalled pharmaceutical products has increased significantly over the past decade in Nepal. The most frequently recalled drugs were the antimicrobials followed by gastrointestinal medicines, vitamins and supplements, pain and palliative medicines among others. Number of imported recalled drugs were slightly higher (153) than domestic recalled drugs (141). Sixty-two percentage of recalled drugs were substandard, 11% were falsified and remaining 27% were not registered at the DDA. Similarly, higher number of modern drugs (62%) were recalled than traditional ones (35%). The hand sanitizers used to minimize the COVID-19 transmission contributed significantly to the list of recalled pharmaceutical products in 2020. Most of these sanitizers contained significant amount of methanol (as high as 75%v/v) instead of appropriate amount of ethyl or isopropyl alcohol. The peer-reviewed research papers reported issues with labeling, unregistered drugs and drugs failed in several laboratory testing.

Conclusions: The substandard and/or falsified drugs that do not meet regulatory standards and quality threaten health of population putting patients' life in danger leading to socio-economic hardship. Our analysis showed that cases of substandard and fake drugs are increasing in Nepal. Since the recall data in this paper did not include number of samples tested and location of samples collected, a systematic study to understand the prevalence of substandard and falsified drugs in Nepal is recommended.

Keywords: Counterfeit drugs, falsified medical products, public health, substandard, fake drugs

Strength and imitations of this study

- This is the first study to evaluate the pattern of drug recall in Nepal.
- We analyzed drug recall data from department of drug administration in Nepal and report that the substandard and falsified pharmaceutical products are increasing significantly.
- This study suggested the problem of substandard and falsified pharmaceutical products is serious in Nepal. Antimicrobial drugs were the most frequently recalled drugs. Drugs manufactured by domestic producers and imported ones were recalled. Allopathic drugs were recalled more than ayurvedic products.
- Since the recall data did not provide number of samples tested and location of sample collection, this study did not report rate of recall and location wise prevalence of substandard and falsified drugs in Nepal.

INTRODUCTION

Pharmaceutical products are essential to treat, prevent, and save lives of millions of people globally[1]. They should be safe, effective, and of good quality. Such products should be prescribed by authorized medical practitioner and used rationally[2]. However, pharmaceutical products that do not meet regulatory standards and quality threaten the health of the population of today and future. Such products may be substandard or low-quality or falsified. Substandard or falsified drugs could lead to drug resistances and put life of patients in danger in addition to creating economic and

social burden to people[3]. There are several reasons for the circulation of such substandard and falsified products in market such as lack of access to affordable, quality, safe and effective medical products, and good governance, poor ethical practices in health care facilities and medicine outlets. Limited technical capacity in manufacturing, quality control, distribution and testing also contribute to the same problem[4,5].

A recent meta-data analysis estimated that about 10.5% of the medicines worldwide are either substandard or falsified. Prevalence of low-quality pharmaceutical products is higher in low- and middle-income countries (13.6%) compared to high income countries. About 18.7% medicines have been estimated to be low-quality in Africa and 13.7% in Asia. The most substandard or falsified drugs are the antimalarials (19.1%)[3].

Nepal is one of the least developed countries that shares open and poorly regulated boarders with India and China. These two countries are considered as the major producers of low-quality and fake pharmaceutical products circulating in the global market[4]. The domestic market for medical products in Nepal was estimated to be 70 billion Nepal rupees in 2019 that included drugs (36 billion), raw materials and surgical equipment[6]. The department of drug administration (DDA) authorizes the distribution of all pharmaceutical products in Nepal including production, distribution, export and import. The DDA in Nepal is equivalent to U.S. FDA and is responsible to prevent the misuse or abuse of drugs and allied pharmaceutical substances[7]. Few studies in past have indicated the circulation of substandard, counterfeit, and unregistered drugs in the Nepali market[8,9,10]. The DDA Nepal recalls marketed drugs if the drugs do not fulfill any requirement as indicated in the drug act 2035 B.S.[7]. It then issues public alerts and warnings when substandard, falsified, and unregistered medicine incidents are detected.

In this study, we report the incidences of poor-quality drugs in Nepal by analyzing drug recall

notice issued by the DDA. We analyzed temporal trend of low-quality drugs, types of drugs and formulations, origin of drugs & manufacturers and reasoning for recall. We also reviewed research publications that reported drug quality data. We found that the low-quality drugs have increased significantly in Nepal that over the last decade and among them antimicrobials are the most found low-quality drugs.

METHODOLOGY

We carefully analyzed drug recall notice published by DDA Nepal from 2010 to 2020. The DDA publishes such notices in its bulletins, websites, and newspapers. We extracted all the information provided on the recall notice such as brand name, dosage form, batch number, manufacturing date, expiry date, recall date, reason of non-compliance, and the manufacturer information. We used National List of Essential Medicines 2016 of Nepal to classify the recalled drugs into essential and non-essential drugs[11] and the WHO definition to identify substandard, falsified and unregistered drugs[12]. According to WHO definition, the substandard drugs are authorized medical products but fail to meet quality standards or specifications or both. Similarly, falsified drugs are medical products that misrepresent their identity, composition or source[13]. Pharmaceutical products that did not pass dissolution test, API assay, microbial test, leakage test, friability, non-compliance with pharmacopeia, physical appearance, fungal count, weight variation, particulate matter test, uniformity test, disintegration test, and pH test were put together under substandard category. Similarly, drugs that contained impurities, active ingredient not meant to be there, had price sticker without approval, and did not have product specification were classified as falsified pharmaceutical products. The drugs that were recalled because they were not registered at DDA Nepal were classified under unregistered category. Unregistered drugs do not undergo evaluation and/or approval by DDA Nepal.

In addition to the recall notice, we also analyzed peer reviewed research articles from electronic databases such as PubMed (2010-2020), Web of Science (2010-2020), Springer link (2010-2020), and Google Scholar (2010-2020). We used the following search terms in conjunction with Boolean search term ("OR", "AND") to identify related articles: "counterfeit*", "substandard*", "falsified*", "fake", "spurious", "unregulated drugs", "unregistered", or "frauds"; combined with "drug", "medicine", or "pharmaceutical"; "Nepal*". In Google Scholar same search terms were used, but instead of "Nepal*", we used "intitle:Nepal". The articles were screened and evaluated manually through the title and abstract based on inclusion criteria: date of publication (2010-2020), the language (English) in which the article was published, the article should contain data/information on the prevalence of falsified/spurious/counterfeit/substandard drugs and the location of experiment/research carried out. Similarly, the articles which did not meet inclusion criteria were excluded. We also did not include opinion articles, letters, notes, conference papers, book chapters, editorials or comments or articles with no abstracts or articles with counterfeit or substandard medicines related to animals.

Statistical analyses of data such as Chi-square test, Fisher exact test and simple linear regression were performed using R version1.4.1106.

Patients and public involvement: Patient or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

We analyzed recalled drugs during the period of 2010 – 2020. During this period 346 pharmaceutical products were recalled by DDA Nepal. The number of recalled low-quality drugs in Nepal has significantly increased in the last decade (figure 1A, linear regression, p-value< 0.05,

adjusted R-squared value= 0.335). We found that only one pharmaceutical product was recalled in 2010. The product was the lactate solution which is commonly used for fluid resuscitation. The lactate was recalled from Nepali market since it did not pass the sterility test. There was no recall in 2012. The year of 2018 had the highest number of pharmaceutical products recalled (123 products, see figure 1a). Forty-six products were recalled in the year 2020, majority of which were hand sanitizers. The recalled pharmaceutical products were from 96 manufacturers mostly from Nepal and India, few from Australia, Bangladesh, and China. Manufacturer of 91 recalled drugs were unknown. The recalled pharmaceutical products included a significantly (two-sided fisher exact test, p-value <0.001) higher number of imported medicines (153) items than domestically manufactured the imported (141) ones which were manufactured mostly in India (97%, figure 1B). Few drugs from Australia, Bangladesh and China were also recalled. Country of origin of 52 recalled pharmaceutical products were not identified.

Figure 1: *(A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of different category of pharmaceutical products in the recall list.*

Sixty percentage (n=346) of recalled pharmaceutical products were modern or allopathic (208) and 35% were traditional or ayurvedic (120) (figure 1B). Two-sided fisher exact test showed that significantly large number of modern pharmaceutical products were recalled (p-value< 0.001). Twenty-seven percentage of the recalled drugs were unregistered at the DDA indicating they were not authorized to distribute and sell in Nepal. Similarly, twenty percentage of the recalled drugs, mostly allopathic, were listed as essential medicines. Essential medicines are distributed free of cost through government health centers. Remaining 40% drugs were non-essential ones (p-value < 0.001) and equal number of ayurvedic drugs were categorized as others since such drugs are not classified as essential or non-essential. Majority of the recalled pharmaceutical products were

substandard (215) followed by unregistered (93) and falsified (38) (see figure 1B). We found that the recall pattern among these three categories were significantly different (one-way chi-square test, p-value < 0.001, X-squared = 142.31, df = 2).

Figure 2: *(A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self life of recalled pharmaceutical products after the recall (in months).*

Based on the brand names of each non-ayurvedic pharmaceutical product, we identified their generic names and then categorized them into different groups based on their therapeutic properties. The top 10 most recalled drugs belonged to antimicrobials (47) followed by gastrointestinal medicines (35), vitamins and minerals (28), antiseptic (23), hormones and contraceptives (18), and pain and palliative care medicines (16), fluid and electrolyte replenishment (13), cardiovascular and renal drugs (7), anti-diabetes (5) and antihistamines (5) (see figure 2A). Remaining recalled drugs were CNS drugs, respiratory system drugs, prostaglandin analogues, antirheumatic. Nineteen drugs were not classified into any of those and labeled as "others" because enough information was not available. Similarly, ayurvedic drugs were not including in this categorization. The DDA provided reason(s) for every recalled pharmaceutical product. Large number of drugs were recalled because they were not registered (93) at DDA. The most common reason for recall among registered drugs was the failure to comply with microbial test (82) followed by failures in dissolution test (40), in quantitative assay for active pharmaceutical ingredient (23), and in physical characteristics and packaging (23). Eleven products did not comply label requirements and 12 had one or more impurity. Few samples categorized as "others" were recalled due to failure in identification test and contained active ingredient in dietary supplements (see figure 2B). Tablets were the most recalled dosages form

followed by powder, solution, capsules, syrups/suspension, cream/ointment. Dosage forms of some products were not identifiable, and they are categorized as "others" (figure 2C). The shelf-life of recalled drugs ranged from less than three months (16.4%) to more than two years at the time of recall (figure 2D).

Low-quality drugs reported in research papers

We also systematically investigated the published research works in order to find the reporting of low-quality drugs in Nepali market. A flow chart of search procedure is given in figure 3. Initially, we identified 467 journal articles through the literature search in four different databases: PubMed, Springer link, Web of science and Google scholar. We removed 13 duplicate articles and brought the number of articles to 454. By screening the title and abstract of these articles, we removed 439 articles and we considered only 15 in next step (*see* Table SI1). We read the full text of these articles and excluded 11 articles because they did not follow the inclusion criteria. At last, four articles[9,10,14,15] were found to be relevant that contained primary information on the prevalence of substandard, falsified, and unregistered medicines in the Nepali market.

