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Incidences of poor-quality pharmaceutical products in Nepal

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Incidences of poor-quality pharmaceutical products in Nepal

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3 **27 ABSTRACT**
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5 **28 Objectives:** To evaluate the pattern of substandard and falsified pharmaceutical products in
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8 **29** Nepal.
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12 **31 Setting:** We analyzed drug recall notices from 2010 – 2020 by the department of drug
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14 **32** administration (DDA), Nepal and systematically reviewed peer reviewed research articles.
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19 **34 Participants:** A total of 72 drug recall notices issued from 2010 to 2020 by DDA were included.
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21 **35** Only four research papers that reported original drug quality data from Nepal were included.
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24 **36**
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26 **37 Results:** A total of 346 pharmaceutical products were recalled during the reported period. The
27
28 **38** number of recalled pharmaceutical products has increased significantly over the past decade in
29
30 **39** Nepal. The most frequently recalled drugs were the antimicrobials followed by gastrointestinal
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32 **40** medicines, vitamins and supplements, pain and palliative medicines among others. Number of
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34 **41** imported recalled drugs were slightly higher (153) than domestic recalled drugs (141). Sixty-two
35
36 **42** percentage of recalled drugs were substandard, 11% were falsified and remaining 27% were not
37
38 **43** registered at the DDA. Similarly, higher number of modern drugs (62%) were recalled than
39
40 **44** traditional ones (35%). The hand sanitizers used to minimize the COVID-19 transmission
41
42 **45** contributed significantly to the list of recalled pharmaceutical products in 2020. Most of these
43
44 **46** sanitizers contained significant amount of methanol (as high as 75%v/v) instead of appropriate
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46 **47** amount of ethyl or isopropyl alcohol. The peer-reviewed research papers reported issues with
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48 **48** labeling, unregistered drugs and drugs failed in several laboratory testing.
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3 50 Conclusions: The substandard and/or falsified drugs that do not meet regulatory standards and
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5 51 quality threaten health of population putting patients' life in danger leading to socio-economic
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7 52 hardship. Our analysis showed that cases of substandard and fake drugs are increasing in Nepal.
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9 53 Since the recall data in this paper did not include number of samples tested and location of
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11 54 samples collected, a systematic study to understand the prevalence of substandard and falsified
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13 55 drugs in Nepal is recommended.
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17 56 **Keywords:** Counterfeit drugs, falsified medical products, public health, substandard, fake drugs
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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.

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60 INTRODUCTION

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44 61 Pharmaceutical products are essential to treat, prevent, and save lives of millions of people
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46 62 globally¹. They should be safe, effective, and of good quality. Such products should be prescribed
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48 63 by authorized medical practitioner and used rationally². However, pharmaceutical products that do
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50 64 not meet regulatory standards and quality threaten the health of the population of today and future.
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52 65 Such products may be substandard or low-quality or falsified. Substandard or falsified drugs could
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54 66 lead to drug resistances and put life of patients in danger in addition to creating economic and
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3 67 social burden to people³. There are several reasons for the circulation of such substandard and
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5 68 falsified products in market such as lack of access to affordable, quality, safe and effective medical
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8 69 products, and good governance, poor ethical practices in health care facilities and medicine outlets.
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10 70 Limited technical capacity in manufacturing, quality control, distribution and testing also
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12 71 contribute to the same problem^{4,5}.

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15 72 A recent meta-data analysis estimated that about 10.5% of the medicines worldwide are either
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17 73 substandard or falsified. Prevalence of low-quality pharmaceutical products is higher in low- and
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19 74 middle-income countries (13.6%) compared to high income countries. About 18.7% medicines
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21 75 have been estimated to be low-quality in Africa and 13.7% in Asia. The most substandard or
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23 76 falsified drugs are the antimalarials (19.1%)³.

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27 77 Nepal is one of the least developed countries that shares open and poorly regulated borders with
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29 78 India and China. These two countries are considered as the major producers of low-quality and
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31 79 fake pharmaceutical products circulating in the global market⁴. The domestic market for medical
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33 80 products in Nepal was estimated to be 70 billion Nepal rupees in 2019 that included drugs (36
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35 81 billion), raw materials and surgical equipment⁶. The department of drug administration (DDA)
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37 82 authorizes the distribution of all pharmaceutical products in Nepal including production,
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39 83 distribution, export and import. The DDA in Nepal is equivalent to U.S. FDA and is responsible
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41 84 to prevent the misuse or abuse of drugs and allied pharmaceutical substances⁷. Few studies in past
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43 85 have indicated the circulation of substandard, counterfeit, and unregistered drugs in the Nepali
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45 86 market^{8,9,10}. The DDA Nepal recalls marketed drugs if the drugs do not fulfill any requirement as
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47 87 indicated in the drug act 2035 B.S.⁷. It then issues public alerts and warnings when substandard,
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49 88 falsified, and unregistered medicine incidents are detected.

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51 89 In this study, we report the incidences of poor-quality drugs in Nepal by analyzing drug recall
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3 90 notice issued by the DDA. We analyzed temporal trend of low-quality drugs, types of drugs and
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5 91 formulations, origin of drugs & manufacturers and reasoning for recall. We also reviewed research
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7 92 publications that reported drug quality data. We found that the low-quality drugs have increased
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9 93 significantly in Nepal that over the last decade and among them antimicrobials are the most found
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11 94 low-quality drugs.
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15 95 **METHODOLOGY**

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18 96 We carefully analyzed drug recall notice published by DDA Nepal from 2010 to 2020. The DDA
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20 97 publishes such notices in its bulletins, websites, and newspapers. We extracted all the information
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22 98 provided on the recall notice such as brand name, dosage form, batch number, manufacturing date,
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24 99 expiry date, recall date, reason of non-compliance, and the manufacturer information. We used
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27 100 National List of Essential Medicines 2016 of Nepal to classify the recalled drugs into essential and
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29 101 non-essential drugs¹¹ and the WHO definition to identify substandard, falsified and unregistered
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31 102 drugs¹². According to WHO definition, the substandard drugs are authorized medical products but
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33 103 fail to meet quality standards or specifications or both. Similarly, falsified drugs are medical
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35 104 products that misrepresent their identity, composition or source¹³. Pharmaceutical products that
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37 105 did not pass dissolution test, API assay, microbial test, leakage test, friability, non-compliance
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39 106 with pharmacopeia, physical appearance, fungal count, weight variation, particulate matter test,
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41 107 uniformity test, disintegration test, and pH test were put together under substandard category.
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43 108 Similarly, drugs that contained impurities, active ingredient not meant to be there, had price sticker
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45 109 without approval, and did not have product specification were classified as falsified
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47 110 pharmaceutical products. The drugs that were recalled because they were not registered at DDA
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49 111 Nepal were classified under unregistered category. Unregistered drugs do not undergo evaluation
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51 112 and/or approval by DDA Nepal.
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3 113 In addition to the recall notice, we also analyzed peer reviewed research articles from electronic
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5 114 databases such as PubMed (2010-2020), Web of Science (2010-2020), Springer link (2010-2020),
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8 115 and Google Scholar (2010-2020). We used the following search terms in conjunction with Boolean
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10 116 search term (“OR”, “AND”) to identify related articles: “counterfeit*”, “substandard*”,
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12 117 “falsified*”, “fake”, “spurious”, “unregulated drugs”, “unregistered”, or “frauds”; combined with
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14 118 “drug”, “medicine”, or “pharmaceutical”; “Nepal*”. In Google Scholar same search terms were
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17 119 used, but instead of “Nepal*”, we used “intitle:Nepal”. The articles were screened and evaluated
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19 120 manually through the title and abstract based on inclusion criteria: date of publication (2010-2020),
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21 121 the language (English) in which the article was published, the article should contain
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23 122 data/information on the prevalence of falsified/spurious/counterfeit/substandard drugs and the
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25 123 location of experiment/research carried out. Similarly, the articles which did not meet inclusion
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28 124 criteria were excluded. We also did not include opinion articles, letters, notes, conference papers,
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30 125 book chapters, editorials or comments or articles with no abstracts or articles with counterfeit or
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32 126 substandard medicines related to animals.

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36 127 Statistical analyses of data such as Chi-square test, Fisher exact test and simple linear regression
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38 128 were performed using R version 1.4.1106.

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41 129 Patients and public involvement: Patient or the public were not involved in the design, or conduct,
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43 130 or reporting, or dissemination plans of our research.

44 45 46 47 131 **RESULTS**

48 132
49 133 We analyzed recalled drugs during the period of 2010 – 2020. During this period 346
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51 134 pharmaceutical products were recalled by DDA Nepal. The number of recalled low-quality drugs
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53 135 in Nepal has significantly increased in the last decade (figure 1A, linear regression, p-value < 0.05,
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3 136 adjusted R-squared value= 0.335). We found that only one pharmaceutical product was recalled in
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5 137 2010. The product was the lactate solution which is commonly used for fluid resuscitation. The
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7 138 lactate was recalled from Nepali market since it did not pass the sterility test. There was no recall
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10 139 in 2012. The year of 2018 had the highest number of pharmaceutical products recalled (123
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12 140 products, see figure 1a). Forty-six products were recalled in the year 2020, majority of which were
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14 141 hand sanitizers. The recalled pharmaceutical products were from 96 manufacturers mostly from
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16 142 Nepal and India, few from Australia, Bangladesh, and China. Manufacturer of 91 recalled drugs
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18 143 were unknown. The recalled pharmaceutical products included a significantly (two-sided fisher
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20 144 exact test, p-value <0.001) higher number of imported medicines (153) items than domestically
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22 145 manufactured the imported (141) ones which were manufactured mostly in India (97%, figure 1B).
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24 146 Few drugs from Australia, Bangladesh and China were also recalled. Country of origin of 52
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26 147 recalled pharmaceutical products were not identified.

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31 148 **Figure 1:** (A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of
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33 149 different category of pharmaceutical products in the recall list.

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36 150 Sixty percentage (n=346) of recalled pharmaceutical products were modern or allopathic (208)
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38 151 and 35% were traditional or ayurvedic (120) (figure 1B). Two-sided fisher exact test showed that
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40 152 significantly large number of modern pharmaceutical products were recalled (p-value< 0.001).
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42 153 Twenty-seven percentage of the recalled drugs were unregistered at the DDA indicating they were
43
44 154 not authorized to distribute and sell in Nepal. Similarly, twenty percentage of the recalled drugs,
45
46 155 mostly allopathic, were listed as essential medicines. Essential medicines are distributed free of
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48 156 cost through government health centers. Remaining 40% drugs were non-essential ones (p-value
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50 157 < 0.001) and equal number of ayurvedic drugs were categorized as others since such drugs are not
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52 158 classified as essential or non-essential. Majority of the recalled pharmaceutical products were
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3 159 substandard (215) followed by unregistered (93) and falsified (38) (see figure 1B). We found that
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5 160 the recall pattern among these three categories were significantly different (one-way chi-square
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8 161 test, p-value < 0.001, X-squared = 142.31, df = 2).
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10 162 **Figure 2:** (A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage
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12 163 forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self
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14 164 life of recalled pharmaceutical products after the recall (in months).
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17 165 Based on the brand names of each non-ayurvedic pharmaceutical product, we identified their
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19 166 generic names and then categorized them into different groups based on their therapeutic
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21 167 properties. The top 10 most recalled drugs belonged to antimicrobials (47) followed by
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23 168 gastrointestinal medicines (35), vitamins and minerals (28), antiseptic (23), hormones and
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25 169 contraceptives (18), and pain and palliative care medicines (16), fluid and electrolyte
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27 170 replenishment (13), cardiovascular and renal drugs (7), anti-diabetes (5) and antihistamines (5)
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29 171 (see figure 2A). Remaining recalled drugs were CNS drugs, respiratory system drugs,
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31 172 prostaglandin analogues, antirheumatic. Nineteen drugs were not classified into any of those and
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33 173 labeled as “others” because enough information was not available. Similarly, ayurvedic drugs were
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35 174 not including in this categorization. The DDA provided reason(s) for every recalled
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37 175 pharmaceutical product. Large number of drugs were recalled because they were not registered
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39 176 (93) at DDA. The most common reason for recall among registered drugs was the failure to comply
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41 177 with microbial test (82) followed by failures in dissolution test (40), in quantitative assay for active
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43 178 pharmaceutical ingredient (23), and in physical characteristics and packaging (23). Eleven
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45 179 products did not comply label requirements and 12 had one or more impurity. Few samples
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47 180 categorized as “others” were recalled due to failure in identification test and contained active
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49 181 ingredient in dietary supplements (see figure 2B). Tablets were the most recalled dosages form
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3 182 followed by powder, solution, capsules, syrups/suspension, cream/ointment. Dosage forms of
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5 183 some products were not identifiable, and they are categorized as “others” (figure 2C). The shelf-
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7 184 life of recalled drugs ranged from less than three months (16.4%) to more than two years at the
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9 185 time of recall (figure 2D).