Figure 3: Flow chart of research papers search procedure

A cross sectional descriptive study reported by Jha et al.[14] assessed the quality of essential medicines available in 62 public health care facilities across 21 districts of Nepal. Out of 244 batches of 20 different generics of essential medicines tested, 37 batches failed to meet the required pharmacopeial standards. 62.2% of failed batches of medicines were supplied by Government of Nepal and remaining 37.8% batches were purchased from local resources. The failed medicines included antibiotics, supplements, anti-diabetics etc. Providing required information on the label is another major issue. Most of the 759 pharmaceutical products from 37 Nepali pharmaceutical companies inspected in Chitwan in 2017 missed at least one critical information on the label such

as drug quantity, name of pharmacopoeia, serial number of pharmaceutical industries, price list, drug classification, and information in Nepali language[9]. In addition, 84% of drugs did not provide the directions of use. Similarly 90% of drug samples (n=40) in Kathmandu did not comply with the existing regulatory requirement on labeling and 42.5% brands did not mention about the pharmacopoeial standard[8]. The same study showed that 40% of domestic and 28% imported brands failed to meet national criteria during laboratory analysis. In average, 32.5% samples were found to be of substandard quality in this study. Another study evaluated the availability and rationality of unregistered fixed-dose drug combinations (FDCs) in Nepal using snowball sampling method and Health Action International Asia-Pacific (HAI-AP) toolkit in 20 retail pharmacies. Forty-one unregistered fixed-dose anti-inflammatory/analgesic/antipyretics drug combinations were found in five major cities of Nepal. Regulatory authorities should initiate strict monitoring and appropriate regulatory mechanisms to prohibit the use of unregistered and irrational FDCs.[10]

DISCUSSION

The low quality medicines or related products are recalled from the market by manufacturing company voluntarily or by the order of national or international drug regulatory bodies[16]. Many recall incidents of poor quality medicine have been reported globally[17]. For example, Johnson and Johnson recalled 200,000 bottles of liquid ibuprofen in 2013 due to possible contamination with plastic particles. Similarly, in 2012, the US FDA recalled the contaminated vials of corticosteroid medication which was manufactured by the New England Compounding Center[18].

Our analysis showed that the overall trend of recalled drugs is increasing in Nepal. Starting from a single drug recall in 2010 to highest numbers (123) in 2018. In this year, most of the drugs (90) were recalled since they were not registered with the DDA. This indicates that the circulation of unregistered drugs in market is a serious issue in Nepal which may been contributed by the open

and unregulated boarder with India. Both allopathic and ayurvedic medicines are widely used in Nepal. The allopathic medicines are the modern medicines that are manufactured synthetically whereas ayurvedic medicines are the traditional medicines which uses the natural remedies to improve health or to treat diseases. Both types of medicines are commercially manufactured in Nepal in addition to be imported mostly from India. There are two groups of manufacturers of ayurvedic drugs in Nepal. They are mostly manufactured by registered companies and sold in market in packages through registered shops. The ayurvedic drugs are also made by individuals or small business holders without being registered at DDA and sell their ayurvedic products in streets, through door-to-door service, and through individual networks. We found that both allopathic and ayurvedic medicines were recalled due to their non-compliance with government standards. Ayurvedic medicines are utilized prominently in Nepali communities, and sometimes, they are used concomitantly with allopathic[19]. There has been an increasing interest in the study of traditional medicine in different parts of world[20]. However, there is still lack of quality research and standards, and stringent regulatory environment in this sector.

Essential medicines are defined by WHO as the medicines that satisfy the priority healthcare needs of the population[21]. The concept of essential medicines was adopted in 1986 A.D. in Nepal to enhance the access of essential medicines to every individual. The main criteria for selection of the medicines in the National List of Essential Medicine (NLEM) of Nepal are public health relevance, efficacy, safety, cost-effectiveness and access of the drugs. The NLEM 2016 of Nepal contains 359 medicines which has 86 medicines more than the NLEM 2011[11]. Following criteria were used for including a medicine in NLEM: approved and licensed in Nepal, relevance to a disease posing public health problem, proven efficacy and safety, aligned with standard treatment guideline of Nepal, stable under storage conditions, cost-effectiveness, access. However in

following conditions medicines were excluded from the NLEM list: banned in Nepal, safety concerns, if medicine with higher efficiency, safety profile and lower-cost is available, irrelevant to public health disease burden, antimicrobial resistant, medicine with abuse and misuse potential[11]. Our study showed that some of the recalled allopathic medicines were essential drugs. Jha et.al[14] indicated the presence of high number of substandard essential medicines and majority of which were purchased by Government of Nepal. Essential medicines for various illnesses are supplied free of cost in Nepal through government hospitals, health care centers and health posts. Poor quality of essential medicines can have serious impact on public health. As significant proportion of drugs recalled by DDA included essential medicines distributed by Government of Nepal, there is enough room to improve the procurement procedure and upgrading of health facilities of Nepal that store and distribute the medicines. In one study[22] that looked into the procurement practices in Nepal reported that the majority of hospital pharmacies in Nepal use an expensive direct-procurement model for purchasing medicines. They relied on doctors' prescriptions to choose a particular brand, which may be influenced by pharmaceutical companies' marketing strategies. Most of the hospital pharmacies procured only registered medicines, a minority reported purchasing unregistered medicines through unauthorized supply-chains. Not all pharmacies followed Basel Statements during procurement of medicines. Such pharmacies may need awareness and training to fully adopt regulation of national and international policies for enhancing accessibility to quality medicines.

Among the recalled groups, antimicrobial group of medicines had the highest frequency of recall incidents. Acharya et.al[23] highlighted the problem of antimicrobial resistance in Nepal as an alarm bell for worse public health situation. Suboptimal dose or poorly manufactured antibiotic medicine increases the chance of antimicrobial resistance[24]. Most of the recalled therapeutic categories of

medicines like vitamins and minerals, NSAID, antipyretic and analgesic, antiseptic, fluid and electrolyte replenishment and others are over-the-counter medicines that can be brought from the pharmacy without the prescriptions. Such medicines can pose a significant threat to the groups of patients who consume them[25]. Few anti-diabetes medicines were also recalled. Consumption of such medicines may increase the incidence of macrovascular and microvascular complications due to compromised glucose control[26].

Our study showed that the drugs were recalled due to failure in various laboratory tests like microbial test, assays, content uniformity test, weight variation, impurity test, dissolution test, frability test, identification and sterility test. Many of these failures might be attributed to the lack of proper quality control during manufacturing and lack of following proper procedures for transportation and storage conditions[13].

Jha et.al pointed out that only 13% of 62 health facility inspected followed medicine storage guidelines for light, heat and humidity[14]. Keeping the temperature and humidity within a range is must necessary because it has a major role in degradation of medicines. Another reason was failure to comply with the claim and incorrect labeling. The DDA regulation requires appropriate labeling of marketed medicines to ensure patient medication safety, which seems to be not followed properly. Thus, the drug analyst and the drug regulators should be encouraged to remain vigilant about counterfeiting possibility and conduct the analysis including chemical, physical, package inspection, and authentication efforts to determine quality more accurately[27].

Domestically produced and imported medicines in Nepal should have the registration license from DDA[7]. Nonetheless, we found that high numbers of unregistered drugs were recalled during the inspection. The drug supplier, whole seller, and retailers should ensure that the drug is registered within the national regulatory body to timely identify substandard products before they reach

patients. Also, the regulatory body should stringent post-market surveillance to ameliorate the situation. The unregistered medical products in Nepal may or may not have been registered in India. Since Nepal shares open and poorly regulated boarder with India, drugs registered in India are also easily sold in Nepali market, especially in bordering districts. We found that nearly half of the total recalled medicines were imported from India. India is the leading country in counterfeit drug production, having as much as 35% of the world production originating within its borders[28].

COVID-19 related recalls

The COVID-19 pandemic has resulted in the surge of substandard and falsified medical products including drugs, masks, sanitizers, diagnostic tests, and vaccines and other essential medical products[29]. Rampant circulation of fake medical products during emergencies has happened throughout the history[29]. Counterfeit respirators and masks pose additional risk to health care workers[30]. Falsified chloroquine was seized in Cameroon, Congo and Niger during March and May 2020. Chloroquine was controversially announced as the drug for the treatment of COVID-19[31]. The US FDA uncovered nearly 1,300 fraudulent products during early days of COVID-19[32]. The DDA Nepal, recently, has amended the standard for Instant Hand Sanitizer in order to prohibit the selling of the substandard, falsified and unregistered sanitizers[33]. In between September and November 2020, the DDA issued the recalled notice for 19 hand sanitizers which failed to comply with the standard guideline. Some sanitizers were found to contain methanol, rather than ethyl alcohol and isopropyl alcohol. As methanol is very toxic, some of the case series indicated use of hand sanitizer containing methanol causes the transdermal absorption and increases the risk of systemic toxicity[34]. The increase in the demand of hand sanitizer and other medicines has increased the growth of e-commerce. Online sale of pharmaceutical products has just started in Nepal during recent years. WHO has reported that 60% of medications purchased through internet could be

counterfeit or substandard, and more than 50% of medications purchased online from sites that concealed their actual physical address was found to be low quality medicine[35]. Nepali regulating agencies should pay special attention to this new method of business in Nepal to protect people from the consumption of low-quality and fake medical products. Inexorable growth of online pharmacies, unregulated websites, and, social media platform for business may contribute to the dispensing of unapproved, subpotent, counterfeit, expired or illegal drugs, and prescription drugs without a valid prescription in Nepal too[36].

CONCLUSION

In this paper, we presented a detailed analysis of low-quality and fake drugs circulating in Nepal in the past decade using recall notice. We showed that the number of recalled drugs has significantly increased. This might be attributed to greater surveillance by DDA or the substandard, falsified and unregistered medicine in the market are actually increasing. Similar to global trend, antimicrobial drugs were the most recalled drugs in Nepal. Since antibiotics are available over the counter in Nepal without doctor's prescription, it is necessary to enforce strict regulation so that the rampant (mis)use of such drugs is minimized and prevent antibiotic resistance. We relied on recall notice from DDA. The recall notice does not provide information on the number of samples collected for testing or inspection and location of sample collection. Therefore, our analysis did not report the rate or prevalence of low-quality drugs. Since sample collection locations were not available, it was not possible to know the most vulnerable districts of Nepal for low-quality drugs. Therefore, a systematic study is needed to understand the prevalence of substandard and falsified drugs in Nepal covering different parts of the country on regular basis. We suggest having more stringent regulatory systems and implementation for pharmaceutical manufacturing industries and post marketing surveillance.

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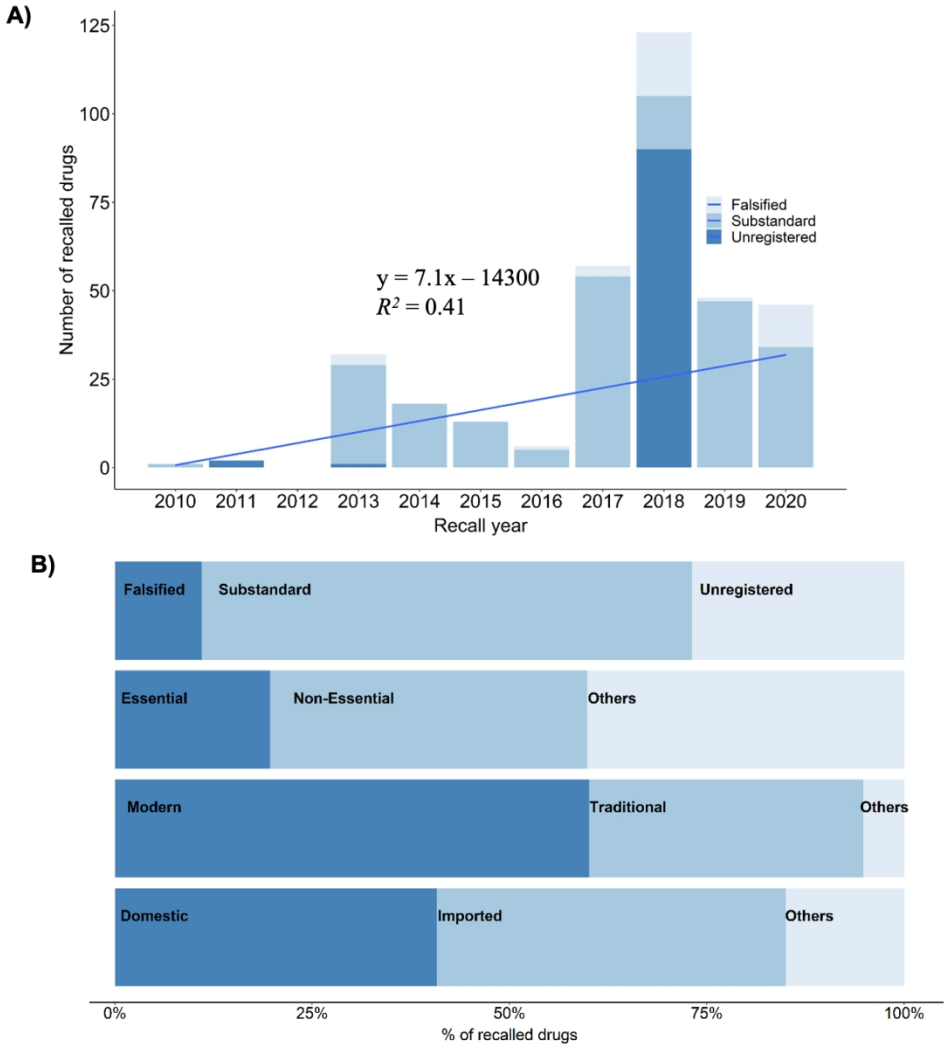
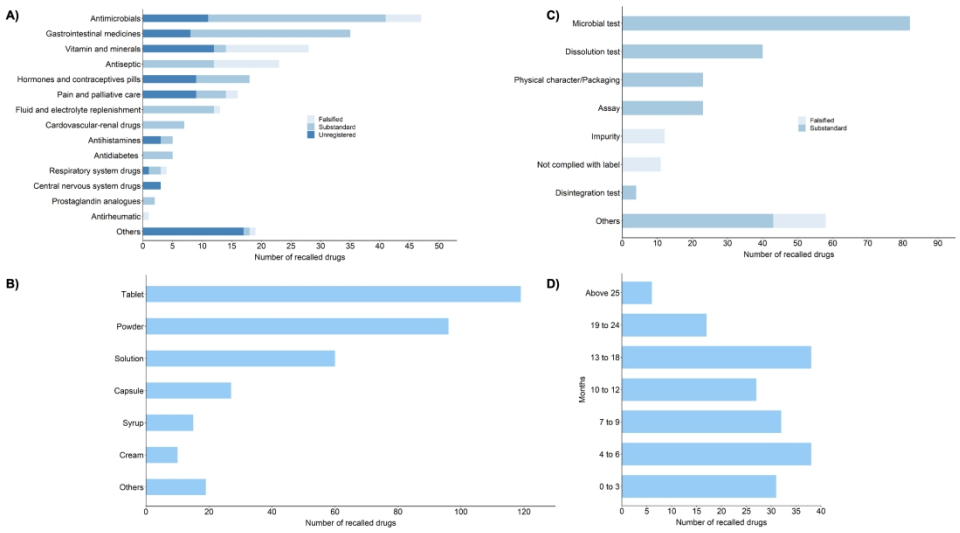
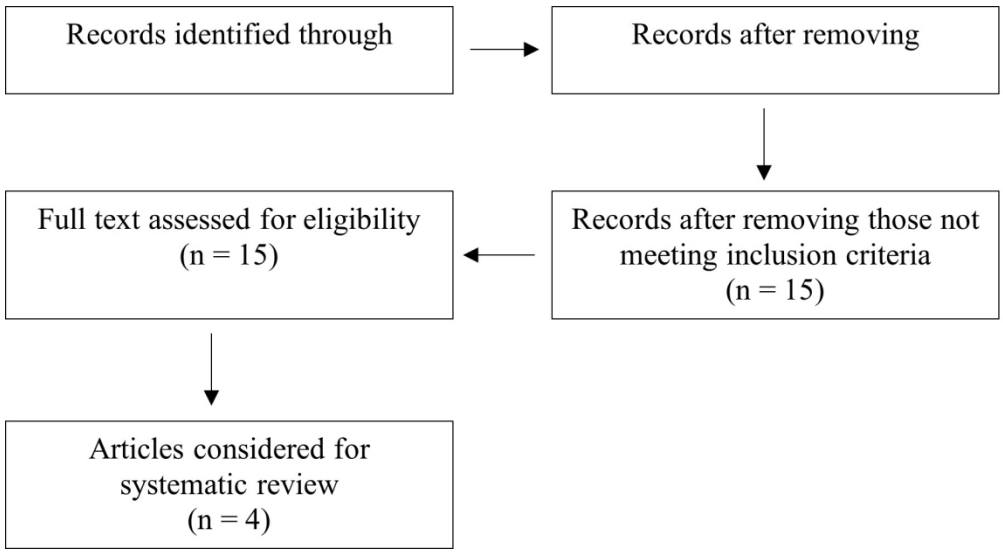

A)
Number of recalled drugs
125
100
75
50
25
0
y = 7.1x – 14300
R^2 = 0.41
Falsified
Substandard
Unregistered
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Recall year
B)
Falsified
Substandard
Unregistered
Essential
Non-Essential
Others
Modern
Traditional
Others
Domestic
Imported
Others
0%
25%
50%
75%
100%
% of recalled drugs


A)
Antimicrobials
Gastrointestinal medicines
Vitamin and minerals
Antiseptic
Hormones and contraceptives pills
Pain and palliative care
Fluid and electrolyte replenishment
Cardovascular-renal drugs
Antihistamines
Antidiabetes
Respiratory system drugs
Central nervous system drugs
Prostaglandin analogues
Antirheumatic
Others
Falsified
Substandard
Unregistered
0 5 10 15 20 25 30 35 40 45 50
Number of recalled drugs
C)
Microbial test
Dissolution test
Physical character/Packaging
Assay
Impurity
Not complied with label
Disintegration test
Others
Falsified
Substandard
0 10 20 30 40 50 60 70 80 90
Number of recalled drugs
B)
Tablet
Powder
Solution
Capsule
Syrup
Cream
Others
0 20 40 60 80 100 120
Number of recalled drugs
D)
Above 25
19 to 24
13 to 18
10 to 12
7 to 9
4 to 6
0 to 3
Months
0 5 10 15 20 25 30 35 40
Number of recalled drugs



138x75mm (330 x 330 DPI)

Incidences of poor-quality pharmaceutical products in Nepal

Astha Neupane, Maheshwor Bastakoti, Sabita Tamang, Basant Giri*

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences, P. O. Box 23002, Kathmandu, Nepal

Supplementary Material

Table SI1: Result of literature search of peer-reviewed documents reporting drug quality data

Keywords	Number of articles found			
	PubMed	Web of Science	Springer link	Google Scholar
Counterfeit* OR substandard* OR fake OR spurious OR unregulated OR unregistered OR falsified* OR fraud	14532	51113	71770	41100
Drug OR medicine OR pharmaceutical	4977168	4579007	1386455	728000
Nepal*	12868	18132	16862	26500
1 AND 2 AND 3	13	10	393	51

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	-
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5&6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5&6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5&6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	-
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	-
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7&9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Page 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-15
	23b	Discuss any limitations of the evidence included in the review.	Page 16
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 15&16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data used for analysis

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

BMJ Open

Pattern of drug recalls and quality of pharmaceutical products in Nepal

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Global health, Health policy, Pharmacology and therapeutics
Keywords:	Public health < INFECTIOUS DISEASES, COVID-19, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Pattern of drug recalls and quality of pharmaceutical products in Nepal

Astha Neupane, Maheshwor Bastakoti, Sabita Tamang, Basant Giri*

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences

P. O. Box 23002, Kathmandu, Nepal

*Correspondence

Dr. Basant Giri

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences

PO BOX 23003, Kathmandu, Nepal

bgiri@kias.org.np, chembasant@gmail.com

Word count: 3702 excluding abstract and references

ABSTRACT

Objectives: To evaluate the pattern of substandard and falsified pharmaceutical products using drug recall notices and via a systematic review in Nepal.

Setting: We analyzed drug recall notices issued by the Department of Drug Administration (DDA), Nepal and systematically reviewed peer reviewed research articles during January 2010 – December 2020.

Participants: This study did not include human participants. However, data was collected from 72 drug recall notices issued by DDA and four research papers.

Results: A total of 346 pharmaceutical products were recalled during the reported period. The number of recalled pharmaceutical products has increased significantly over the past decade in Nepal. The most frequently recalled drugs were antimicrobials followed by gastrointestinal medicines, vitamins and supplements, pain and palliative medicines among others. Number of imported recalled drugs were slightly higher (42.2%) than domestic recalled drugs (40.7%). Sixty-two percentage of recalled drugs were substandard, 11% were falsified and remaining 27% were not registered at the DDA. Similarly, higher number of modern drugs (62%) were recalled than traditional ones (35%). Hand sanitizers used to minimize COVID-19 transmission contributed significantly to the list of recalled pharmaceutical products in 2020. Most of these sanitizers contained significant amounts of methanol (as high as 75%v/v) instead of appropriate amount of ethyl or isopropyl alcohol. The peer-reviewed research papers reported issues with labelling, unregistered drugs and drugs failed in several laboratory testing.

Conclusion: Our analysis showed that number of recalls of substandard and fake drugs are increasing in Nepal. Since the recall data in this paper did not include number of samples tested

and location of samples collected, more studies to understand the prevalence of substandard and falsified drugs in Nepal is recommended.

Keywords: Counterfeit drugs, falsified medical products, public health, substandard, fake drugs

Strength and imitations of this study

- This is the first study to evaluate the pattern of drug recall in Nepal.
- A comprehensive analysis of drug recall notice issued by Department of Drug Administration, Nepal from January 2010 to December 2020.
- Also includes a systematic review of peer-reviewed publications from 2010 to 2020 which reported poor quality drugs in Nepal.
- It does not include number of samples tested, location of sample collected, and impact of recall notice.
- Since we looked at pattern of recall drugs, it did not report the rate of low-quality drugs over the last decade.

INTRODUCTION

Pharmaceutical products are essential to treat, prevent, and save lives of millions of people globally[1]. They should be safe, effective, and of good quality. Such products should be prescribed by authorized medical practitioner and used rationally[2]. However, pharmaceutical products that do not meet regulatory standards and quality threaten the health of the population of today and future. Such products may be substandard or low-quality or falsified. Substandard or falsified drugs could lead to drug resistance and put the lives of patients at risk in addition to increasing the economic and social burden on people[3]. There are several reasons for the circulation of such substandard and falsified products in market such as lack of access to affordable, quality, safe and effective medical products and good governance as well as poor ethical practices in health care facilities and medicine outlets. Limited technical capacity in manufacturing, quality control, distribution and testing also contribute to this problem[4,5].

Ozawa et al. in a 2018 meta-analysis estimated that about 10.5% of the medicines worldwide are

either substandard or falsified. Prevalence of low-quality pharmaceutical products is higher in low- and middle-income countries (13.6%) compared to high income countries. About 18.7% medicines have been estimated to be low-quality in Africa and 13.7% in Asia. The most substandard or falsified drugs are the antimalarials (19.1%)[3].