186 **Low-quality drugs reported in research papers**

15 187 We also systematically investigated the published research works in order to find the reporting of
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17 188 low-quality drugs in Nepali market. A flow chart of search procedure is given in figure 3. Initially,
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19 189 we identified 467 journal articles through the literature search in four different databases: PubMed,
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21 190 Springer link, Web of science and Google scholar. We removed 13 duplicate articles and brought
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23 191 the number of articles to 454. By screening the title and abstract of these articles, we removed 439
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25 192 articles and we considered only 15 in next step (*see* Table SI1). We read the full text of these
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27 193 articles and excluded 11 articles because they did not follow the inclusion criteria. At last, four
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29 194 articles^{9,10,14,15} were found to be relevant that contained primary information on the prevalence of
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31 195 substandard, falsified, and unregistered medicines in the Nepali market.

36 196 *Figure 3: Flow chart of research papers search procedure*

38 197 A cross sectional descriptive study reported by Jha et al.¹⁴ assessed the quality of essential
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40 198 medicines available in 62 public health care facilities across 21 districts of Nepal. Out of 244
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42 199 batches of 20 different generics of essential medicines tested, 37 batches failed to meet the required
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44 200 pharmacopeial standards. 62.2% of failed batches of medicines were supplied by Government of
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46 201 Nepal and remaining 37.8% batches were purchased from local resources. The failed medicines
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48 202 included antibiotics, supplements, anti-diabetics etc. Providing required information on the label
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50 203 is another major issue. Most of the 759 pharmaceutical products from 37 Nepali pharmaceutical
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52 204 companies inspected in Chitwan in 2017 missed at least one critical information on the label such
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3 205 as drug quantity, name of pharmacopoeia, serial number of pharmaceutical industries, price list,
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5 206 drug classification, and information in Nepali language⁹. In addition, 84% of drugs did not provide
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7 207 the directions of use. Similarly 90% of drug samples (n=40) in Kathmandu did not comply with
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10 208 the existing regulatory requirement on labeling and 42.5% brands did not mention about the
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12 209 pharmacopoeial standard⁸. The same study showed that 40% of domestic and 28% imported brands
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14 210 failed to meet national criteria during laboratory analysis. In average, 32.5% samples were found
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16 211 to be of substandard quality in this study. Another study evaluated the availability and rationality
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18 212 of unregistered fixed-dose drug combinations (FDCs) in Nepal using snowball sampling method
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20 213 and Health Action International Asia-Pacific (HAI-AP) toolkit in 20 retail pharmacies. Forty-one
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22 214 unregistered fixed-dose anti-inflammatory/analgesic/antipyretics drug combinations were found
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24 215 in five major cities of Nepal. Regulatory authorities should initiate strict monitoring and
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26 216 appropriate regulatory mechanisms to prohibit the use of unregistered and irrational FDCs.¹⁰
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31 **DISCUSSION**

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34 219 The low quality medicines or related products are recalled from the market by manufacturing
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36 220 company voluntarily or by the order of national or international drug regulatory bodies¹⁶. Many
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38 221 recall incidents of poor quality medicine have been reported globally¹⁷. For example, Johnson and
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40 222 Johnson recalled 200,000 bottles of liquid ibuprofen in 2013 due to possible contamination with
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42 223 plastic particles. Similarly, in 2012, the US FDA recalled the contaminated vials of corticosteroid
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44 224 medication which was manufactured by the New England Compounding Center¹⁸.
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48 225 Our analysis showed that the overall trend of recalled drugs is increasing in Nepal. Starting from
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50 226 a single drug recall in 2010 to highest numbers (123) in 2018. In this year, most of the drugs (90)
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52 227 were recalled since they were not registered with the DDA. This indicates that the circulation of
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54 228 unregistered drugs in market is a serious issue in Nepal which may be contributed by the open
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3 229 and unregulated boarder with India. Both allopathic and ayurvedic medicines are widely used in
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5 230 Nepal. The allopathic medicines are the modern medicines that are manufactured synthetically
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8 231 whereas ayurvedic medicines are the traditional medicines which uses the natural remedies to
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10 232 improve health or to treat diseases. Both types of medicines are commercially manufactured in
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12 233 Nepal in addition to be imported mostly from India. There are two groups of manufacturers of
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14 234 ayurvedic drugs in Nepal. They are mostly manufactured by registered companies and sold in
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16 235 market in packages through registered shops. The ayurvedic drugs are also made by individuals or
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18 236 small business holders without being registered at DDA and sell their ayurvedic products in streets,
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20 237 through door-to-door service, and through individual networks. We found that both allopathic and
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22 238 ayurvedic medicines were recalled due to their non-compliance with government standards.
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24 239 Ayurvedic medicines are utilized prominently in Nepali communities, and sometimes, they are
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26 240 used concomitantly with allopathic¹⁹. There has been an increasing interest in the study of
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28 241 traditional medicine in different parts of world²⁰. However, there is still lack of quality research
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30 242 and standards, and stringent regulatory environment in this sector.
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36 243 Essential medicines are defined by WHO as the medicines that satisfy the priority healthcare needs
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38 244 of the population²¹. The concept of essential medicines was adopted in 1986 A.D. in Nepal to
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40 245 enhance the access of essential medicines to every individual. The main criteria for selection of
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42 246 the medicines in the National List of Essential Medicine (NLEM) of Nepal are public health
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44 247 relevance, efficacy, safety, cost-effectiveness and access of the drugs. The NLEM 2016 of Nepal
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46 248 contains 359 medicines which has 86 medicines more than the NLEM 2011¹¹. Following criteria
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48 249 were used for including a medicine in NLEM: approved and licensed in Nepal, relevance to a
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50 250 disease posing public health problem, proven efficacy and safety, aligned with standard treatment
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52 251 guideline of Nepal, stable under storage conditions, cost-effectiveness, access. However in
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3 252 following conditions medicines were excluded from the NLEM list: banned in Nepal, safety
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5 253 concerns, if medicine with higher efficiency, safety profile and lower-cost is available, irrelevant
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8 254 to public health disease burden, antimicrobial resistant, medicine with abuse and misuse
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10 255 potential¹¹. Our study showed that some of the recalled allopathic medicines were essential drugs.
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12 256 Jha et.al¹⁴ indicated the presence of high number of substandard essential medicines and majority
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14 257 of which were purchased by Government of Nepal. Essential medicines for various illnesses are
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16 258 supplied free of cost in Nepal through government hospitals, health care centers and health posts.
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18 259 Poor quality of essential medicines can have serious impact on public health. As significant
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20 260 proportion of drugs recalled by DDA included essential medicines distributed by Government of
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22 261 Nepal, there is enough room to improve the procurement procedure and upgrading of health
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24 262 facilities of Nepal that store and distribute the medicines. In one study²² that looked into the
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26 263 procurement practices in Nepal reported that the majority of hospital pharmacies in Nepal use an
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28 264 expensive direct-procurement model for purchasing medicines. They relied on doctors'
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30 265 prescriptions to choose a particular brand, which may be influenced by pharmaceutical companies'
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32 266 marketing strategies. Most of the hospital pharmacies procured only registered medicines, a
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34 267 minority reported purchasing unregistered medicines through unauthorized supply-chains. Not all
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36 268 pharmacies followed Basel Statements during procurement of medicines. Such pharmacies may
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38 269 need awareness and training to fully adopt regulation of national and international policies for
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40 270 enhancing accessibility to quality medicines.

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42 271 Among the recalled groups, antimicrobial group of medicines had the highest frequency of recall
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44 272 incidents. Acharya et.al²³ highlighted the problem of antimicrobial resistance in Nepal as an alarm
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46 273 bell for worse public health situation. Suboptimal dose or poorly manufactured antibiotic medicine
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48 274 increases the chance of antimicrobial resistance²⁴. Most of the recalled therapeutic categories of
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3 275 medicines like vitamins and minerals, NSAID, antipyretic and analgesic, antiseptic, fluid and
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5 276 electrolyte replenishment and others are over-the-counter medicines that can be brought from the
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7 277 pharmacy without the prescriptions. Such medicines can pose a significant threat to the groups of
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9 278 patients who consume them²⁵. Few anti-diabetes medicines were also recalled. Consumption of
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11 279 such medicines may increase the incidence of macrovascular and microvascular complications due
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13 280 to compromised glucose control²⁶.

14
15 281 Our study showed that the drugs were recalled due to failure in various laboratory tests like
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17 282 microbial test, assays, content uniformity test, weight variation, impurity test, dissolution test,
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19 283 friability test, identification and sterility test. Many of these failures might be attributed to the lack
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21 284 of proper quality control during manufacturing and lack of following proper procedures for
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23 285 transportation and storage conditions¹³.

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25 286 Jha et.al pointed out that only 13% of 62 health facility inspected followed medicine storage
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27 287 guidelines for light, heat and humidity¹⁴. Keeping the temperature and humidity within a range is
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29 288 must necessary because it has a major role in degradation of medicines. Another reason was failure
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31 289 to comply with the claim and incorrect labeling. The DDA regulation requires appropriate labeling
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33 290 of marketed medicines to ensure patient medication safety, which seems to be not followed
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35 291 properly. Thus, the drug analyst and the drug regulators should be encouraged to remain vigilant
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37 292 about counterfeiting possibility and conduct the analysis including chemical, physical, package
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39 293 inspection, and authentication efforts to determine quality more accurately²⁷.

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41 294 Domestically produced and imported medicines in Nepal should have the registration license from
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43 295 DDA⁷. Nonetheless, we found that high numbers of unregistered drugs were recalled during the
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45 296 inspection. The drug supplier, whole seller, and retailers should ensure that the drug is registered
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47 297 within the national regulatory body to timely identify substandard products before they reach
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3 298 patients. Also, the regulatory body should stringent post-market surveillance to ameliorate the
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5 299 situation. The unregistered medical products in Nepal may or may not have been registered in
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8 300 India. Since Nepal shares open and poorly regulated boarder with India, drugs registered in India
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10 301 are also easily sold in Nepali market, especially in bordering districts. We found that nearly half
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12 302 of the total recalled medicines were imported from India. India is the leading country in counterfeit
13
14 303 drug production, having as much as 35% of the world production originating within its borders²⁸.

17 304 **COVID-19 related recalls**

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20 305 The COVID-19 pandemic has resulted in the surge of substandard and falsified medical products
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22 306 including drugs, masks, sanitizers, diagnostic tests, and vaccines and other essential medical
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24 307 products²⁹. Rampant circulation of fake medical products during emergencies has happened
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26 308 throughout the history²⁹. Counterfeit respirators and masks pose additional risk to health care
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28 309 workers³⁰. Falsified chloroquine was seized in Cameroon, Congo and Niger during March and
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30 310 May 2020. Chloroquine was controversially announced as the drug for the treatment of COVID-
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32 311 19³¹. The US FDA uncovered nearly 1,300 fraudulent products during early days of COVID-19³².
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34 312 The DDA Nepal, recently, has amended the standard for Instant Hand Sanitizer in order to prohibit
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36 313 the selling of the substandard, falsified and unregistered sanitizers³³. In between September and
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38 314 November 2020, the DDA issued the recalled notice for 19 hand sanitizers which failed to comply
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40 315 with the standard guideline. Some sanitizers were found to contain methanol, rather than ethyl
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42 316 alcohol and isopropyl alcohol. As methanol is very toxic, some of the case series indicated use of
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44 317 hand sanitizer containing methanol causes the transdermal absorption and increases the risk of
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46 318 systemic toxicity³⁴. The increase in the demand of hand sanitizer and other medicines has increased
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48 319 the growth of e-commerce. Online sale of pharmaceutical products has just started in Nepal during
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50 320 recent years. WHO has reported that 60% of medications purchased through internet could be
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3 321 counterfeit or substandard, and more than 50% of medications purchased online from sites that
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5 322 concealed their actual physical address was found to be low quality medicine³⁵. Nepali regulating
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7 323 agencies should pay special attention to this new method of business in Nepal to protect people
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9 324 from the consumption of low-quality and fake medical products. Inexorable growth of online
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11 325 pharmacies, unregulated websites, and, social media platform for business may contribute to the
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13 326 dispensing of unapproved, subpotent, counterfeit, expired or illegal drugs, and prescription drugs
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15 327 without a valid prescription in Nepal too³⁶.
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20 328 **CONCLUSION**

21
22 329 In this paper, we presented a detailed analysis of low-quality and fake drugs circulating in Nepal
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24 330 in the past decade using recall notice. We showed that the number of recalled drugs has
25
26 331 significantly increased. This might be attributed to greater surveillance by DDA or the substandard,
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28 332 falsified and unregistered medicine in the market are actually increasing. Similar to global trend,
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30 333 antimicrobial drugs were the most recalled drugs in Nepal. Since antibiotics are available over the
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32 334 counter in Nepal without doctor's prescription, it is necessary to enforce strict regulation so that
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34 335 the rampant (mis)use of such drugs is minimized and prevent antibiotic resistance. We relied on
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36 336 recall notice from DDA. The recall notice does not provide information on the number of samples
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38 337 collected for testing or inspection and location of sample collection. Therefore, our analysis did
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40 338 not report the rate or prevalence of low-quality drugs. Since sample collection locations were not
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42 339 available, it was not possible to know the most vulnerable districts of Nepal for low-quality drugs.
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44 340 Therefore, a systematic study is needed to understand the prevalence of substandard and falsified
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46 341 drugs in Nepal covering different parts of the country on regular basis. We suggest having more
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48 342 stringent regulatory systems and implementation for pharmaceutical manufacturing industries and
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50 343 post marketing surveillance.
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3 344 Contributors: BG contributed to conceptualization and study design, data analysis, manuscript
4 345 revision. AN, MB contributed to data collection, analysis and first draft. ST contributed to data
5 346 collection. All authors gave approval for the final version of the manuscript.
6 347

7
8 348 Funding: No specific funding supported this.
9 349

10 350 Competing interests: None declared.
11 351

12 352 Data sharing: All data are provided in the manuscript and supplementary material. Raw data can
13 353 be obtained by emailing corresponding author.
14 354

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16 355 Ethical approval: Since this research did not include human subject and used publicly available
17 356 data, ethical approval was not required.
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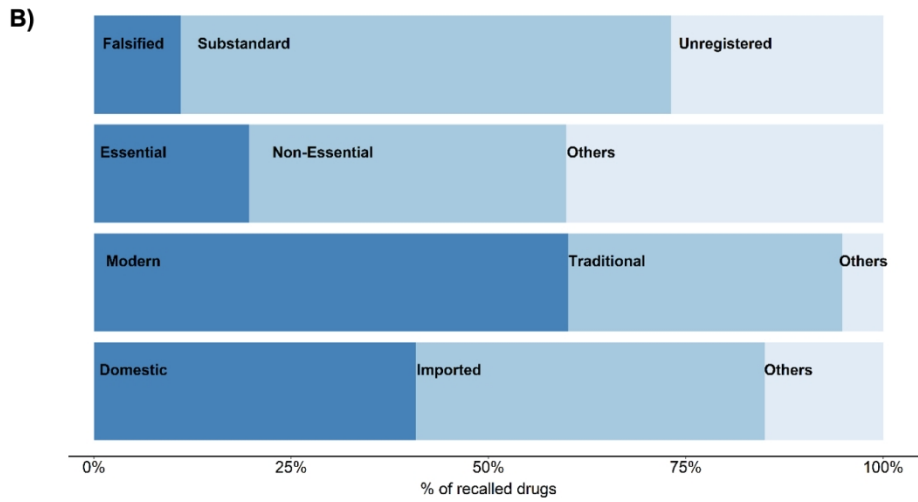
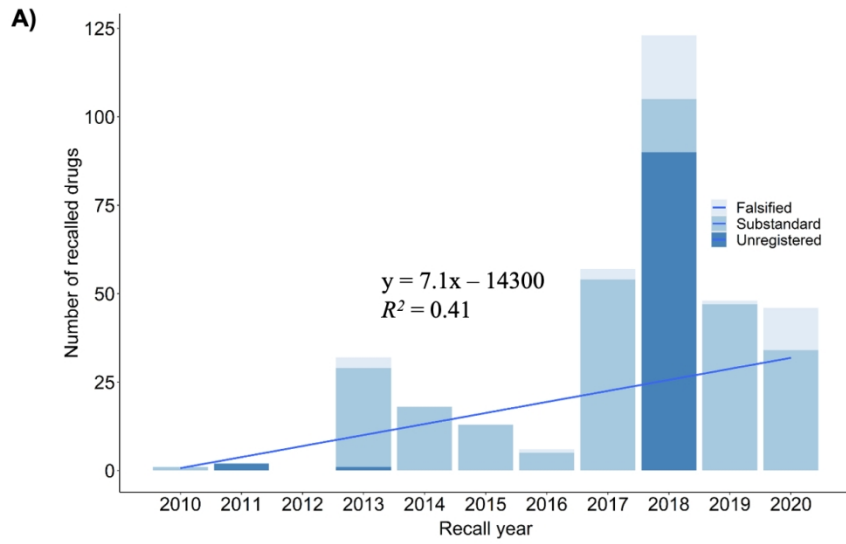
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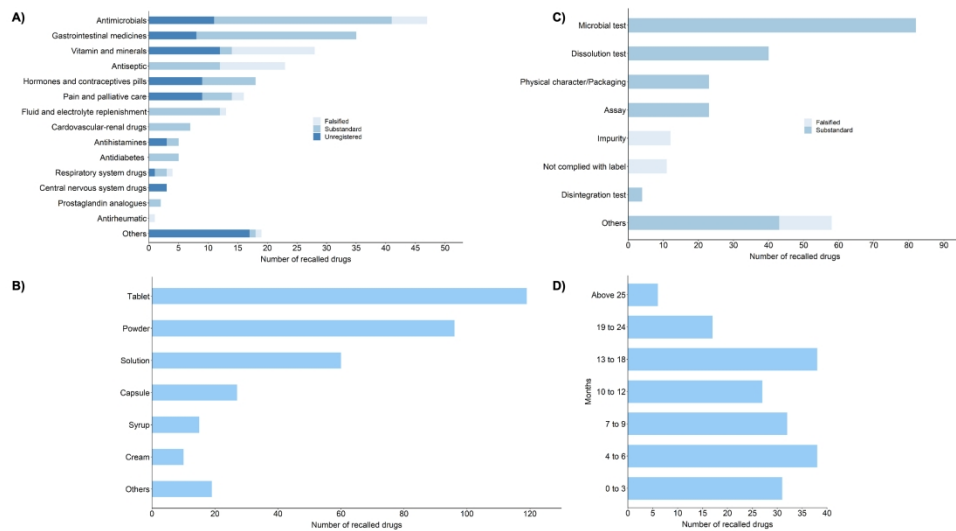
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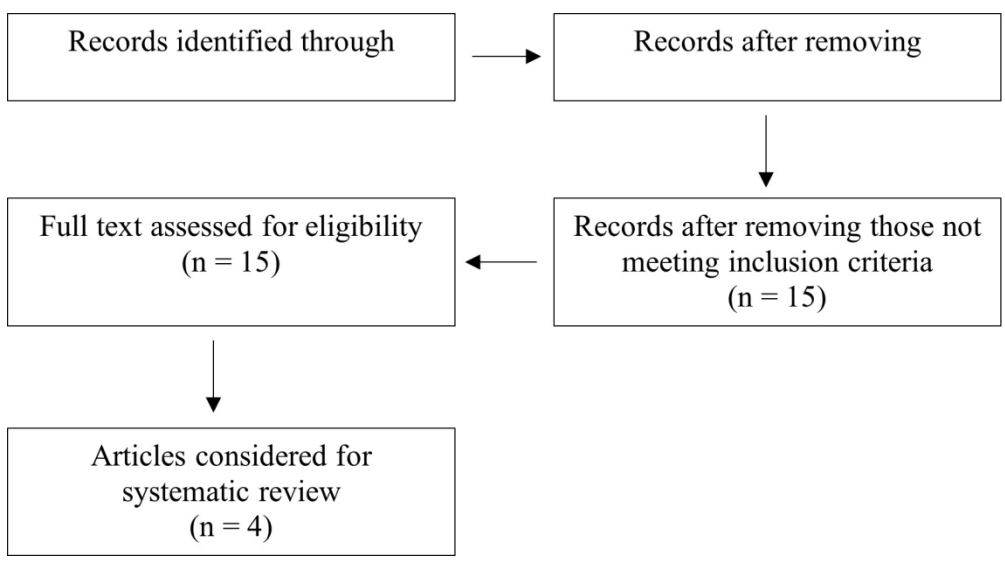
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138x75mm (330 x 330 DPI)

Incidences of poor-quality pharmaceutical products in Nepal

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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 Science	of 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. https://www.bmj.com/submit/guidelines.xhtml	Data used for analysis



PRISMA 2020 Checklist

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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/>

For peer review only

BMJ Open

Pattern of drug recalls and quality of pharmaceutical products in Nepal

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-053479.R1
Article Type:	Original research
Date Submitted by the Author:	23-Oct-2021
Complete List of Authors:	Neupane, Astha; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences Bastakoti, Maheshwor; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences Tamang, Sabita; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences Giri, Basant; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences
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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1 **Pattern of drug recalls and quality of pharmaceutical products in**

2 **Nepal**

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16 **Word count:** 3702 excluding abstract and references

26 ABSTRACT

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

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

32 **Participants:** This study did not include human participants. However, data was collected from
33 72 drug recall notices issued by DDA and four research papers.

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

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

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3 48 and location of samples collected, more studies to understand the prevalence of substandard and
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5 49 falsified drugs in Nepal is recommended.
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8 50 **Keywords:** Counterfeit drugs, falsified medical products, public health, substandard, fake drugs
9

10 **Strength and imitations of this study**

- 11 • This is the first study to evaluate the pattern of drug recall in Nepal.
- 12 • A comprehensive analysis of drug recall notice issued by Department of Drug
13 Administration, Nepal from January 2010 to December 2020.
- 14 • Also includes a systematic review of peer-reviewed publications from 2010 to
15 2020 which reported poor quality drugs in Nepal.
- 16 • It does not include number of samples tested, location of sample collected, and
17 impact of recall notice.
- 18 • Since we looked at pattern of recall drugs, it did not report the rate of low-quality
19 drugs over the last decade.
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27 52 **INTRODUCTION**
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30 53 Pharmaceutical products are essential to treat, prevent, and save lives of millions of people
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32 54 globally¹. They should be safe, effective, and of good quality. Such products should be prescribed
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34 55 by authorized medical practitioner and used rationally². However, pharmaceutical products that do
35
36 56 not meet regulatory standards and quality threaten the health of the population of today and future.
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38 57 Such products may be substandard or low-quality or falsified. Substandard or falsified drugs could
39
40 58 lead to drug resistance and put the lives of patients at risk in addition to increasing the economic
41
42 59 and social burden on people³. There are several reasons for the circulation of such substandard and
43
44 60 falsified products in market such as lack of access to affordable, quality, safe and effective medical
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46 61 products and good governance as well as poor ethical practices in health care facilities and
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48 62 medicine outlets. Limited technical capacity in manufacturing, quality control, distribution and
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50 63 testing also contribute to this problem^{4,5}.
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56 64 Ozawa et al. in a 2018 meta-analysis estimated that about 10.5% of the medicines worldwide are
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3 65 either substandard or falsified. Prevalence of low-quality pharmaceutical products is higher in low-
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5 66 and middle-income countries (13.6%) compared to high income countries. About 18.7% medicines
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7 67 have been estimated to be low-quality in Africa and 13.7% in Asia. The most substandard or
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10 68 falsified drugs are the antimalarials (19.1%)³.