Nepal is one of the least developed countries[6] that shares open and poorly regulated boarders with India and China. These two countries are considered as the major producers of low-quality and fake pharmaceutical products circulating in the global market[4]. The domestic market for medical products in Nepal was estimated to be 70 billion Nepal rupees in 2019 which included drugs (36 billion), raw materials and surgical equipment[7]. The Department of Drug Administration (DDA) authorizes the distribution of all pharmaceutical products in Nepal including production, distribution, export and import. The DDA in Nepal is equivalent to the U.S. FDA and is responsible to prevent the misuse or abuse of drugs and allied pharmaceutical substances[8]. Few studies in the past have indicated the circulation of substandard, counterfeit, and unregistered drugs in the Nepali market[9,10,11]. DDA Nepal recalls marketed drugs if the drugs do not fulfill any requirement as indicated in the drug act 2035 B.S.[8]. It then issues public alerts and warnings when substandard, falsified, and unregistered medicine incidents are detected.

It is important to understand major issues responsible for the availability of poor-quality drugs in the market. Analysis of pattern of drug alerts, regulatory recalls and company led recalls could be helpful to devise actions to mitigate the issues related to poor-quality drugs[12]. In this study, we report the pattern of recall of poor-quality drugs in Nepal by analyzing drug recall notice issued by the DDA. We analyzed temporal trend of low-quality drugs, types of drugs and formulations, origin of drugs & manufacturers and reasoning for recall. We also reviewed research publications that reported drug quality data.

METHODOLOGY

We analyzed drug recall notices published by DDA Nepal from January 2010 to December 2020. The DDA publishes such notices in its bulletins, websites, and newspapers (https://dda.gov.np/). We extracted all the information provided on the recall notice such as brand name, dosage form, batch number, manufacturing date, expiry date, recall date, reason for non-compliance, and the manufacturer information. We used National List of Essential Medicines 2016 of Nepal to classify the recalled drugs into essential and non-essential drugs[13] and the WHO definition to identify substandard, falsified and unregistered drugs[14]. According to WHO definition, substandard drugs are authorized medical products but fail to meet quality standards or specifications or both. Similarly, falsified drugs are medical products that misrepresent their identity, composition or source[15]. Pharmaceutical products that did not pass dissolution test, active pharmaceutical ingredient (API) assay, microbial test, leakage test, friability, were non-compliance with the pharmacopeia for physical appearance, fungal count, weight variation, particulate matter test, uniformity test, disintegration test, and pH test were put together under the substandard category. Similarly, drugs that contained impurities, active ingredient not meant to be there, had price sticker without approval, or did not have product specification were classified as falsified pharmaceutical products. The drugs that were recalled as being not registered at DDA Nepal were classified under unregistered category. Unregistered drugs do not undergo evaluation and/or approval by DDA Nepal. Based on the brand names of each non-ayurvedic pharmaceutical product, we identified their generic names and then categorized them into different groups based on their therapeutic properties.

In addition to the recall notice, we systematically reviewed the published research works to find the reporting of low-quality drugs in Nepali market. We specifically searched peer reviewed

research articles from electronic databases such as PubMed (2010-2020), Web of Science (2010-2020), Springer link (2010-2020), and Google Scholar (2010-2020). We used the following search terms in conjunction with Boolean search term ("OR", "AND") to identify related articles: "counterfeit*", "substandard*", "falsified*", "fake", "spurious", "unregulated drugs", "unregistered", or "frauds"; combined with "drug", "medicine", or "pharmaceutical"; "Nepal*". In Google Scholar same search terms were used, but instead of "Nepal*", we used "intitle:Nepal". The articles were screened and evaluated manually through the title and abstract based on inclusion criteria: date of publication (2010-2020), the language (English) in which the article was published, the article should contain data/information on the prevalence of falsified/spurious/counterfeit/substandard drugs and the location of experiment/research carried out. Articles that did not meet the inclusion criteria were excluded. Also excluded were opinion articles, letters, notes, conference papers, book chapters, editorials or comments or articles with no abstracts or articles with counterfeit or substandard medicines related to animals.

A flow chart of search procedure is given in figure 1. Initially, we identified 467 journal articles after a search of literature in four different databases: PubMed, Springer link, Web of science and Google scholar. We removed 13 duplicate articles and brought the number of articles to 454. By screening the title and abstract of these articles, we removed 439 articles and we considered only 15 in next step (*see* Table SI1 in supplementary information). We read the full text of these articles and excluded 11 articles because they did not follow the inclusion criteria. At last, four articles[10,11,16,17] were found to be relevant that contained primary information on the prevalence of substandard, falsified, and unregistered medicines in the Nepali market.

Figure 1: Flow chart of research papers search procedure

Statistical analyses of data such as Chi-square test, Fisher exact test and simple linear regression were performed using R version1.4.1106.

Patients and public involvement: Patient or the public were not involved in the design, conduct, reporting, and dissemination plans for this study.

RESULTS

We analyzed recalled drugs during the period of 2010 – 2020. During this period 346 pharmaceutical products were recalled by DDA Nepal. The number of recalled low-quality drugs in Nepal has significantly increased in the last decade (Figure 2A, linear regression, p-value< 0.05, adjusted R-squared value= 0.335). We found that only one pharmaceutical product was recalled in 2010. The product was a lactate solution which is commonly used for fluid resuscitation. The solution was recalled from the Nepali market because it did not pass the sterility test. There was no recall in 2012. The year 2018 had the highest number of pharmaceutical products recalled (123 products, see Figure 2A). Forty-six products were recalled in the year 2020, majority of which were hand sanitizers. The recalled pharmaceutical products were from 96 manufacturers mostly from Nepal and India, few from Australia, Bangladesh, and China. Manufacturer of 91 recalled drugs were unknown. The recalled pharmaceutical products included a significantly (two-sided Fisher exact test, p-value <0.001) higher number of imported medicines (153) items than domestically manufactured ones (141). The imported recalled products were manufactured mostly in India (97%, Figure 2B) and in drugs from Australia, Bangladesh and China. Country of origin of 52 recalled pharmaceutical products were not identified.

Figure 2: *(A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of different categories of pharmaceutical products in the recall list.*

Sixty percentage (n=346) of recalled pharmaceutical products were modern or allopathic (208) and 35% were traditional or ayurvedic (120) (Figure 2B). Two-sided Fisher exact test showed that significantly higher number of modern pharmaceutical products were recalled (p-value< 0.001). Twenty-seven percentage of the recalled drugs were unregistered at the DDA indicating they were not authorized to be distributed and sold in Nepal. Similarly, twenty percentage of the recalled drugs, mostly allopathic, were listed as essential medicines. 40% of the recalled drugs were non-essential allopathic (p-value <0.001) and 40% were ayurvedic drugs. Essential medicines are distributed free of cost through government health centers[13] and only allopathic drugs are listed as essential ones. Majority of the recalled pharmaceutical products were substandard (62%) followed by unregistered (27%) and falsified (11%) (see Figure 2B). We found that the recall pattern among these three categories were significantly different (one-way chi-square test, p-value < 0.001, χ^2 = 142.31, df = 2).

Figure 3: *(A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self life of recalled pharmaceutical products after the recall (in months).*

The top 10 most recalled drugs were antimicrobials (13.6%) followed by gastrointestinal medicines (10.1%), vitamins and minerals (8.1%), antiseptic (6.6), hormones and contraceptives (5.2%), and pain and palliative care medicines (4.6), fluid and electrolyte replenishment items (3.7%), cardiovascular and renal drugs (2.0%), anti-diabetes (1.4%) and antihistamines (1.4%) (see Figure 3A). Remaining recalled drugs were CNS drugs, respiratory system drugs, prostaglandin analogues, and antirheumatic agents. Nineteen drugs were not classified into any of those and labelled as “others” because sufficient information was not available. Ayurvedic drugs were not included in this categorization.

The DDA provided reason(s) for every recalled pharmaceutical product. Large number of drugs (26.8%) were recalled because they were not registered at DDA. The most common reason for recall among registered drugs was the failure to comply with microbial test (23.7%) followed by failures in dissolution test (11.5%), in quantitative assay for active pharmaceutical ingredient (6.6%), and in physical characteristics and packaging (6.6%). Eleven products did not comply with labelling requirements and 12 had one or more impurities. Few samples categorized as "others" were recalled due to failure in identification test and contained active ingredient in dietary supplements (see Figure 3B). Tablets were the most recalled dosages forms followed by powder, solution, capsules, syrups/suspension, and cream/ointment. Dosage forms of some products were not identifiable, and they are categorized as "others" (Figure 3C). The shelf-life of recalled drugs ranged from less than three months (16.4%) to more than two years at the time of recall (Figure 2D).

Low-quality drugs reported in research papers

As stated in method section, only four research articles were included for detailed analysis. One of these articles reported by Jha et al.[16] assessed the quality of essential medicines available in 62 public health care facilities across 21 districts of Nepal. The authors tested 244 batches of 20 different generics of essential medicines and found that 37 batches failed to meet the required pharmacopeial standards. The quality failed medicines included both supplied by Government of Nepal (62.2%) and purchased from local pharmacies (37.8%). The failed medicines included antibiotics, supplements, anti-diabetics etc.

Providing required information on the label is another major issue. Most of the 759 pharmaceutical products from 37 Nepali pharmaceutical companies inspected in Chitwan in 2017 missed at least one critical information on the label such as drug quantity, name of pharmacopoeia, serial number

of pharmaceutical industries, price list, drug classification, and information in Nepali language[10]. The reports showed that labels of 84% of drugs did not provide the directions for use. Similarly 90% of drug samples (n=40) in Kathmandu did not comply with the existing regulatory requirement on labeling and 42.5% brands did not indicate the Pharmacopoeial standard[9]. The same study showed that 40% of domestic and 28% imported brands failed to meet national criteria during laboratory analysis. On average, 32.5% samples were found to be of substandard quality in this study. Another study evaluated the availability and rationality of unregistered fixed-dose drug combinations (FDCs) in Nepal using snowball sampling method and Health Action International Asia-Pacific (HAI-AP) toolkit in 20 retail pharmacies. Forty-one unregistered fixed-dose anti-inflammatory/analgesic/antipyretics drug combinations were found in five major cities of Nepal. Regulatory authorities should initiate strict monitoring and appropriate regulatory mechanisms to prohibit the use of unregistered and irrational FDCs.[11]

DISCUSSION

Low-quality medicines or related products are recalled from the market by manufacturing companies voluntarily or by the order of national or international drug regulatory bodies[18]. Many recall incidents of poor quality medicine have been reported globally[19]. For example, Johnson and Johnson recalled 200,000 bottles of liquid ibuprofen in 2013 due to possible contamination with plastic particles. Similarly, in 2012, the US FDA recalled the contaminated vials of corticosteroid medication which was manufactured by the New England Compounding Center[20].

Our analysis showed that the overall trend of recalled drugs is increasing in Nepal. Starting from a single drug recall in 2010 to highest numbers (123) in 2018. In this year, most of the recalled drugs (90) were due to them not registered with the DDA. This indicates that the circulation of

unregistered drugs in market is a serious issue in Nepal which may be contributed to by the open and unregulated border with India.

Both allopathic and ayurvedic medicines are widely used in Nepal. Allopathic medicines are the modern medicines that are manufactured synthetically whereas ayurvedic medicines are the traditional medicines which uses the natural remedies to improve health or to treat diseases. Both types of medicines are commercially manufactured in Nepal in addition to being imported mostly from India. There are two groups of manufacturers of ayurvedic drugs in Nepal. The first being the registered companies which sell their products in packages through registered shops. Secondly, the ayurvedic drugs are made by individuals or small business holders without being registered at DDA and sell their ayurvedic products in streets, through door-to-door service, and through individual networks. We found that both allopathic and ayurvedic medicines were recalled due to their non-compliance with government standards. Ayurvedic medicines are utilized prominently in Nepali communities, and sometimes, they are used concomitantly with allopathic medicines[21]. There has been an increasing interest in the study of traditional medicine in different parts of world[22]. However, there is still lack of quality research and standards, and stringent regulatory environment for this sector.

Essential medicines are defined by WHO as the medicines that satisfy the priority healthcare needs of the population[23]. The concept of essential medicines was adopted in 1986 A.D. in Nepal to enhance access of essential medicines to every individual. The main criteria for selection of the medicines in the National List of Essential Medicine (NLEM) of Nepal are public health relevance, efficacy, safety, cost-effectiveness and access of the drugs. The NLEM 2016 of Nepal contains 359 medicines thus having 86 medicines more than NLEM 2011[13]. The following criteria were used for including a medicine in NLEM: approved and licensed in Nepal, relevance to a disease

posing public health problem, proven efficacy and safety, aligned with standard treatment guideline of Nepal, stable under storage conditions, cost-effective, and access. However in certain conditions, some medicines are excluded from the NLEM list: those banned in Nepal, over safety concerns, if medicine with higher efficiency, safety profile and lower cost is available, irrelevant to public health disease burden, antimicrobial resistant, medicine with abuse and misuse potential[13]. Our study showed that some of the recalled allopathic medicines were essential drugs. Jha et al.[16] indicated the presence of high number of substandard essential medicines and majority of which were purchased by Government of Nepal. Essential medicines for various illnesses are supplied free of cost in Nepal through government hospitals, health care centers and health posts. Poor quality of essential medicines can have serious impact on public health. As significant proportion of drugs recalled by DDA included essential medicines distributed by Government of Nepal, there is enough room to improve the procurement practices and upgrading of health facilities in Nepal that store and distribute medicines. In one study[24] that looked into the procurement practices in Nepal, it was reported that the majority of hospital pharmacies in Nepal use an expensive direct procurement model for purchasing medicines. They relied on doctors' prescriptions to choose a particular brand, which may be influenced by pharmaceutical companies' marketing strategies. Most of the hospital pharmacies procured only registered medicines, a minority reported purchasing unregistered medicines through unauthorized supply-chains. Not all pharmacies followed Basel Statements during procurement of medicines. Such pharmacies may need awareness and training to fully adopt regulation of national and international policies to enhance accessibility to quality medicines.

Among the recalled groups, antimicrobial group of medicines had the highest frequency of recall incidents. Acharya et.al[25] highlighted the problem of antimicrobial resistance in Nepal as an alarm

bell for worse public health situation. Suboptimal dose or poorly manufactured antibiotic medicine increases the chance of antimicrobial resistance[26]. Most of the recalled therapeutic categories of medicines like vitamins and minerals, NSAIDs, other antipyretic and analgesic agents, antiseptics, fluid and electrolyte replenishment items and others are over-the-counter medicines that can be brought from the pharmacy without prescription. Such medicines can pose a significant threat patients who consume them[27]. Few anti-diabetes medicines were also recalled. Consumption of such medicines may increase the incidence of macrovascular and microvascular complications due to compromised glucose control[28].

Our study showed that some of the drugs were recalled due to failure in various laboratory tests like microbial test, assays, content uniformity test, weight variation, impurity test, dissolution test, friability test as well as identification and sterility test. Many of these failures can be linked to inadequate quality control measures during manufacturing and inappropriate procedures for transportation and storage and other logistic issues[15].

Jha *et. al.* pointed out that only 13% of 62 health facility inspected followed medicine storage guidelines for light, heat and humidity[16]. Keeping the temperature and humidity within a specified range is necessary because it has a major role in degradation of medicines. Another reason was failure to comply with claims and incorrect labelling. The DDA regulation requires appropriate labelling of marketed medicines to ensure patient safety. Thus, drug analysts and the drug regulators should be encouraged to remain vigilant about the possibility of counterfeiting possibility. They should conduct appropriate analysis including chemical, physical, package inspection, and authentication efforts to ensure quality and safety of drugs getting to the ultimate user[29].

Domestically produced and imported medicines in Nepal should have the registration license from DDA[8]. Nonetheless, we found that high numbers of unregistered drugs were recalled during the inspection. Drug suppliers, wholesalers, and even retailers should ensure that the drugs they are handling is duly registered with the national regulatory body to ensure only safe and efficacious drugs get to the patient. Also, the regulatory body should conduct post-market surveillance to ameliorate the situation. Unregistered medical products in Nepal may or may not have been registered in India. Since Nepal shares open and poorly regulated boarder with India, drugs registered in India are also easily sold in the Nepali market, especially in bordering districts. We found that nearly half of the total recalled medicines were imported from India. India is the leading country in counterfeit drug production, having as much as 35% of the world production originating within its borders[30].

The COVID-19 pandemic has resulted in the surge of substandard and falsified medical products including drugs, masks, sanitizers, diagnostic tests, and vaccines and other essential medical products[31]. Rampant circulation of fake medical products during emergencies has happened throughout history[31]. Counterfeit respirators and masks pose additional risk to health care workers[32]. Falsified chloroquine was seized in Cameroon, Congo and Niger between March and May 2020. Chloroquine was controversially announced as the drug for the treatment of COVID-19[33]. The US FDA uncovered nearly 1,300 fraudulent products during early days of COVID-19[34]. DDA Nepal has recently amended the standard for Instant Hand Sanitizer in order to prohibit selling of substandard, falsified and unregistered sanitizers[35]. Between September and November 2020, the DDA issued recall notices for 19 hand sanitizers which failed to comply with the standard guideline. Some sanitizers were found to contain methanol, rather than ethyl alcohol and isopropyl alcohol. Methanol is very toxic. Use of hand sanitizer containing methanol may cause transdermal

absorption and increases the risk of systemic toxicity[36]. The increase in the demand for hand sanitizers and other medicines in the face of COVID-19 has increased the growth of e-commerce. Online sale of pharmaceutical products has just started in Nepal during recent years. WHO has reported that 60% of medications purchased through the internet could be counterfeit or substandard, and more than 50% of medications purchased online from sites that concealed their actual physical address were found to be low quality medicines[37]. Nepali regulating agencies should pay special attention to this new method of doing business in Nepal to protect the people from consumption of low-quality and fake medical products. Inexorable growth of online pharmacies, unregulated websites and social media platforms for business may contribute to the dispensing of unapproved, subpotent, counterfeit, expired or illegal drugs, and prescription drugs without valid prescriptions[38].

CONCLUSION

In this paper, we presented a detailed pattern of low-quality and fake drugs circulating in Nepal in the past decade using recall notice. We showed that the number of recalled drugs has significantly increased. This might be attributed either to a greater surveillance by DDA or actual increase in the levels of substandard, falsified, and unregistered medicines in the market. However, our analysis was not enough to identify the exact cause of increase in the recalled drugs. Like global trends, antimicrobial drugs were the most recalled drugs in Nepal. The recall notices used did not provide information on the number of samples collected for testing or inspection and location of sample collection. Therefore, our analysis did not report the rate or prevalence of low-quality drugs. Since sample collection locations were not available, it was not possible to know the most vulnerable districts of Nepal for low-quality drugs. Therefore, more studies are needed to understand the prevalence of substandard and falsified drugs in Nepal covering different parts of

the country on regular basis. We suggest having more stringent regulatory systems and implementation for pharmaceutical manufacturing industries and enhanced post marketing surveillance.

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Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information. Author compiled & curated raw data will be made available with a reasonable request to corresponding author.

Ethical approval: This study does not involve human participants.

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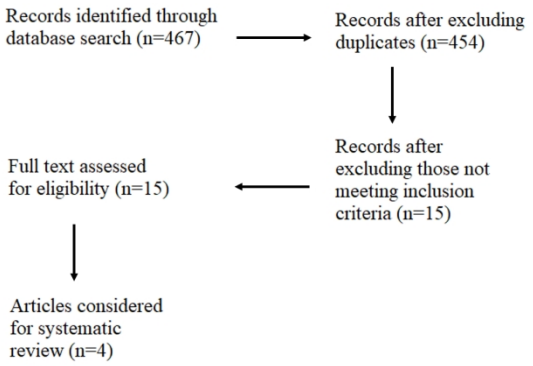

Figure 1: Flow chart of research papers search procedure

1283x721mm (38 x 38 DPI)

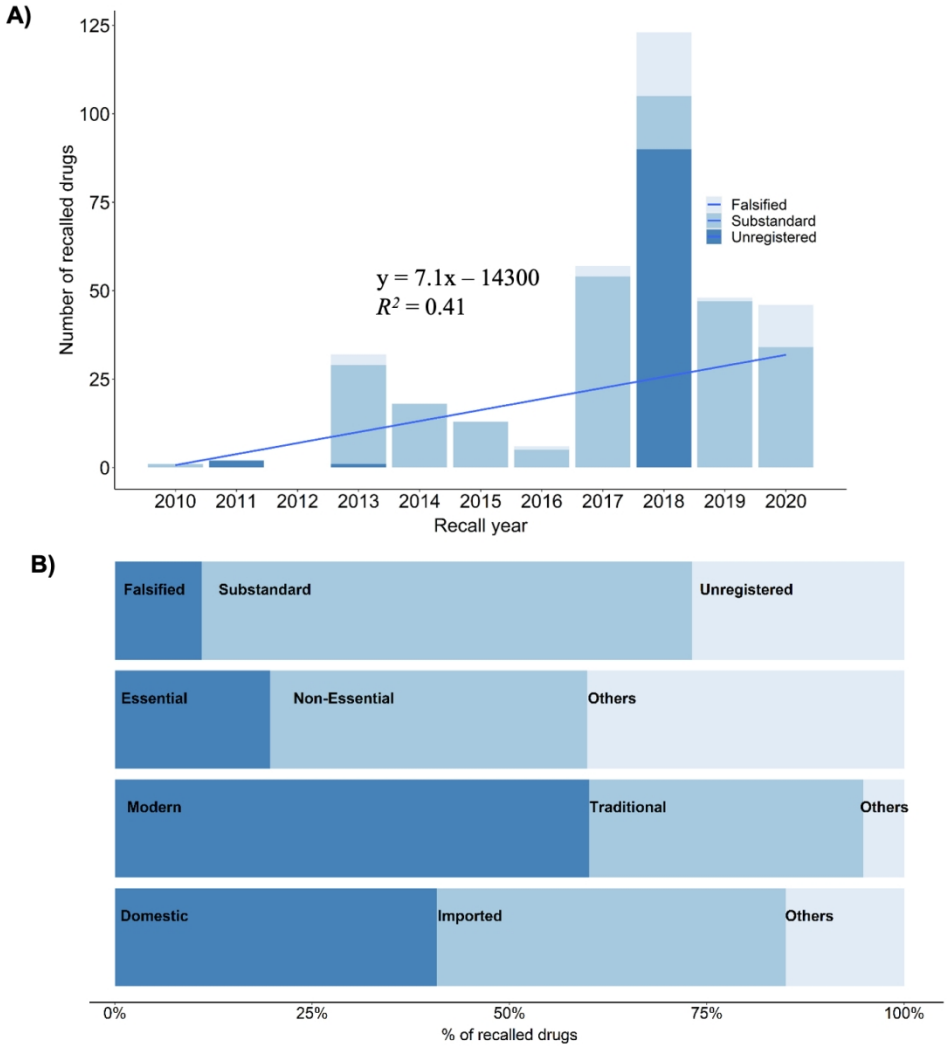

Figure 2: (A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of different categories of pharmaceutical products in the recall list.