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13 69 Nepal is one of the least developed countries⁶ that shares open and poorly regulated borders with
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15 70 India and China. These two countries are considered as the major producers of low-quality and
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17 71 fake pharmaceutical products circulating in the global market⁴. The domestic market for medical
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19 72 products in Nepal was estimated to be 70 billion Nepal rupees in 2019 which included drugs (36
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21 73 billion), raw materials and surgical equipment⁷. The Department of Drug Administration (DDA)
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23 74 authorizes the distribution of all pharmaceutical products in Nepal including production,
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25 75 distribution, export and import. The DDA in Nepal is equivalent to the U.S. FDA and is responsible
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27 76 to prevent the misuse or abuse of drugs and allied pharmaceutical substances⁸. Few studies in the
28
29 77 past have indicated the circulation of substandard, counterfeit, and unregistered drugs in the Nepali
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31 78 market^{9,10,11}. DDA Nepal recalls marketed drugs if the drugs do not fulfill any requirement as
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33 79 indicated in the drug act 2035 B.S.⁸. It then issues public alerts and warnings when substandard,
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35 80 falsified, and unregistered medicine incidents are detected.

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41 81 It is important to understand major issues responsible for the availability of poor-quality drugs in
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43 82 the market. Analysis of pattern of drug alerts, regulatory recalls and company led recalls could be
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45 83 helpful to devise actions to mitigate the issues related to poor-quality drugs¹². In this study, we
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47 84 report the pattern of recall of poor-quality drugs in Nepal by analyzing drug recall notice issued
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49 85 by the DDA. We analyzed temporal trend of low-quality drugs, types of drugs and formulations,
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51 86 origin of drugs & manufacturers and reasoning for recall. We also reviewed research publications
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53 87 that reported drug quality data.

88 **METHODOLOGY**

89 We analyzed drug recall notices published by DDA Nepal from January 2010 to December 2020.

90 The DDA publishes such notices in its bulletins, websites, and newspapers (<https://dda.gov.np/>).

91 We extracted all the information provided on the recall notice such as brand name, dosage form,

92 batch number, manufacturing date, expiry date, recall date, reason for non-compliance, and the

93 manufacturer information. We used National List of Essential Medicines 2016 of Nepal to classify

94 the recalled drugs into essential and non-essential drugs¹³ and the WHO definition to identify

95 substandard, falsified and unregistered drugs¹⁴. According to WHO definition, substandard drugs

96 are authorized medical products but fail to meet quality standards or specifications or both.

97 Similarly, falsified drugs are medical products that misrepresent their identity, composition or

98 source¹⁵. Pharmaceutical products that did not pass dissolution test, active pharmaceutical

99 ingredient (API) assay, microbial test, leakage test, friability, were non-compliance with the

100 pharmacopeia for physical appearance, fungal count, weight variation, particulate matter test,

101 uniformity test, disintegration test, and pH test were put together under the substandard category.

102 Similarly, drugs that contained impurities, active ingredient not meant to be there, had price sticker

103 without approval, or did not have product specification were classified as falsified pharmaceutical

104 products. The drugs that were recalled as being not registered at DDA Nepal were classified under

105 unregistered category. Unregistered drugs do not undergo evaluation and/or approval by DDA

106 Nepal. Based on the brand names of each non-ayurvedic pharmaceutical product, we identified

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

108 properties.

109 In addition to the recall notice, we systematically reviewed the published research works to find

110 the reporting of low-quality drugs in Nepali market. We specifically searched peer reviewed

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3 111 research articles from electronic databases such as PubMed (2010-2020), Web of Science (2010-
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5 112 2020), Springer link (2010-2020), and Google Scholar (2010-2020). We used the following search
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7 113 terms in conjunction with Boolean search term (“OR”, “AND”) to identify related articles:
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9 114 “counterfeit*”, “substandard*”, “falsified*”, “fake”, “spurious”, “unregulated drugs”,
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11 “unregistered”, or “frauds”; combined with “drug”, “medicine”, or “pharmaceutical”; “Nepal*”.
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13 115
14 116 In Google Scholar same search terms were used, but instead of “Nepal*”, we used “intitle:Nepal”.
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16 117 The articles were screened and evaluated manually through the title and abstract based on inclusion
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18 118 criteria: date of publication (2010-2020), the language (English) in which the article was published,
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20 119 the article should contain data/information on the prevalence of
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22 120 falsified/spurious/counterfeit/substandard drugs and the location of experiment/research carried
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24 121 out. Articles that did not meet the inclusion criteria were excluded. Also excluded were opinion
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26 122 articles, letters, notes, conference papers, book chapters, editorials or comments or articles with no
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28 123 abstracts or articles with counterfeit or substandard medicines related to animals.
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33 124 A flow chart of search procedure is given in figure 1. Initially, we identified 467 journal articles
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35 125 after a search of literature in four different databases: PubMed, Springer link, Web of science and
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37 126 Google scholar. We removed 13 duplicate articles and brought the number of articles to 454. By
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39 127 screening the title and abstract of these articles, we removed 439 articles and we considered only
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41 128 15 in next step (*see* Table S11 in supplementary information). We read the full text of these articles
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43 129 and excluded 11 articles because they did not follow the inclusion criteria. At last, four
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45 130 articles^{10,11,16,17} were found to be relevant that contained primary information on the prevalence of
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47 131 substandard, falsified, and unregistered medicines in the Nepali market.
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52 132 *Figure 1: Flow chart of research papers search procedure*
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3 133 Statistical analyses of data such as Chi-square test, Fisher exact test and simple linear regression
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5 134 were performed using R version 1.4.1106.
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8 135 Patients and public involvement: Patient or the public were not involved in the design, conduct,
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10 136 reporting, and dissemination plans for this study.
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13 14 137 **RESULTS**

15 138
16 139 We analyzed recalled drugs during the period of 2010 – 2020. During this period 346
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18 140 pharmaceutical products were recalled by DDA Nepal. The number of recalled low-quality drugs
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20 141 in Nepal has significantly increased in the last decade (Figure 2A, linear regression, p -value < 0.05,
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22 142 adjusted R-squared value = 0.335). We found that only one pharmaceutical product was recalled in
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24 143 2010. The product was a lactate solution which is commonly used for fluid resuscitation. The
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26 144 solution was recalled from the Nepali market because it did not pass the sterility test. There was
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28 145 no recall in 2012. The year 2018 had the highest number of pharmaceutical products recalled (123
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30 146 products, see Figure 2A). Forty-six products were recalled in the year 2020, majority of which
31
32 147 were hand sanitizers. The recalled pharmaceutical products were from 96 manufacturers mostly
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34 148 from Nepal and India, few from Australia, Bangladesh, and China. Manufacturer of 91 recalled
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36 149 drugs were unknown. The recalled pharmaceutical products included a significantly (two-sided
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38 150 Fisher exact test, p -value < 0.001) higher number of imported medicines (153) items than
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40 151 domestically manufactured ones (141). The imported recalled products were manufactured mostly
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42 152 in India (97%, Figure 2B) and in drugs from Australia, Bangladesh and China. Country of origin
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44 153 of 52 recalled pharmaceutical products were not identified.
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51 154 **Figure 2:** (A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of
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53 155 different categories of pharmaceutical products in the recall list.
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3 156 Sixty percentage (n=346) of recalled pharmaceutical products were modern or allopathic (208)
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5 157 and 35% were traditional or ayurvedic (120) (Figure 2B). Two-sided Fisher exact test showed that
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7 158 significantly higher number of modern pharmaceutical products were recalled (p-value < 0.001).
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10 159 Twenty-seven percentage of the recalled drugs were unregistered at the DDA indicating they were
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12 160 not authorized to be distributed and sold in Nepal. Similarly, twenty percentage of the recalled
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14 161 drugs, mostly allopathic, were listed as essential medicines. 40% of the recalled drugs were non-
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16 162 essential allopathic (p-value < 0.001) and 40% were ayurvedic drugs. Essential medicines are
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18 163 distributed free of cost through government health centers¹³ and only allopathic drugs are listed as
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20 164 essential ones. Majority of the recalled pharmaceutical products were substandard (62%) followed
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22 165 by unregistered (27%) and falsified (11%) (see Figure 2B). We found that the recall pattern among
23
24 166 these three categories were significantly different (one-way chi-square test, p-value < 0.001, $\chi^2 =$
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26 167 142.31, df = 2).
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31 168 **Figure 3:** (A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage
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33 169 forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self
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35 170 life of recalled pharmaceutical products after the recall (in months).
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38 171 The top 10 most recalled drugs were antimicrobials (13.6%) followed by gastrointestinal
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40 172 medicines (10.1%), vitamins and minerals (8.1%), antiseptic (6.6), hormones and contraceptives
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42 173 (5.2%), and pain and palliative care medicines (4.6), fluid and electrolyte replenishment items
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44 174 (3.7%), cardiovascular and renal drugs (2.0%), anti-diabetes (1.4%) and antihistamines (1.4%)
45
46 175 (see Figure 3A). Remaining recalled drugs were CNS drugs, respiratory system drugs,
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48 176 prostaglandin analogues, and antirheumatic agents. Nineteen drugs were not classified into any of
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50 177 those and labelled as “others” because sufficient information was not available. Ayurvedic drugs
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52 178 were not included in this categorization.
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3 179 The DDA provided reason(s) for every recalled pharmaceutical product. Large number of drugs
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5 180 (26.8%) were recalled because they were not registered at DDA. The most common reason for
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8 181 recall among registered drugs was the failure to comply with microbial test (23.7%) followed by
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10 182 failures in dissolution test (11.5%), in quantitative assay for active pharmaceutical ingredient
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12 183 (6.6%), and in physical characteristics and packaging (6.6%). Eleven products did not comply with
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14 184 labelling requirements and 12 had one or more impurities. Few samples categorized as “others”
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16 185 were recalled due to failure in identification test and contained active ingredient in dietary
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18 186 supplements (see Figure 3B). Tablets were the most recalled dosage forms followed by powder,
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20 187 solution, capsules, syrups/suspension, and cream/ointment. Dosage forms of some products were
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22 188 not identifiable, and they are categorized as “others” (Figure 3C). The shelf-life of recalled drugs
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24 189 ranged from less than three months (16.4%) to more than two years at the time of recall (Figure
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26 190 2D).

31 191 **Low-quality drugs reported in research papers**

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34 192 As stated in method section, only four research articles were included for detailed analysis. One
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36 193 of these articles reported by Jha et al.¹⁶ assessed the quality of essential medicines available in 62
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38 194 public health care facilities across 21 districts of Nepal. The authors tested 244 batches of 20
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40 195 different generics of essential medicines and found that 37 batches failed to meet the required
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42 196 pharmacopeial standards. The quality failed medicines included both supplied by Government of
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44 197 Nepal (62.2%) and purchased from local pharmacies (37.8%). The failed medicines included
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46 198 antibiotics, supplements, anti-diabetics etc.