671x719mm (57 x 57 DPI)

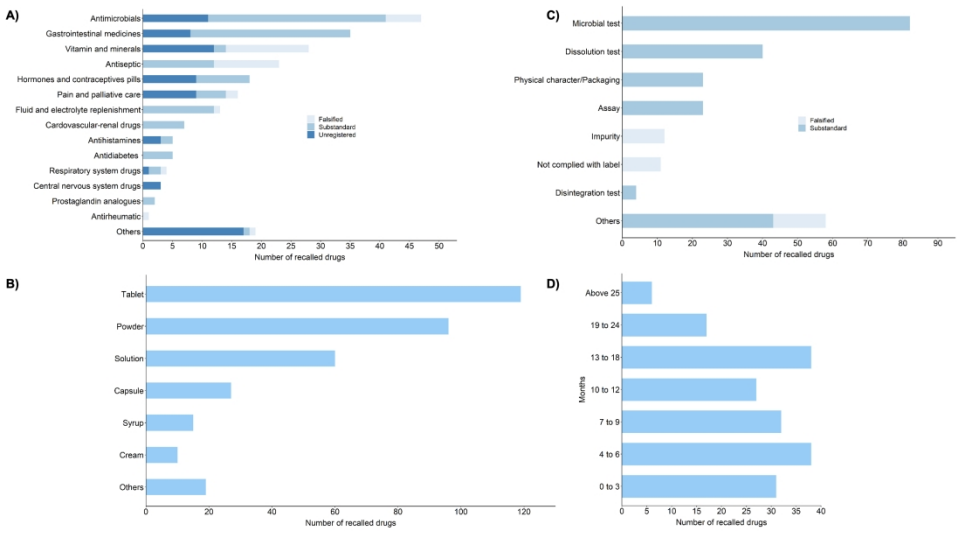

Figure 3: (A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self life of recalled pharmaceutical products after the recall (in months).

1283x719mm (57 x 57 DPI)

Pattern of drug recalls and quality of pharmaceutical products in Nepal

Astha Neupane, Maheshwor Bastakoti, Sabita Tamang, Basant Giri*

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences, P. O. Box 23002, Kathmandu, Nepal

Supplementary Material

Table S1: Result of literature search of peer-reviewed documents reporting drug quality data

Keywords	Number of articles found			
	PubMed	Web of Science	Springer link	Google Scholar
Counterfeit* OR substandard* OR fake OR spurious OR unregulated OR unregistered OR falsified* OR fraud	14532	51113	71770	41100
Drug OR medicine OR pharmaceutical	4977168	4579007	1386455	728000
Nepal*	12868	18132	16862	26500
1 AND 2 AND 3	13	10	393	51

List of research papers that included drug quality in Nepal

1. Poudel, Ramesh Sharma, et al. "Assessment of primary labeling of medicines manufactured by Nepalese pharmaceutical industries." *Journal of pharmaceutical policy and practice* 11.1 (2018): 1-6.
2. Gyanwali, P., et al. "Surveillance of Quality of Medicines Available in the Nepalese Market: A Study from Kathmandu Valley." *Journal of Nepal Health Research Council* (2015).
3. Poudel, Arjun, et al. "Assessment of the availability and rationality of unregistered fixed dose drug combinations in Nepal: a multicenter cross-sectional study." *Global health research and policy* 2.1 (2017): 1-13.
4. Jha, A. K., et al. *Quality of essential medicines in public health care facilities of Nepal–2019*. Nepal Health Research Council, 2019.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	-
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5&6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5&6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5&6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	-
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	-
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7&9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Page 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-15
	23b	Discuss any limitations of the evidence included in the review.	Page 16
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 15&16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data used for analysis

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

BMJ Open

A review of drug recalls and quality of pharmaceutical products in Nepal

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Secondary Subject Heading:	Global health, Health policy, Pharmacology and therapeutics
Keywords:	Public health < INFECTIOUS DISEASES, COVID-19, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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A review of drug recalls and quality of pharmaceutical products in Nepal

Astha Neupane, Maheshwor Bastakoti, Sabita Tamang, Basant Giri*

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences

P. O. Box 23002, Kathmandu, Nepal

*Correspondence

Dr. Basant Giri

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences

PO BOX 23003, Kathmandu, Nepal

bgiri@kias.org.np, chembasant@gmail.com

Word count: 3702 excluding abstract and references

ABSTRACT

Objectives: To evaluate the pattern of substandard and falsified pharmaceutical products recall in Nepal.

Setting: We analyzed drug recall notices issued by the Department of Drug Administration (DDA), Nepal and systematically reviewed peer reviewed research articles during January 2010 – December 2020.

Participants: This study did not include human participants. However, data was collected from 72 drug recall notices issued by DDA and four research papers.

Results: A total of 346 pharmaceutical products were recalled during the reported period. The number of recalled pharmaceutical products has increased significantly over the past decade in Nepal. The most frequently recalled drugs were antimicrobials followed by gastrointestinal medicines, vitamins and supplements, and pain and palliative medicines among others. Number of imported recalled drugs were slightly higher (42.2%) than domestic recalled drugs (40.7%). Sixty-two percentage of recalled drugs were substandard, 11% were falsified and remaining 27% were not registered at the DDA. Similarly, higher number of modern drugs (62%) were recalled than traditional ones (35%). Hand sanitizers used to minimize COVID-19 transmission contributed significantly to the list of recalled pharmaceutical products in 2020. Most of these sanitizers contained significant amounts of methanol (as high as 75%v/v) instead of appropriate amount of ethyl or isopropyl alcohol. The peer-reviewed research papers reported issues with labelling, unregistered drugs and drugs failed in several laboratory testing.

Conclusion: Our analysis showed that number of recalls of substandard and falsified drugs are increasing in Nepal. Since the recall data in this paper did not include number of samples tested

and location of samples collected, more studies to understand the prevalence of substandard and falsified drugs in Nepal is recommended.

Keywords: Counterfeit drugs, falsified medical products, public health, substandard, falsified drugs

Strength and limitations of this study

- This is the first study to evaluate the pattern of drug recall in Nepal.
- A comprehensive analysis of drug recall notice issued by Department of Drug Administration, Nepal from January 2010 to December 2020.
- Also includes a systematic review of peer-reviewed publications from 2010 to 2020 which reported poor quality drugs in Nepal.
- It does not include number of samples tested, location of sample collected, and impact of recall notice.
- Since we looked at pattern of recall drugs, it did not report the rate of low-quality drugs over the last decade.

INTRODUCTION

Pharmaceutical products are essential to treat, prevent, and save lives of millions of people globally[1]. They should be safe, effective, and of good quality. Such products should be prescribed by authorized medical practitioner and used rationally[2]. However, pharmaceutical products that do not meet regulatory standards and quality threaten the health of the population of today and future. Such products may be substandard or low-quality or falsified. Substandard or falsified drugs could lead to drug resistance and put the lives of patients at risk in addition to increasing the economic and social burden on people[3]. There are several reasons for the circulation of such substandard and falsified products in market such as lack of access to affordable, quality, safe and effective medical products, and good governance as well as poor ethical practices in health care facilities and medicine outlets. Limited technical capacity in manufacturing, quality control, distribution and testing also contribute to this problem[4,5].

Ozawa et al. in a 2018 meta-analysis estimated that about 10.5% of the medicines worldwide are either substandard or falsified. Prevalence of low-quality pharmaceutical products is higher in low- and middle-income countries (13.6%) compared to high income countries. About 18.7% medicines have been estimated to be low-quality in Africa and 13.7% in Asia. The most substandard or falsified drugs are the antimalarials (19.1%)[3].

Nepal is one of the least developed countries[6] that shares open and poorly regulated boarders with India and China. These two countries are considered as major producers of low-quality and falsified pharmaceutical products circulating in the global market[4]. The domestic market for medical products in Nepal was estimated to be 70 billion Nepal rupees in 2019 which included drugs (36 billion), raw materials and surgical equipment[7]. The Department of Drug Administration (DDA) authorizes the distribution of all pharmaceutical products in Nepal including production, distribution, export, and import. The DDA in Nepal is equivalent to the U.S. FDA and is responsible to prevent the misuse or abuse of drugs and allied pharmaceutical substances[8]. Few studies in the past have indicated the circulation of substandard, counterfeit, and unregistered drugs in the Nepali market[9,10,11]. DDA Nepal recalls marketed drugs if the drugs do not fulfill any requirement as indicated in the drug act 2035 B.S.[8]. It then issues public alerts and warnings when substandard, falsified, and unregistered medicine incidents are detected. Analysis of pattern of drug alerts, regulatory recalls and company led recalls could be helpful to understand major issues responsible for the availability of poor-quality drugs and devise appropriate actions to mitigate the problem[12,13]. Analysis of medical product recall and alert are available from few countries such as the United Kingdom[12], the Saudi Arabia[14], which have shown a significant increase in the number of recall drugs.

In this study, we report the pattern of recall of poor-quality drugs in Nepal by analyzing drug recall

notice issued by the DDA. We analyzed temporal trend of low-quality drugs, types of drugs and formulations, origin of drugs & manufacturers and reasoning for recall. We also reviewed research publications that reported drug quality data.

METHODOLOGY

We analyzed drug recall notices published by DDA Nepal from January 2010 to December 2020. The DDA publishes such notices in its bulletins, websites, and newspapers (https://dda.gov.np/). We extracted all the information provided on the recall notice such as brand name, dosage form, batch number, manufacturing date, expiry date, recall date, reason for non-compliance, and the manufacturer information. We used National List of Essential Medicines 2016 of Nepal to classify the recalled drugs into essential and non-essential drugs[15] and the WHO definition to identify substandard, falsified and unregistered drugs[16]. According to WHO definition, substandard drugs are authorized medical products but fail to meet quality standards or specifications or both. Similarly, falsified drugs are medical products that misrepresent their identity, composition or source[17]. Pharmaceutical products that did not pass dissolution test, active pharmaceutical ingredient (API) assay, microbial test, leakage test, friability, were non-compliance with the pharmacopeia for physical appearance, fungal count, weight variation, particulate matter test, uniformity test, disintegration test, and pH test were put together under the substandard category. Similarly, drugs that contained impurities, active ingredient not meant to be there, had price sticker without approval, or did not have product specification were classified as falsified pharmaceutical products. The drugs that were recalled as being not registered at DDA Nepal were classified under unregistered category. Unregistered drugs do not undergo evaluation and/or approval by DDA Nepal. Based on the brand names of each non-ayurvedic pharmaceutical product, we identified

their generic names and then categorized them into different groups based on their therapeutic properties.

In addition to the recall notice, we systematically reviewed the published research works to find the reporting of low-quality drugs in Nepali market. We specifically searched peer reviewed research articles from electronic databases such as PubMed (2010-2020), Web of Science (2010-2020), Springer link (2010-2020), and Google Scholar (2010-2020). We used the following search terms in conjunction with Boolean search term ("OR", "AND") to identify related articles: "counterfeit*", "substandard*", "falsified*", "fake", "spurious", "unregulated drugs", "unregistered", or "frauds"; combined with "drug", "medicine", or "pharmaceutical"; "Nepal*". In Google Scholar same search terms were used, but instead of "Nepal*", we used "intitle:Nepal". The articles were screened and evaluated manually through the title and abstract based on inclusion criteria: date of publication (2010-2020), the language (English) in which the article was published, the article should contain data/information on the prevalence of falsified/spurious/counterfeit/substandard drugs and the location of experiment/research carried out. Articles that did not meet the inclusion criteria were excluded. Also excluded were opinion articles, letters, notes, conference papers, book chapters, editorials or comments or articles with no abstracts or articles with counterfeit or substandard medicines related to animals.

A flow chart of search procedure is given in figure 1. Initially, we identified 467 journal articles after a search of literature in four different databases: PubMed, Springer link, Web of science and Google scholar. We removed 13 duplicate articles and brought the number of articles to 454. By screening the title and abstract of these articles, we removed 439 articles and we considered only 15 in next step (*see* Table SI1 in supplementary information). We read the full text of these articles and excluded 11 articles because they did not follow the inclusion criteria. At last, four

articles[10,11,18,19] were found to be relevant that contained primary information on the prevalence of substandard, falsified, and unregistered medicines in the Nepali market.