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50 199 Providing required information on the label is another major issue. Most of the 759 pharmaceutical
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52 200 products from 37 Nepali pharmaceutical companies inspected in Chitwan in 2017 missed at least
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54 201 one critical information on the label such as drug quantity, name of pharmacopoeia, serial number

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3 202 of pharmaceutical industries, price list, drug classification, and information in Nepali language¹⁰.
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5 203 The reports showed that labels of 84% of drugs did not provide the directions for use. Similarly
6
7 204 90% of drug samples (n=40) in Kathmandu did not comply with the existing regulatory
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9 205 requirement on labeling and 42.5% brands did not indicate the Pharmacopoeial standard⁹. The
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11 206 same study showed that 40% of domestic and 28% imported brands failed to meet national criteria
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13 207 during laboratory analysis. On average, 32.5% samples were found to be of substandard quality in
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15 208 this study. Another study evaluated the availability and rationality of unregistered fixed-dose drug
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17 209 combinations (FDCs) in Nepal using snowball sampling method and Health Action International
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19 210 Asia-Pacific (HAI-AP) toolkit in 20 retail pharmacies. Forty-one unregistered fixed-dose anti-
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21 211 inflammatory/analgesic/antipyretics drug combinations were found in five major cities of Nepal.
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23 212 Regulatory authorities should initiate strict monitoring and appropriate regulatory mechanisms to
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25 213 prohibit the use of unregistered and irrational FDCs.¹¹
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32 214 **DISCUSSION**

33 215
34 216 Low-quality medicines or related products are recalled from the market by manufacturing
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36 217 companies voluntarily or by the order of national or international drug regulatory bodies¹⁸. Many
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38 218 recall incidents of poor quality medicine have been reported globally¹⁹. For example, Johnson and
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40 219 Johnson recalled 200,000 bottles of liquid ibuprofen in 2013 due to possible contamination with
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42 220 plastic particles. Similarly, in 2012, the US FDA recalled the contaminated vials of corticosteroid
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44 221 medication which was manufactured by the New England Compounding Center²⁰.
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48 222 Our analysis showed that the overall trend of recalled drugs is increasing in Nepal. Starting from
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50 223 a single drug recall in 2010 to highest numbers (123) in 2018. In this year, most of the recalled
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52 224 drugs (90) were due to them not registered with the DDA. This indicates that the circulation of
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3 225 unregistered drugs in market is a serious issue in Nepal which may be contributed to by the open
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5 226 and unregulated border with India.
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8 227 Both allopathic and ayurvedic medicines are widely used in Nepal. Allopathic medicines are the
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10 228 modern medicines that are manufactured synthetically whereas ayurvedic medicines are the
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12 229 traditional medicines which uses the natural remedies to improve health or to treat diseases. Both
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14 230 types of medicines are commercially manufactured in Nepal in addition to being imported mostly
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16 231 from India. There are two groups of manufacturers of ayurvedic drugs in Nepal. The first being
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18 232 the registered companies which sell their products in packages through registered shops. Secondly,
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20 233 the ayurvedic drugs are made by individuals or small business holders without being registered at
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22 234 DDA and sell their ayurvedic products in streets, through door-to-door service, and through
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24 235 individual networks. We found that both allopathic and ayurvedic medicines were recalled due to
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26 236 their non-compliance with government standards. Ayurvedic medicines are utilized prominently
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28 237 in Nepali communities, and sometimes, they are used concomitantly with allopathic medicines²¹.
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30 238 There has been an increasing interest in the study of traditional medicine in different parts of
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32 239 world²². However, there is still lack of quality research and standards, and stringent regulatory
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34 240 environment for this sector.
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41 241 Essential medicines are defined by WHO as the medicines that satisfy the priority healthcare needs
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43 242 of the population²³. The concept of essential medicines was adopted in 1986 A.D. in Nepal to
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45 243 enhance access of essential medicines to every individual. The main criteria for selection of the
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47 244 medicines in the National List of Essential Medicine (NLEM) of Nepal are public health relevance,
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49 245 efficacy, safety, cost-effectiveness and access of the drugs. The NLEM 2016 of Nepal contains
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51 246 359 medicines thus having 86 medicines more than NLEM 2011¹³. The following criteria were
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53 247 used for including a medicine in NLEM: approved and licensed in Nepal, relevance to a disease
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3 248 posing public health problem, proven efficacy and safety, aligned with standard treatment
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5 249 guideline of Nepal, stable under storage conditions, cost-effective, and access. However in certain
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8 250 conditions, some medicines are excluded from the NLEM list: those banned in Nepal, over safety
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10 251 concerns, if medicine with higher efficiency, safety profile and lower cost is available, irrelevant
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12 252 to public health disease burden, antimicrobial resistant, medicine with abuse and misuse
13
14 253 potential¹³. Our study showed that some of the recalled allopathic medicines were essential drugs.
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16
17 254 Jha et al.¹⁶ indicated the presence of high number of substandard essential medicines and majority
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19 255 of which were purchased by Government of Nepal. Essential medicines for various illnesses are
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21 256 supplied free of cost in Nepal through government hospitals, health care centers and health posts.
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24 257 Poor quality of essential medicines can have serious impact on public health. As significant
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26 258 proportion of drugs recalled by DDA included essential medicines distributed by Government of
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28 259 Nepal, there is enough room to improve the procurement practices and upgrading of health
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30 260 facilities in Nepal that store and distribute medicines. In one study²⁴ that looked into the
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32 261 procurement practices in Nepal, it was reported that the majority of hospital pharmacies in Nepal
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34 262 use an expensive direct procurement model for purchasing medicines. They relied on doctors'
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36 263 prescriptions to choose a particular brand, which may be influenced by pharmaceutical companies'
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38 264 marketing strategies. Most of the hospital pharmacies procured only registered medicines, a
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40 265 minority reported purchasing unregistered medicines through unauthorized supply-chains. Not all
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42 266 pharmacies followed Basel Statements during procurement of medicines. Such pharmacies may
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45 267 need awareness and training to fully adopt regulation of national and international policies to
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47 268 enhance accessibility to quality medicines.
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52 269 Among the recalled groups, antimicrobial group of medicines had the highest frequency of recall
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54 270 incidents. Acharya et al.²⁵ highlighted the problem of antimicrobial resistance in Nepal as an alarm

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3 271 bell for worse public health situation. Suboptimal dose or poorly manufactured antibiotic medicine
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5 272 increases the chance of antimicrobial resistance²⁶. Most of the recalled therapeutic categories of
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8 273 medicines like vitamins and minerals, NSAIDs, other antipyretic and analgesic agents, antiseptics,
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10 274 fluid and electrolyte replenishment items and others are over-the-counter medicines that can be
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12 275 brought from the pharmacy without prescription. Such medicines can pose a significant threat
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15 276 patients who consume them²⁷. Few anti-diabetes medicines were also recalled. Consumption of
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17 277 such medicines may increase the incidence of macrovascular and microvascular complications due
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19 278 to compromised glucose control²⁸.

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21 279 Our study showed that some of the drugs were recalled due to failure in various laboratory tests
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23
24 280 like microbial test, assays, content uniformity test, weight variation, impurity test, dissolution test,
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26 281 friability test as well as identification and sterility test. Many of these failures can be linked to
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28 282 inadequate quality control measures during manufacturing and inappropriate procedures for
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31 283 transportation and storage and other logistic issues¹⁵.

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33 284 Jha *et al.* pointed out that only 13% of 62 health facility inspected followed medicine storage
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36 285 guidelines for light, heat and humidity¹⁶. Keeping the temperature and humidity within a specified
37
38 286 range is necessary because it has a major role in degradation of medicines. Another reason was
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40 287 failure to comply with claims and incorrect labelling. The DDA regulation requires appropriate
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42 288 labelling of marketed medicines to ensure patient safety. Thus, drug analysts and the drug
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45 289 regulators should be encouraged to remain vigilant about the possibility of counterfeiting
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47 290 possibility. They should conduct appropriate analysis including chemical, physical, package
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50 291 inspection, and authentication efforts to ensure quality and safety of drugs getting to the ultimate
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52 292 user²⁹.

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3 293 Domestically produced and imported medicines in Nepal should have the registration license from
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5 294 DDA⁸. Nonetheless, we found that high numbers of unregistered drugs were recalled during the
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8 295 inspection. Drug suppliers, wholesalers, and even retailers should ensure that the drugs they are
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10 296 handling is duly registered with the national regulatory body to ensure only safe and efficacious
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12 297 drugs get to the patient. Also, the regulatory body should conduct post-market surveillance to
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14 298 ameliorate the situation. Unregistered medical products in Nepal may or may not have been
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16 299 registered in India. Since Nepal shares open and poorly regulated boarder with India, drugs
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18 300 registered in India are also easily sold in the Nepali market, especially in bordering districts. We
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21 301 found that nearly half of the total recalled medicines were imported from India. India is the leading
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23 302 country in counterfeit drug production, having as much as 35% of the world production originating
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25
26 303 within its borders³⁰.

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29 304 The COVID-19 pandemic has resulted in the surge of substandard and falsified medical products
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31 305 including drugs, masks, sanitizers, diagnostic tests, and vaccines and other essential medical
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33 306 products³¹. Rampant circulation of fake medical products during emergencies has happened
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35 307 throughout history³¹. Counterfeit respirators and masks pose additional risk to health care
36
37 308 workers³². Falsified chloroquine was seized in Cameroon, Congo and Niger between March and
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39 309 May 2020. Chloroquine was controversially announced as the drug for the treatment of COVID-
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41 310 19³³. The US FDA uncovered nearly 1,300 fraudulent products during early days of COVID-19³⁴.
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44 311 DDA Nepal has recently amended the standard for Instant Hand Sanitizer in order to prohibit
45
46 312 selling of substandard, falsified and unregistered sanitizers³⁵. Between September and November
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48 313 2020, the DDA issued recall notices for 19 hand sanitizers which failed to comply with the standard
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50 314 guideline. Some sanitizers were found to contain methanol, rather than ethyl alcohol and isopropyl
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52 315 alcohol. Methanol is very toxic. Use of hand sanitizer containing methanol may cause transdermal
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3 316 absorption and increases the risk of systemic toxicity³⁶. The increase in the demand for hand
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5 317 sanitizers and other medicines in the face of COVID-19 has increased the growth of e-commerce.
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7 318 Online sale of pharmaceutical products has just started in Nepal during recent years. WHO has
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9 319 reported that 60% of medications purchased through the internet could be counterfeit or
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11 320 substandard, and more than 50% of medications purchased online from sites that concealed their
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13 321 actual physical address were found to be low quality medicines³⁷. Nepali regulating agencies
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15 322 should pay special attention to this new method of doing business in Nepal to protect the people
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17 323 from consumption of low-quality and fake medical products. Inexorable growth of online
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19 324 pharmacies, unregulated websites and social media platforms for business may contribute to the
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21 325 dispensing of unapproved, subpotent, counterfeit, expired or illegal drugs, and prescription drugs
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23 326 without valid prescriptions³⁸.

327 **CONCLUSION**

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

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3 339 the country on regular basis. We suggest having more stringent regulatory systems and
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5 340 implementation for pharmaceutical manufacturing industries and enhanced post marketing
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8 341 surveillance.

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10 342 Contributors: BG contributed to conceptualization and study design, data analysis, manuscript
11 343 revision. AN, MB contributed to data collection, analysis and first draft. ST contributed to data
12 344 collection. All authors gave approval for the final version of the manuscript.

13 345
14
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17 348 Competing interests: None declared.

18 349
19 350 Data sharing: All data relevant to the study are included in the article or uploaded as supplementary
20 351 information. Author compiled & curated raw data will be made available with a reasonable request
21 352 to corresponding author.

22 353
23 354 Ethical approval: This study does not involve human participants.

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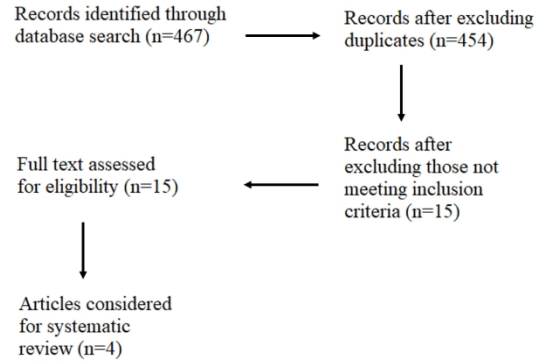


Figure 1: Flow chart of research papers search procedure

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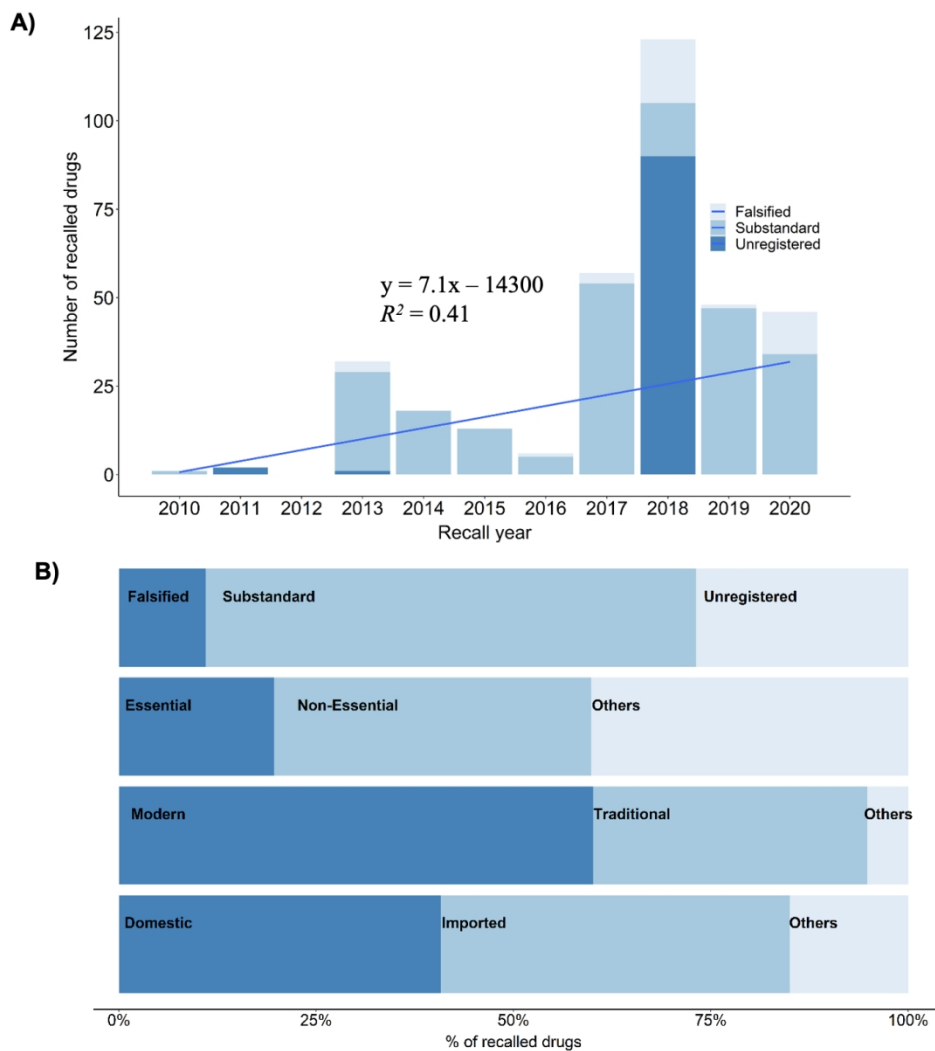


Figure 2: (A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of different categories of pharmaceutical products in the recall list.

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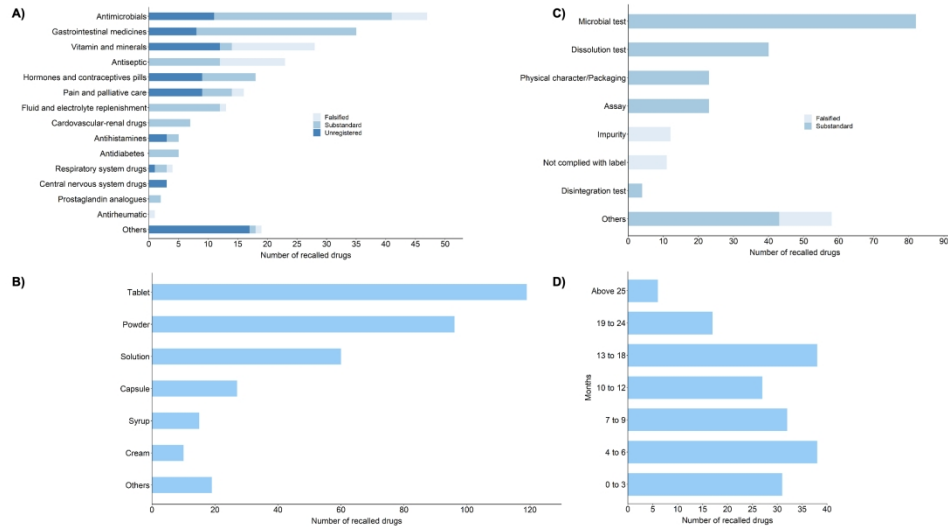


Figure 3: (A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self life of recalled pharmaceutical products after the recall (in months).

1283x719mm (57 x 57 DPI)

1 Pattern of drug recalls and quality of pharmaceutical products in

2 Nepal

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

5 Kathmandu, Nepal

7 Supplementary Material

8 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

9 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.
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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

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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/>

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-053479.R2
Article Type:	Original research
Date Submitted by the Author:	11-May-2022
Complete List of Authors:	Neupane, Astha; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences Bastakoti, Maheshwor; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences Tamang, Sabita; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences Giri, Basant; Kathmandu Institute of Applied Sciences, Center for Analytical Sciences
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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4 1 **A review of drug recalls and quality of pharmaceutical products in**
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7 2 **Nepal**

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33 16 **Word count:** 3702 excluding abstract and references

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2
3 **26 ABSTRACT**
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5 **27 Objectives:** To evaluate the pattern of substandard and falsified pharmaceutical products recall
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8 in Nepal.
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10 **29 Setting:** We analyzed drug recall notices issued by the Department of Drug Administration
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12 (DDA), Nepal and systematically reviewed peer reviewed research articles during January 2010
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15 – December 2020.
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17 **32 Participants:** This study did not include human participants. However, data was collected from
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20 72 drug recall notices issued by DDA and four research papers.
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22 **34 Results:** A total of 346 pharmaceutical products were recalled during the reported period. The
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24 number of recalled pharmaceutical products has increased significantly over the past decade in
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26 Nepal. The most frequently recalled drugs were antimicrobials followed by gastrointestinal
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28 medicines, vitamins and supplements, and pain and palliative medicines among others. Number
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30 of imported recalled drugs were slightly higher (42.2%) than domestic recalled drugs (40.7%).
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33 Sixty-two percentage of recalled drugs were substandard, 11% were falsified and remaining 27%
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35 were not registered at the DDA. Similarly, higher number of modern drugs (62%) were recalled
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37 than traditional ones (35%). Hand sanitizers used to minimize COVID-19 transmission
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39 contributed significantly to the list of recalled pharmaceutical products in 2020. Most of these
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41 sanitizers contained significant amounts of methanol (as high as 75%v/v) instead of appropriate
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43 amount of ethyl or isopropyl alcohol. The peer-reviewed research papers reported issues with
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45 labelling, unregistered drugs and drugs failed in several laboratory testing.
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49 **46 Conclusion:** Our analysis showed that number of recalls of substandard and falsified drugs are
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51 increasing in Nepal. Since the recall data in this paper did not include number of samples tested
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3 48 and location of samples collected, more studies to understand the prevalence of substandard and
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5 49 falsified drugs in Nepal is recommended.
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8 50 **Keywords:** Counterfeit drugs, falsified medical products, public health, substandard, falsified
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10 51 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.

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53 INTRODUCTION

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31 54 Pharmaceutical products are essential to treat, prevent, and save lives of millions of people
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33 55 globally¹. They should be safe, effective, and of good quality. Such products should be prescribed
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35 56 by authorized medical practitioner and used rationally². However, pharmaceutical products that do
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37 57 not meet regulatory standards and quality threaten the health of the population of today and future.
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39 58 Such products may be substandard or low-quality or falsified. Substandard or falsified drugs could
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41 59 lead to drug resistance and put the lives of patients at risk in addition to increasing the economic
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43 60 and social burden on people³. There are several reasons for the circulation of such substandard and
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45 61 falsified products in market such as lack of access to affordable, quality, safe and effective medical
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47 62 products, and good governance as well as poor ethical practices in health care facilities and
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49 63 medicine outlets. Limited technical capacity in manufacturing, quality control, distribution and
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51 64 testing also contribute to this problem^{4,5}.

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3 65 Ozawa et al. in a 2018 meta-analysis estimated that about 10.5% of the medicines worldwide are
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5 66 either substandard or falsified. Prevalence of low-quality pharmaceutical products is higher in low-
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7 67 and middle-income countries (13.6%) compared to high income countries. About 18.7% medicines
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9 68 have been estimated to be low-quality in Africa and 13.7% in Asia. The most substandard or
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11 69 falsified drugs are the antimalarials (19.1%)³.

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15 70 Nepal is one of the least developed countries⁶ that shares open and poorly regulated borders with
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17 71 India and China. These two countries are considered as major producers of low-quality and
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19 72 falsified pharmaceutical products circulating in the global market⁴. The domestic market for
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21 73 medical products in Nepal was estimated to be 70 billion Nepal rupees in 2019 which included
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23 74 drugs (36 billion), raw materials and surgical equipment⁷. The Department of Drug Administration
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25 75 (DDA) authorizes the distribution of all pharmaceutical products in Nepal including production,
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27 76 distribution, export, and import. The DDA in Nepal is equivalent to the U.S. FDA and is
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29 77 responsible to prevent the misuse or abuse of drugs and allied pharmaceutical substances⁸. Few
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31 78 studies in the past have indicated the circulation of substandard, counterfeit, and unregistered drugs
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33 79 in the Nepali market^{9,10,11}. DDA Nepal recalls marketed drugs if the drugs do not fulfill any
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35 80 requirement as indicated in the drug act 2035 B.S.⁸. It then issues public alerts and warnings when
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37 81 substandard, falsified, and unregistered medicine incidents are detected. Analysis of pattern of
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39 82 drug alerts, regulatory recalls and company led recalls could be helpful to understand major issues
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41 83 responsible for the availability of poor-quality drugs and devise appropriate actions to mitigate the
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43 84 problem^{12,13}. Analysis of medical product recall and alert are available from few countries such as
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45 85 the United Kingdom¹², the Saudi Arabia¹⁴, which have shown a significant increase in the number
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47 86 of recall drugs.