Figure 1: Flow chart of research papers search procedure

Statistical analyses of data such as Chi-square test, Fisher exact test and simple linear regression were performed using R version1.4.1106.

Patients and public involvement: Patient or the public were not involved in the design, conduct, reporting, and dissemination plans for this study.

RESULTS

We analyzed recalled drugs during the period of 2010 – 2020. During this period 346 pharmaceutical products were recalled by DDA Nepal. The number of recalled low-quality drugs in Nepal has significantly increased in the last decade (Figure 2A, linear regression, p-value< 0.05, adjusted R-squared value= 0.335). We found that only one pharmaceutical product was recalled in 2010. The product was a lactate solution which is commonly used for fluid resuscitation. The solution was recalled from the Nepali market because it did not pass the sterility test. There was no recall in 2012. The year 2018 had the highest number of pharmaceutical products recalled (123 products, see Figure 2A). Forty-six products were recalled in the year 2020, majority of which were hand sanitizers. The recalled pharmaceutical products were from 96 manufacturers mostly from Nepal and India, few from Australia, Bangladesh, and China. Manufacturer of 91 recalled drugs were unknown. The recalled pharmaceutical products included a significantly (two-sided Fisher exact test, p-value <0.001) higher number of imported medicines (153) items than domestically manufactured ones (141). The imported recalled products were manufactured mostly in India (97%, Figure 2B) and in drugs from Australia, Bangladesh and China. Country of origin of 52 recalled pharmaceutical products were not identified.

Figure 2: *(A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of different categories of pharmaceutical products in the recall list.*

Sixty percentage (n=346) of recalled pharmaceutical products were modern or allopathic (208) and 35% were traditional or ayurvedic (120) (Figure 2B). Two-sided Fisher exact test showed that significantly higher number of modern pharmaceutical products were recalled (p-value< 0.001). Twenty-seven percentage of the recalled drugs were unregistered at the DDA indicating they were not authorized to be distributed and sold in Nepal. Similarly, twenty percentage of the recalled drugs, mostly allopathic, were listed as essential medicines. 40% of the recalled drugs were non-essential allopathic (p-value <0.001) and 40% were ayurvedic drugs. Essential medicines are distributed free of cost through government health centers[15] and only allopathic drugs are listed as essential ones. Majority of the recalled pharmaceutical products were substandard (62%) followed by unregistered (27%) and falsified (11%) (see Figure 2B). We found that the recall pattern among these three categories were significantly different (one-way chi-square test, p-value < 0.001, χ^2 = 142.31, df = 2).

Figure 3: *(A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self life of recalled pharmaceutical products after the recall (in months).*

The top 10 most recalled drugs were antimicrobials (13.6%) followed by gastrointestinal medicines (10.1%), vitamins and minerals (8.1%), antiseptic (6.6), hormones and contraceptives (5.2%), and pain and palliative care medicines (4.6), fluid and electrolyte replenishment items (3.7%), cardiovascular and renal drugs (2.0%), anti-diabetes (1.4%) and antihistamines (1.4%) (see Figure 3A). Remaining recalled drugs were CNS drugs, respiratory system drugs, prostaglandin analogues, and antirheumatic agents. Nineteen drugs were not classified into any of

those and labelled as "others" because sufficient information was not available. Ayurvedic drugs were not included in this categorization.

The DDA provided reason(s) for every recalled pharmaceutical product. Large number of drugs (26.8%) were recalled because they were not registered at DDA. The most common reason for recall among registered drugs was the failure to comply with microbial test (23.7%) followed by failures in dissolution test (11.5%), in quantitative assay for active pharmaceutical ingredient (6.6%), and in physical characteristics and packaging (6.6%). Eleven products did not comply with labelling requirements and 12 had one or more impurities. Few samples categorized as "others" were recalled due to failure in identification test and contained active ingredient in dietary supplements (see Figure 3B). Tablets were the most recalled dosages forms followed by powder, solution, capsules, syrups/suspension, and cream/ointment. Dosage forms of some products were not identifiable, and they are categorized as "others" (Figure 3C). The shelf-life of recalled drugs ranged from less than three months (16.4%) to more than two years at the time of recall (Figure 3D).

Low-quality drugs reported in research papers

As stated in method section, only four research articles were included for detailed analysis. One of these articles reported by Jha et al.[18] assessed the quality of essential medicines available in 62 public health care facilities across 21 districts of Nepal. The authors tested 244 batches of 20 different generics of essential medicines and found that 37 batches failed to meet the required pharmacopeial standards. The quality failed medicines included both supplied by Government of Nepal (62.2%) and purchased from local pharmacies (37.8%). The failed medicines included antibiotics, supplements, anti-diabetics etc.

Providing required information on the label is another major issue. Most of the 759 pharmaceutical products from 37 Nepali pharmaceutical companies inspected in Chitwan in 2017 missed at least one critical information on the label such as drug quantity, name of pharmacopoeia, serial number of pharmaceutical industries, price list, drug classification, and information in Nepali language[10]. The reports showed that labels of 84% of drugs did not provide the directions for use. Similarly 90% of drug samples (n=40) in Kathmandu did not comply with the existing regulatory requirement on labeling and 42.5% brands did not indicate the Pharmacopoeial standard[9]. The same study showed that 40% of domestic and 28% imported brands failed to meet national criteria during laboratory analysis. On average, 32.5% samples were found to be of substandard quality in this study. Another study evaluated the availability and rationality of unregistered fixed-dose drug combinations (FDCs) in Nepal using snowball sampling method and Health Action International Asia-Pacific (HAI-AP) toolkit in 20 retail pharmacies. Forty-one unregistered fixed-dose anti-inflammatory/analgesic/antipyretics drug combinations were found in five major cities of Nepal. Regulatory authorities should initiate strict monitoring and appropriate regulatory mechanisms to prohibit the use of unregistered and irrational FDCs.[11]

DISCUSSION

Low-quality medicines or related products are recalled from the market by manufacturing companies voluntarily or by the order of national or international drug regulatory bodies[20]. Many recall incidents of poor quality medicine have been reported globally[21]. For example, Johnson and Johnson recalled 200,000 bottles of liquid ibuprofen in 2013 due to possible contamination with plastic particles. The US FDA had recalled the contaminated vials of corticosteroid medication in 2012 which was manufactured by the New England Compounding Center[22]. An analysis of drug recall in the UK has shown a tenfold increase in the defective medicines from 2001 to 2011 mostly

due to contamination and issues with packaging[12]. Similarly, the number of drug recall reported by Saudi Arabia Drug Authority increased six-folds from 2010 to 2018, in which the most commonly recalled drugs were antihypertensive drugs and antibiotics due to contamination and issues with non-compliance with manufacturer's specifications.[14]

Our analysis showed that the overall trend of recalled drugs is increasing in Nepal. Starting from a single drug recall in 2010 to highest numbers (123) in 2018. In this year, most of the recalled drugs (90) were due to them not registered with the DDA. This indicates that the circulation of unregistered drugs in market is a serious issue in Nepal which may be contributed to by the open and unregulated border with India.

Both allopathic and ayurvedic medicines are widely used in Nepal. Allopathic medicines are the modern medicines that are manufactured synthetically whereas ayurvedic medicines are the traditional medicines which uses the natural remedies to improve health or to treat diseases. Both types of medicines are commercially manufactured in Nepal in addition to being imported mostly from India. There are two groups of manufacturers of ayurvedic drugs in Nepal. The first being the registered companies which sell their products in packages through registered shops. Secondly, the ayurvedic drugs are made by individuals or small business holders without being registered at DDA and sell their ayurvedic products in streets, through door-to-door service, and through individual networks. We found that both allopathic and ayurvedic medicines were recalled due to their non-compliance with government standards. Ayurvedic medicines are utilized prominently in Nepali communities, and sometimes, they are used concomitantly with allopathic medicines[23]. There has been an increasing interest in the study of traditional medicine in different parts of world[24]. However, there is still lack of quality research and standards, and stringent regulatory environment for this sector.

Essential medicines are defined by WHO as the medicines that satisfy the priority healthcare needs of the population[25]. The concept of essential medicines was adopted in 1986 A.D. in Nepal to enhance access of essential medicines to every individual. The main criteria for selection of the medicines in the National List of Essential Medicine (NLEM) of Nepal are public health relevance, efficacy, safety, cost-effectiveness and access of the drugs. The NLEM 2016 of Nepal contains 359 medicines thus having 86 medicines more than NLEM 2011[15]. The following criteria were used for including a medicine in NLEM: approved and licensed in Nepal, relevance to a disease posing public health problem, proven efficacy and safety, aligned with standard treatment guideline of Nepal, stable under storage conditions, cost-effective, and access. However in certain conditions, some medicines are excluded from the NLEM list: those banned in Nepal, over safety concerns, if medicine with higher efficiency, safety profile and lower cost is available, irrelevant to public health disease burden, antimicrobial resistant, medicine with abuse and misuse potential[15]. Our study showed that some of the recalled allopathic medicines were essential drugs. Jha et al.[18] indicated the presence of high number of substandard essential medicines and majority of which were purchased by Government of Nepal. Essential medicines for various illnesses are supplied free of cost in Nepal through government hospitals, health care centers and health posts. Poor quality of essential medicines can have serious impact on public health. As significant proportion of drugs recalled by DDA included essential medicines distributed by Government of Nepal, there is enough room to improve the procurement practices and upgrading of health facilities in Nepal that store and distribute medicines. In one study[26] that looked into the procurement practices in Nepal, it was reported that the majority of hospital pharmacies in Nepal use an expensive direct procurement model for purchasing medicines. They relied on doctors' prescriptions to choose a particular brand, which may be influenced by pharmaceutical companies'

marketing strategies. Most of the hospital pharmacies procured only registered medicines, a minority reported purchasing unregistered medicines through unauthorized supply-chains. Not all pharmacies followed Basel Statements during procurement of medicines. Such pharmacies may need awareness and training to fully adopt regulation of national and international policies to enhance accessibility to quality medicines.

Among the recalled groups, antimicrobial group of medicines had the highest frequency of recall incidents. Acharya et.al[27] highlighted the problem of antimicrobial resistance in Nepal as an alarm bell for worse public health situation. Suboptimal dose or poorly manufactured antibiotic medicine increases the chance of antimicrobial resistance[28]. Most of the recalled therapeutic categories of medicines like vitamins and minerals, NSAIDs, other antipyretic and analgesic agents, antiseptics, fluid and electrolyte replenishment items and others are over-the-counter medicines that can be brought from the pharmacy without prescription. Such medicines can pose a significant threat patients who consume them[29]. Few anti-diabetes medicines were also recalled. Consumption of such medicines may increase the incidence of macrovascular and microvascular complications due to compromised glucose control[30].

Our study showed that some of the drugs were recalled due to failure in various laboratory tests like microbial test, assays, content uniformity test, weight variation, impurity test, dissolution test, friability test as well as identification and sterility test. Many of these failures can be linked to inadequate quality control measures during manufacturing and inappropriate procedures for transportation and storage and other logistic issues[17].

Jha *et. al.* pointed out that only 13% of 62 health facility inspected followed medicine storage guidelines for light, heat and humidity[18]. Keeping the temperature and humidity within a specified range is necessary because it has a major role in degradation of medicines. Another reason was

failure to comply with claims and incorrect labelling. The DDA regulation requires appropriate labelling of marketed medicines to ensure patient safety. Thus, drug analysts and the drug regulators should be encouraged to remain vigilant about the possibility of counterfeiting possibility. They should conduct appropriate analysis including chemical, physical, package inspection, and authentication efforts to ensure quality and safety of drugs getting to the ultimate user[31].