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52 87 In this study, we report the pattern of recall of poor-quality drugs in Nepal by analyzing drug recall
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3 88 notice issued by the DDA. We analyzed temporal trend of low-quality drugs, types of drugs and
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5 89 formulations, origin of drugs & manufacturers and reasoning for recall. We also reviewed research
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8 90 publications that reported drug quality data.
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11 91 **METHODOLOGY**

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14 92 We analyzed drug recall notices published by DDA Nepal from January 2010 to December 2020.
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16 93 The DDA publishes such notices in its bulletins, websites, and newspapers (<https://dda.gov.np/>).
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18 94 We extracted all the information provided on the recall notice such as brand name, dosage form,
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21 95 batch number, manufacturing date, expiry date, recall date, reason for non-compliance, and the
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23 96 manufacturer information. We used National List of Essential Medicines 2016 of Nepal to classify
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25 97 the recalled drugs into essential and non-essential drugs¹⁵ and the WHO definition to identify
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27 98 substandard, falsified and unregistered drugs¹⁶. According to WHO definition, substandard drugs
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29 99 are authorized medical products but fail to meet quality standards or specifications or both.
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32 100 Similarly, falsified drugs are medical products that misrepresent their identity, composition or
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34 101 source¹⁷. Pharmaceutical products that did not pass dissolution test, active pharmaceutical
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36 102 ingredient (API) assay, microbial test, leakage test, friability, were non-compliance with the
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38 103 pharmacopeia for physical appearance, fungal count, weight variation, particulate matter test,
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40 104 uniformity test, disintegration test, and pH test were put together under the substandard category.
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43 105 Similarly, drugs that contained impurities, active ingredient not meant to be there, had price sticker
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45 106 without approval, or did not have product specification were classified as falsified pharmaceutical
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47 107 products. The drugs that were recalled as being not registered at DDA Nepal were classified under
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49 108 unregistered category. Unregistered drugs do not undergo evaluation and/or approval by DDA
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51 109 Nepal. Based on the brand names of each non-ayurvedic pharmaceutical product, we identified
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3 110 their generic names and then categorized them into different groups based on their therapeutic
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5 111 properties.

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8 112 In addition to the recall notice, we systematically reviewed the published research works to find
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10 113 the reporting of low-quality drugs in Nepali market. We specifically searched peer reviewed
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12 114 research articles from electronic databases such as PubMed (2010-2020), Web of Science (2010-
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14 115 2020), Springer link (2010-2020), and Google Scholar (2010-2020). We used the following search
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16 116 terms in conjunction with Boolean search term (“OR”, “AND”) to identify related articles:
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18 117 “counterfeit*”, “substandard*”, “falsified*”, “fake”, “spurious”, “unregulated drugs”,
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20 118 “unregistered”, or “frauds”; combined with “drug”, “medicine”, or “pharmaceutical”; “Nepal*”.

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22 119 In Google Scholar same search terms were used, but instead of “Nepal*”, we used “intitle:Nepal”.

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24 120 The articles were screened and evaluated manually through the title and abstract based on inclusion
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26 121 criteria: date of publication (2010-2020), the language (English) in which the article was published,
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28 122 the article should contain data/information on the prevalence of
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30 123 falsified/spurious/counterfeit/substandard drugs and the location of experiment/research carried
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32 124 out. Articles that did not meet the inclusion criteria were excluded. Also excluded were opinion
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34 125 articles, letters, notes, conference papers, book chapters, editorials or comments or articles with no
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36 126 abstracts or articles with counterfeit or substandard medicines related to animals.

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38 127 A flow chart of search procedure is given in figure 1. Initially, we identified 467 journal articles
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40 128 after a search of literature in four different databases: PubMed, Springer link, Web of science and
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42 129 Google scholar. We removed 13 duplicate articles and brought the number of articles to 454. By
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44 130 screening the title and abstract of these articles, we removed 439 articles and we considered only
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46 131 15 in next step (*see* Table S11 in supplementary information). We read the full text of these articles
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48 132 and excluded 11 articles because they did not follow the inclusion criteria. At last, four
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3 133 articles^{10,11,18,19} were found to be relevant that contained primary information on the prevalence of
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5 134 substandard, falsified, and unregistered medicines in the Nepali market.
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8 135 *Figure 1: Flow chart of research papers search procedure*
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10 136 Statistical analyses of data such as Chi-square test, Fisher exact test and simple linear regression
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12 137 were performed using R version 1.4.1106.
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15 138 Patients and public involvement: Patient or the public were not involved in the design, conduct,
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17 139 reporting, and dissemination plans for this study.
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21 140 **RESULTS**

22 141
23 142 We analyzed recalled drugs during the period of 2010 – 2020. During this period 346
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25 143 pharmaceutical products were recalled by DDA Nepal. The number of recalled low-quality drugs
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27 144 in Nepal has significantly increased in the last decade (Figure 2A, linear regression, p -value < 0.05,
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29 145 adjusted R-squared value = 0.335). We found that only one pharmaceutical product was recalled in
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31 146 2010. The product was a lactate solution which is commonly used for fluid resuscitation. The
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33 147 solution was recalled from the Nepali market because it did not pass the sterility test. There was
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35 148 no recall in 2012. The year 2018 had the highest number of pharmaceutical products recalled (123
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37 149 products, see Figure 2A). Forty-six products were recalled in the year 2020, majority of which
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39 150 were hand sanitizers. The recalled pharmaceutical products were from 96 manufacturers mostly
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41 151 from Nepal and India, few from Australia, Bangladesh, and China. Manufacturer of 91 recalled
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43 152 drugs were unknown. The recalled pharmaceutical products included a significantly (two-sided
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45 153 Fisher exact test, p -value < 0.001) higher number of imported medicines (153) items than
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47 154 domestically manufactured ones (141). The imported recalled products were manufactured mostly
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49 155 in India (97%, Figure 2B) and in drugs from Australia, Bangladesh and China. Country of origin
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51 156 of 52 recalled pharmaceutical products were not identified.
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3 157 **Figure 2:** (A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of
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5 158 different categories of pharmaceutical products in the recall list.

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9 159 Sixty percentage (n=346) of recalled pharmaceutical products were modern or allopathic (208)
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11 160 and 35% were traditional or ayurvedic (120) (Figure 2B). Two-sided Fisher exact test showed that
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13 161 significantly higher number of modern pharmaceutical products were recalled (p-value < 0.001).
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15 162 Twenty-seven percentage of the recalled drugs were unregistered at the DDA indicating they were
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17 163 not authorized to be distributed and sold in Nepal. Similarly, twenty percentage of the recalled
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19 164 drugs, mostly allopathic, were listed as essential medicines. 40% of the recalled drugs were non-
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21 165 essential allopathic (p-value < 0.001) and 40% were ayurvedic drugs. Essential medicines are
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23 166 distributed free of cost through government health centers¹⁵ and only allopathic drugs are listed as
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25 167 essential ones. Majority of the recalled pharmaceutical products were substandard (62%) followed
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27 168 by unregistered (27%) and falsified (11%) (see Figure 2B). We found that the recall pattern among
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29 169 these three categories were significantly different (one-way chi-square test, p-value < 0.001, $\chi^2 =$
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31 170 142.31, df = 2).

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36 171 **Figure 3:** (A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage
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38 172 forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self
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40 173 life of recalled pharmaceutical products after the recall (in months).

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44 174 The top 10 most recalled drugs were antimicrobials (13.6%) followed by gastrointestinal
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46 175 medicines (10.1%), vitamins and minerals (8.1%), antiseptic (6.6), hormones and contraceptives
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48 176 (5.2%), and pain and palliative care medicines (4.6), fluid and electrolyte replenishment items
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50 177 (3.7%), cardiovascular and renal drugs (2.0%), anti-diabetes (1.4%) and antihistamines (1.4%)
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52 178 (see Figure 3A). Remaining recalled drugs were CNS drugs, respiratory system drugs,
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54 179 prostaglandin analogues, and antirheumatic agents. Nineteen drugs were not classified into any of

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3 180 those and labelled as “others” because sufficient information was not available. Ayurvedic drugs
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5 181 were not included in this categorization.
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8 182 The DDA provided reason(s) for every recalled pharmaceutical product. Large number of drugs
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10 183 (26.8%) were recalled because they were not registered at DDA. The most common reason for
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12 184 recall among registered drugs was the failure to comply with microbial test (23.7%) followed by
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14 185 failures in dissolution test (11.5%), in quantitative assay for active pharmaceutical ingredient
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16 186 (6.6%), and in physical characteristics and packaging (6.6%). Eleven products did not comply with
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18 187 labelling requirements and 12 had one or more impurities. Few samples categorized as “others”
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20 188 were recalled due to failure in identification test and contained active ingredient in dietary
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22 189 supplements (see Figure 3B). Tablets were the most recalled dosages forms followed by powder,
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24 190 solution, capsules, syrups/suspension, and cream/ointment. Dosage forms of some products were
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26 191 not identifiable, and they are categorized as “others” (Figure 3C). The shelf-life of recalled drugs
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28 192 ranged from less than three months (16.4%) to more than two years at the time of recall (Figure
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30 193 3D).
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35 194 **Low-quality drugs reported in research papers**

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38 195 As stated in method section, only four research articles were included for detailed analysis. One
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40 196 of these articles reported by Jha et al.¹⁸ assessed the quality of essential medicines available in 62
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42 197 public health care facilities across 21 districts of Nepal. The authors tested 244 batches of 20
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44 198 different generics of essential medicines and found that 37 batches failed to meet the required
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46 199 pharmacopeial standards. The quality failed medicines included both supplied by Government of
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48 200 Nepal (62.2%) and purchased from local pharmacies (37.8%). The failed medicines included
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50 201 antibiotics, supplements, anti-diabetics etc.
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3 202 Providing required information on the label is another major issue. Most of the 759 pharmaceutical
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5 203 products from 37 Nepali pharmaceutical companies inspected in Chitwan in 2017 missed at least
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7 204 one critical information on the label such as drug quantity, name of pharmacopoeia, serial number
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9 205 of pharmaceutical industries, price list, drug classification, and information in Nepali language¹⁰.
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11 206 The reports showed that labels of 84% of drugs did not provide the directions for use. Similarly
12
13 207 90% of drug samples (n=40) in Kathmandu did not comply with the existing regulatory
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15 208 requirement on labeling and 42.5% brands did not indicate the Pharmacopoeial standard⁹. The
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17 209 same study showed that 40% of domestic and 28% imported brands failed to meet national criteria
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19 210 during laboratory analysis. On average, 32.5% samples were found to be of substandard quality in
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21 211 this study. Another study evaluated the availability and rationality of unregistered fixed-dose drug
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23 212 combinations (FDCs) in Nepal using snowball sampling method and Health Action International
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25 213 Asia-Pacific (HAI-AP) toolkit in 20 retail pharmacies. Forty-one unregistered fixed-dose anti-
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27 214 inflammatory/analgesic/antipyretics drug combinations were found in five major cities of Nepal.
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29 215 Regulatory authorities should initiate strict monitoring and appropriate regulatory mechanisms to
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31 216 prohibit the use of unregistered and irrational FDCs.¹¹
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38 217 **DISCUSSION**