Domestically produced and imported medicines in Nepal should have the registration license from DDA[8]. Nonetheless, we found that high numbers of unregistered drugs were recalled during the inspection. Drug suppliers, wholesalers, and even retailers should ensure that the drugs they are handling is duly registered with the national regulatory body to ensure only safe and efficacious drugs get to the patient. Also, the regulatory body should conduct post-market surveillance to ameliorate the situation. Unregistered medical products in Nepal may or may not have been registered in India. Since Nepal shares open and poorly regulated boarder with India, drugs registered in India are also easily sold in the Nepali market, especially in bordering districts. We found that nearly half of the total recalled medicines were imported from India. India is the leading country in counterfeit drug production, having as much as 35% of the world production originating within its borders[32].

The COVID-19 pandemic has resulted in the surge of substandard and falsified medical products including drugs, masks, sanitizers, diagnostic tests, and vaccines and other essential medical products[33]. Rampant circulation of falsified medical products during emergencies has happened throughout history[33]. Counterfeit respirators and masks pose additional risk to health care workers[34]. Falsified chloroquine was seized in Cameroon, Congo and Niger between March and May 2020. Chloroquine was controversially announced as the drug for the treatment of COVID-

19[35]. The US FDA uncovered nearly 1,300 fraudulent products during early days of COVID-19[36]. DDA Nepal has recently amended the standard for Instant Hand Sanitizer in order to prohibit selling of substandard, falsified and unregistered sanitizers[37]. Between September and November 2020, the DDA issued recall notices for 19 hand sanitizers which failed to comply with the standard guideline. Some sanitizers were found to contain methanol, rather than ethyl alcohol and isopropyl alcohol. Methanol is very toxic. Use of hand sanitizer containing methanol may cause transdermal absorption and increases the risk of systemic toxicity[38]. The increase in the demand for hand sanitizers and other medicines in the face of COVID-19 has increased the growth of e-commerce. Online sale of pharmaceutical products has just started in Nepal during recent years. WHO has reported that 60% of medications purchased through the internet could be counterfeit or substandard, and more than 50% of medications purchased online from sites that concealed their actual physical address were found to be low quality medicines[39]. Nepali regulating agencies should pay special attention to this new method of doing business in Nepal to protect the people from consumption of low-quality and falsified medical products. Inexorable growth of online pharmacies, unregulated websites and social media platforms for business may contribute to the dispensing of unapproved, subpotent, counterfeit, expired or illegal drugs, and prescription drugs without valid prescriptions[40].

Recall and alert from regulating agencies is important step, however more actions are necessary to fully understand the substandard and falsified drugs circulation in the market and their potential impact. Naughton and Akgul[13] argued that freely available drug alert and recall are not enough to estimate medicine quality. Researchers have suggested to regulatory agencies to publish more information such as exact number of recalled packs, numbers of samples collected and tested, performed tests and results etc. Further, sampling methodologies for SF prevalence studies are

variable in terms of sample size, design methods consistency, reporting contextual factors, resulting in not reliable comparison across studies.[41] Therefore a standardize protocol for testing and reporting, global legal framework and surveillance systems of substandard and falsified drugs are needed[42]. This could potentially help to compare the results from different countries and understand from each other and make better policy interventions globally.[13]

CONCLUSION

In this paper, we presented a detailed pattern of low-quality and falsified drugs circulating in Nepal in the past decade using recall notice. We showed that the number of recalled drugs has significantly increased. This might be attributed either to a greater surveillance by DDA or actual increase in the levels of substandard, falsified, and unregistered medicines in the market, similar to previous studies[12]. However, our analysis was not enough to identify the exact cause of increase in the recalled drugs. Like global trends, antimicrobial drugs were the most recalled drugs in Nepal. The recall notices used did not provide information on the number of samples collected for testing or inspection and location of sample collection. Therefore, our analysis did not report the rate or prevalence of low-quality drugs. Since sample collection locations were not available, it was not possible to know the most vulnerable districts of Nepal for low-quality drugs. Therefore, more studies are needed to understand the prevalence of substandard and falsified drugs in Nepal covering different parts of the country on regular basis. We suggest having more stringent regulatory systems and implementation for pharmaceutical manufacturing industries and enhanced post marketing surveillance.

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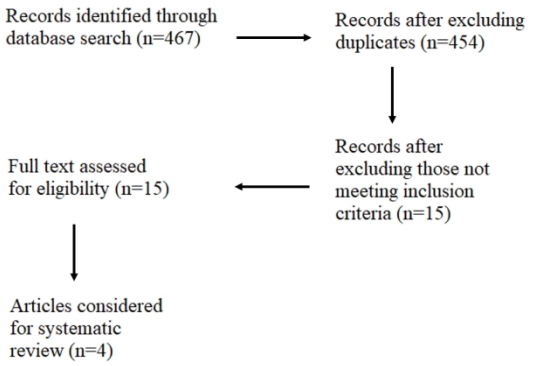

Figure 1: Flow chart of research papers search procedure

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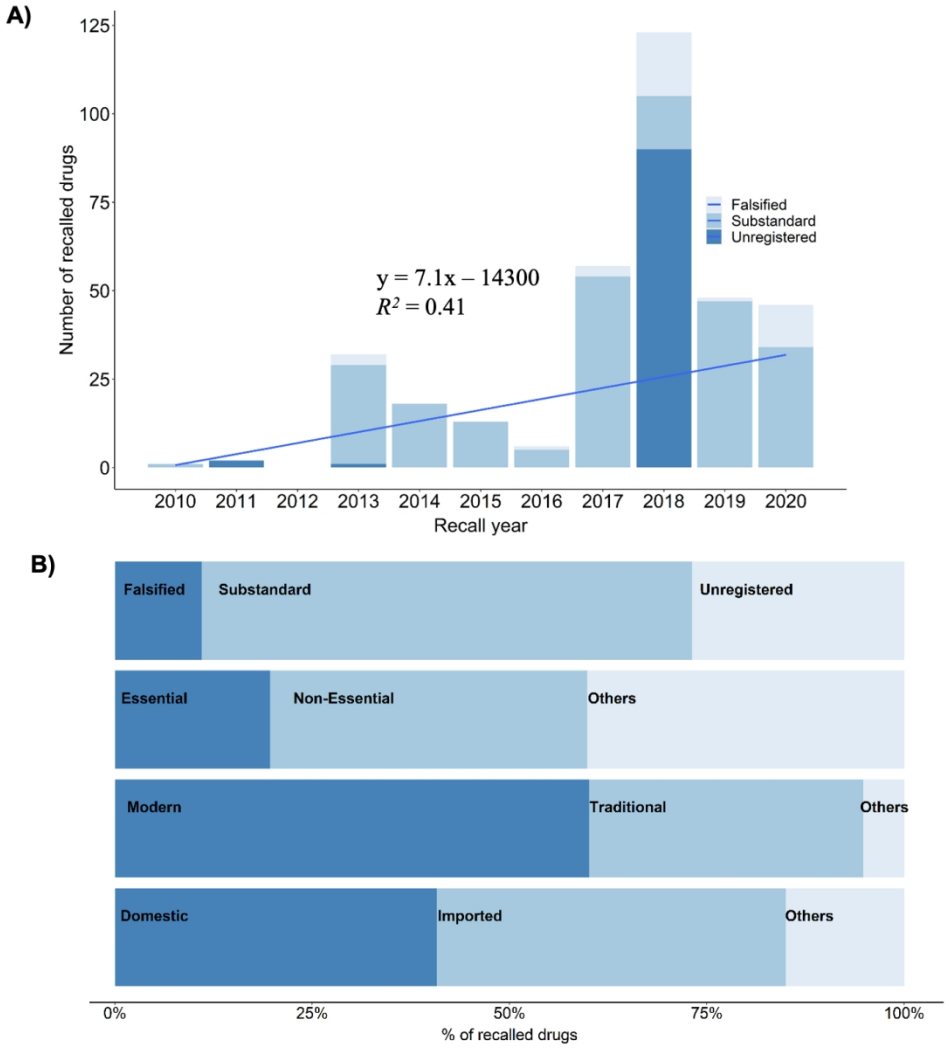

Figure 2: (A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of different categories of pharmaceutical products in the recall list.

671x719mm (57 x 57 DPI)

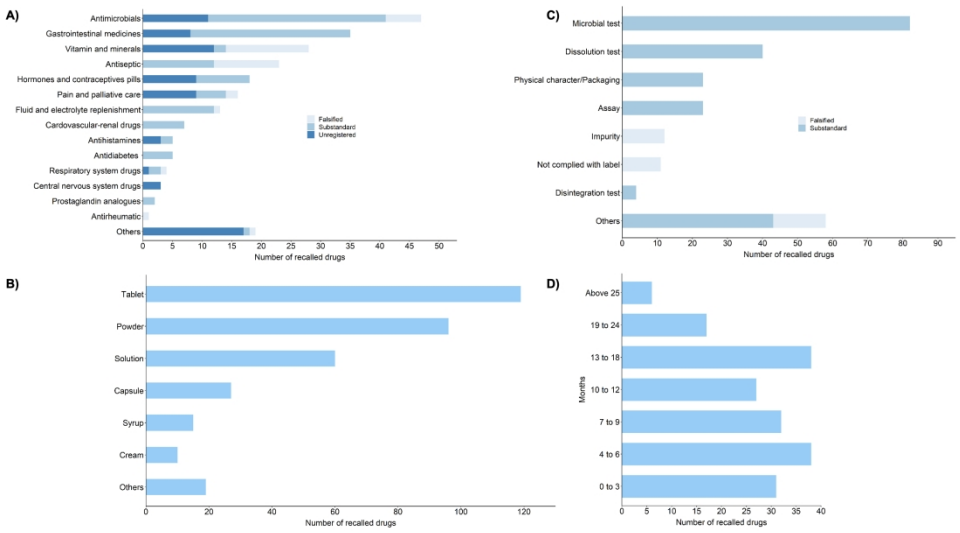

Figure 3: (A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self life of recalled pharmaceutical products after the recall (in months).

1283x719mm (57 x 57 DPI)

Pattern of drug recalls and quality of pharmaceutical products in Nepal

Astha Neupane, Maheshwor Bastakoti, Sabita Tamang, Basant Giri*

Center for Analytical Sciences, Kathmandu Institute of Applied Sciences, P. O. Box 23002, Kathmandu, Nepal

Supplementary Material

Table S1: Result of literature search of peer-reviewed documents reporting drug quality data

Keywords	Number of articles found			
	PubMed	Web of Science	Springer link	Google Scholar
Counterfeit* OR substandard* OR fake OR spurious OR unregulated OR unregistered OR falsified* OR fraud	14532	51113	71770	41100
Drug OR medicine OR pharmaceutical	4977168	4579007	1386455	728000
Nepal*	12868	18132	16862	26500
1 AND 2 AND 3	13	10	393	51

List of research papers that included drug quality in Nepal

1. Poudel, Ramesh Sharma, et al. "Assessment of primary labeling of medicines manufactured by Nepalese pharmaceutical industries." *Journal of pharmaceutical policy and practice* 11.1 (2018): 1-6.
2. Gyanwali, P., et al. "Surveillance of Quality of Medicines Available in the Nepalese Market: A Study from Kathmandu Valley." *Journal of Nepal Health Research Council* (2015).
3. Poudel, Arjun, et al. "Assessment of the availability and rationality of unregistered fixed dose drug combinations in Nepal: a multicenter cross-sectional study." *Global health research and policy* 2.1 (2017): 1-13.
4. Jha, A. K., et al. *Quality of essential medicines in public health care facilities of Nepal–2019*. Nepal Health Research Council, 2019.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	-
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5&6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5&6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5&6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	-
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	-
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7&9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Page 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-15
	23b	Discuss any limitations of the evidence included in the review.	Page 16
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 15&16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data used for analysis

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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