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40 219 Low-quality medicines or related products are recalled from the market by manufacturing
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42 220 companies voluntarily or by the order of national or international drug regulatory bodies²⁰. Many
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44 221 recall incidents of poor quality medicine have been reported globally²¹. For example, Johnson and
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46 222 Johnson recalled 200,000 bottles of liquid ibuprofen in 2013 due to possible contamination with
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48 223 plastic particles. The US FDA had recalled the contaminated vials of corticosteroid medication in
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50 224 2012 which was manufactured by the New England Compounding Center²². An analysis of drug
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52 225 recall in the UK has shown a tenfold increase in the defective medicines from 2001 to 2011 mostly
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3 226 due to contamination and issues with packaging¹². Similarly, the number of drug recall reported
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5 227 by Saudi Arabia Drug Authority increased six-folds from 2010 to 2018, in which the most
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8 228 commonly recalled drugs were antihypertensive drugs and antibiotics due to contamination and
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10 229 issues with non-compliance with manufacturer's specifications.¹⁴
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13 230 Our analysis showed that the overall trend of recalled drugs is increasing in Nepal. Starting from
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15 231 a single drug recall in 2010 to highest numbers (123) in 2018. In this year, most of the recalled
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17 232 drugs (90) were due to them not registered with the DDA. This indicates that the circulation of
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20 233 unregistered drugs in market is a serious issue in Nepal which may be contributed to by the open
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22 234 and unregulated border with India.
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25 235 Both allopathic and ayurvedic medicines are widely used in Nepal. Allopathic medicines are the
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27 236 modern medicines that are manufactured synthetically whereas ayurvedic medicines are the
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29 237 traditional medicines which uses the natural remedies to improve health or to treat diseases. Both
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31 238 types of medicines are commercially manufactured in Nepal in addition to being imported mostly
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34 239 from India. There are two groups of manufacturers of ayurvedic drugs in Nepal. The first being
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36 240 the registered companies which sell their products in packages through registered shops. Secondly,
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38 241 the ayurvedic drugs are made by individuals or small business holders without being registered at
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41 242 DDA and sell their ayurvedic products in streets, through door-to-door service, and through
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43 243 individual networks. We found that both allopathic and ayurvedic medicines were recalled due to
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45 244 their non-compliance with government standards. Ayurvedic medicines are utilized prominently
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48 245 in Nepali communities, and sometimes, they are used concomitantly with allopathic medicines²³.
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50 246 There has been an increasing interest in the study of traditional medicine in different parts of
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52 247 world²⁴. However, there is still lack of quality research and standards, and stringent regulatory
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55 248 environment for this sector.
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3 249 Essential medicines are defined by WHO as the medicines that satisfy the priority healthcare needs
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5 250 of the population²⁵. The concept of essential medicines was adopted in 1986 A.D. in Nepal to
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7 251 enhance access of essential medicines to every individual. The main criteria for selection of the
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10 252 medicines in the National List of Essential Medicine (NLEM) of Nepal are public health relevance,
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12 253 efficacy, safety, cost-effectiveness and access of the drugs. The NLEM 2016 of Nepal contains
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14 254 359 medicines thus having 86 medicines more than NLEM 2011¹⁵. The following criteria were
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17 255 used for including a medicine in NLEM: approved and licensed in Nepal, relevance to a disease
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19 256 posing public health problem, proven efficacy and safety, aligned with standard treatment
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21 257 guideline of Nepal, stable under storage conditions, cost-effective, and access. However in certain
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23 258 conditions, some medicines are excluded from the NLEM list: those banned in Nepal, over safety
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26 259 concerns, if medicine with higher efficiency, safety profile and lower cost is available, irrelevant
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28 260 to public health disease burden, antimicrobial resistant, medicine with abuse and misuse
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30 261 potential¹⁵. Our study showed that some of the recalled allopathic medicines were essential drugs.
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33 262 Jha et al.¹⁸ indicated the presence of high number of substandard essential medicines and majority
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35 263 of which were purchased by Government of Nepal. Essential medicines for various illnesses are
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37 264 supplied free of cost in Nepal through government hospitals, health care centers and health posts.
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40 265 Poor quality of essential medicines can have serious impact on public health. As significant
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42 266 proportion of drugs recalled by DDA included essential medicines distributed by Government of
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44 267 Nepal, there is enough room to improve the procurement practices and upgrading of health
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46 268 facilities in Nepal that store and distribute medicines. In one study²⁶ that looked into the
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49 269 procurement practices in Nepal, it was reported that the majority of hospital pharmacies in Nepal
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51 270 use an expensive direct procurement model for purchasing medicines. They relied on doctors'
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53 271 prescriptions to choose a particular brand, which may be influenced by pharmaceutical companies'

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3 272 marketing strategies. Most of the hospital pharmacies procured only registered medicines, a
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5 273 minority reported purchasing unregistered medicines through unauthorized supply-chains. Not all
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7 274 pharmacies followed Basel Statements during procurement of medicines. Such pharmacies may
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10 275 need awareness and training to fully adopt regulation of national and international policies to
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12 276 enhance accessibility to quality medicines.

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16 277 Among the recalled groups, antimicrobial group of medicines had the highest frequency of recall
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18 278 incidents. Acharya et.al²⁷ highlighted the problem of antimicrobial resistance in Nepal as an alarm
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20 279 bell for worse public health situation. Suboptimal dose or poorly manufactured antibiotic medicine
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22 280 increases the chance of antimicrobial resistance²⁸. Most of the recalled therapeutic categories of
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24 281 medicines like vitamins and minerals, NSAIDs, other antipyretic and analgesic agents, antiseptics,
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26 282 fluid and electrolyte replenishment items and others are over-the-counter medicines that can be
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28 283 brought from the pharmacy without prescription. Such medicines can pose a significant threat
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30 284 patients who consume them²⁹. Few anti-diabetes medicines were also recalled. Consumption of
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32 285 such medicines may increase the incidence of macrovascular and microvascular complications due
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34 286 to compromised glucose control³⁰.

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39 287 Our study showed that some of the drugs were recalled due to failure in various laboratory tests
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41 288 like microbial test, assays, content uniformity test, weight variation, impurity test, dissolution test,
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43 289 friability test as well as identification and sterility test. Many of these failures can be linked to
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45 290 inadequate quality control measures during manufacturing and inappropriate procedures for
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47 291 transportation and storage and other logistic issues¹⁷.

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50 292 Jha *et. al.* pointed out that only 13% of 62 health facility inspected followed medicine storage
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52 293 guidelines for light, heat and humidity¹⁸. Keeping the temperature and humidity within a specified
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54 294 range is necessary because it has a major role in degradation of medicines. Another reason was
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3 295 failure to comply with claims and incorrect labelling. The DDA regulation requires appropriate
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5 296 labelling of marketed medicines to ensure patient safety. Thus, drug analysts and the drug
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7 297 regulators should be encouraged to remain vigilant about the possibility of counterfeiting
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10 298 possibility. They should conduct appropriate analysis including chemical, physical, package
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12 299 inspection, and authentication efforts to ensure quality and safety of drugs getting to the ultimate
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14 300 user³¹.

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17 301 Domestically produced and imported medicines in Nepal should have the registration license from
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19 302 DDA⁸. Nonetheless, we found that high numbers of unregistered drugs were recalled during the
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21 303 inspection. Drug suppliers, wholesalers, and even retailers should ensure that the drugs they are
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23 304 handling is duly registered with the national regulatory body to ensure only safe and efficacious
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25 305 drugs get to the patient. Also, the regulatory body should conduct post-market surveillance to
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27 306 ameliorate the situation. Unregistered medical products in Nepal may or may not have been
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29 307 registered in India. Since Nepal shares open and poorly regulated boarder with India, drugs
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31 308 registered in India are also easily sold in the Nepali market, especially in bordering districts. We
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33 309 found that nearly half of the total recalled medicines were imported from India. India is the leading
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35 310 country in counterfeit drug production, having as much as 35% of the world production originating
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37 311 within its borders³².

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43 312 The COVID-19 pandemic has resulted in the surge of substandard and falsified medical products
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45 313 including drugs, masks, sanitizers, diagnostic tests, and vaccines and other essential medical
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47 314 products³³. Rampant circulation of falsified medical products during emergencies has happened
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49 315 throughout history³³. Counterfeit respirators and masks pose additional risk to health care
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51 316 workers³⁴. Falsified chloroquine was seized in Cameroon, Congo and Niger between March and
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53 317 May 2020. Chloroquine was controversially announced as the drug for the treatment of COVID-
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3 318 19³⁵. The US FDA uncovered nearly 1,300 fraudulent products during early days of COVID-19³⁶.
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5 319 DDA Nepal has recently amended the standard for Instant Hand Sanitizer in order to prohibit
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7 320 selling of substandard, falsified and unregistered sanitizers³⁷. Between September and November
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9 321 2020, the DDA issued recall notices for 19 hand sanitizers which failed to comply with the standard
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11 322 guideline. Some sanitizers were found to contain methanol, rather than ethyl alcohol and isopropyl
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13 323 alcohol. Methanol is very toxic. Use of hand sanitizer containing methanol may cause transdermal
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15 324 absorption and increases the risk of systemic toxicity³⁸. The increase in the demand for hand
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17 325 sanitizers and other medicines in the face of COVID-19 has increased the growth of e-commerce.
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19 326 Online sale of pharmaceutical products has just started in Nepal during recent years. WHO has
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21 327 reported that 60% of medications purchased through the internet could be counterfeit or
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23 328 substandard, and more than 50% of medications purchased online from sites that concealed their
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25 329 actual physical address were found to be low quality medicines³⁹. Nepali regulating agencies
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27 330 should pay special attention to this new method of doing business in Nepal to protect the people
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29 331 from consumption of low-quality and falsified medical products. Inexorable growth of online
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31 332 pharmacies, unregulated websites and social media platforms for business may contribute to the
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33 333 dispensing of unapproved, subpotent, counterfeit, expired or illegal drugs, and prescription drugs
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35 334 without valid prescriptions⁴⁰.
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38 335 Recall and alert from regulating agencies is important step, however more actions are necessary to
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40 336 fully understand the substandard and falsified drugs circulation in the market and their potential
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42 337 impact. Naughton and Akgul¹³ argued that freely available drug alert and recall are not enough to
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44 338 estimate medicine quality. Researchers have suggested to regulatory agencies to publish more
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46 339 information such as exact number of recalled packs, numbers of samples collected and tested,
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48 340 performed tests and results etc. Further, sampling methodologies for SF prevalence studies are
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3 341 variable in terms of sample size, design methods consistency, reporting contextual factors,
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5 342 resulting in not reliable comparison across studies.⁴¹ Therefore a standardize protocol for testing
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7 343 and reporting, global legal framework and surveillance systems of substandard and falsified drugs
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9 344 are needed⁴². This could potentially help to compare the results from different countries and
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11 345 understand from each other and make better policy interventions globally.¹³
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15 346 **CONCLUSION**

16
17 347 In this paper, we presented a detailed pattern of low-quality and falsified drugs circulating in Nepal
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19 348 in the past decade using recall notice. We showed that the number of recalled drugs has
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21 349 significantly increased. This might be attributed either to a greater surveillance by DDA or actual
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23 350 increase in the levels of substandard, falsified, and unregistered medicines in the market, similar
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25 351 to previous studies¹². However, our analysis was not enough to identify the exact cause of increase
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27 352 in the recalled drugs. Like global trends, antimicrobial drugs were the most recalled drugs in Nepal.
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29 353 The recall notices used did not provide information on the number of samples collected for testing
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31 354 or inspection and location of sample collection. Therefore, our analysis did not report the rate or
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33 355 prevalence of low-quality drugs. Since sample collection locations were not available, it was not
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35 356 possible to know the most vulnerable districts of Nepal for low-quality drugs. Therefore, more
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37 357 studies are needed to understand the prevalence of substandard and falsified drugs in Nepal
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39 358 covering different parts of the country on regular basis. We suggest having more stringent
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41 359 regulatory systems and implementation for pharmaceutical manufacturing industries and enhanced
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43 360 post marketing surveillance.
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50 361
51 362 **Contributors:** BG contributed to conceptualization and study design, data analysis, manuscript
52
53 363 revision. AN, MB contributed to data collection, analysis and first draft. ST contributed to data
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55 364 collection. All authors gave approval for the final version of the manuscript.
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10 368 **Competing interests:** None declared.

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14 370 **Data sharing:** All data relevant to the study are included in the article or uploaded as
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17 371 supplementary information. Author compiled & curated raw data will be made available with a
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19 372 reasonable request to corresponding author.

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23 374 **Ethical approval:** This study does not involve human participants.

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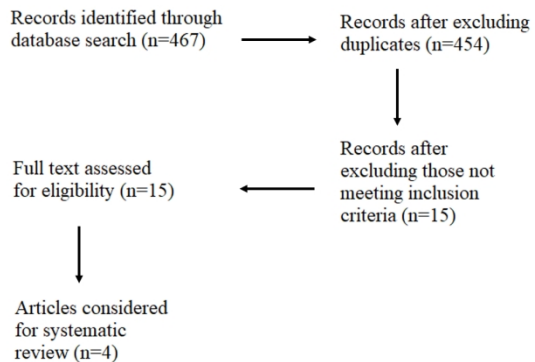


Figure 1: Flow chart of research papers search procedure

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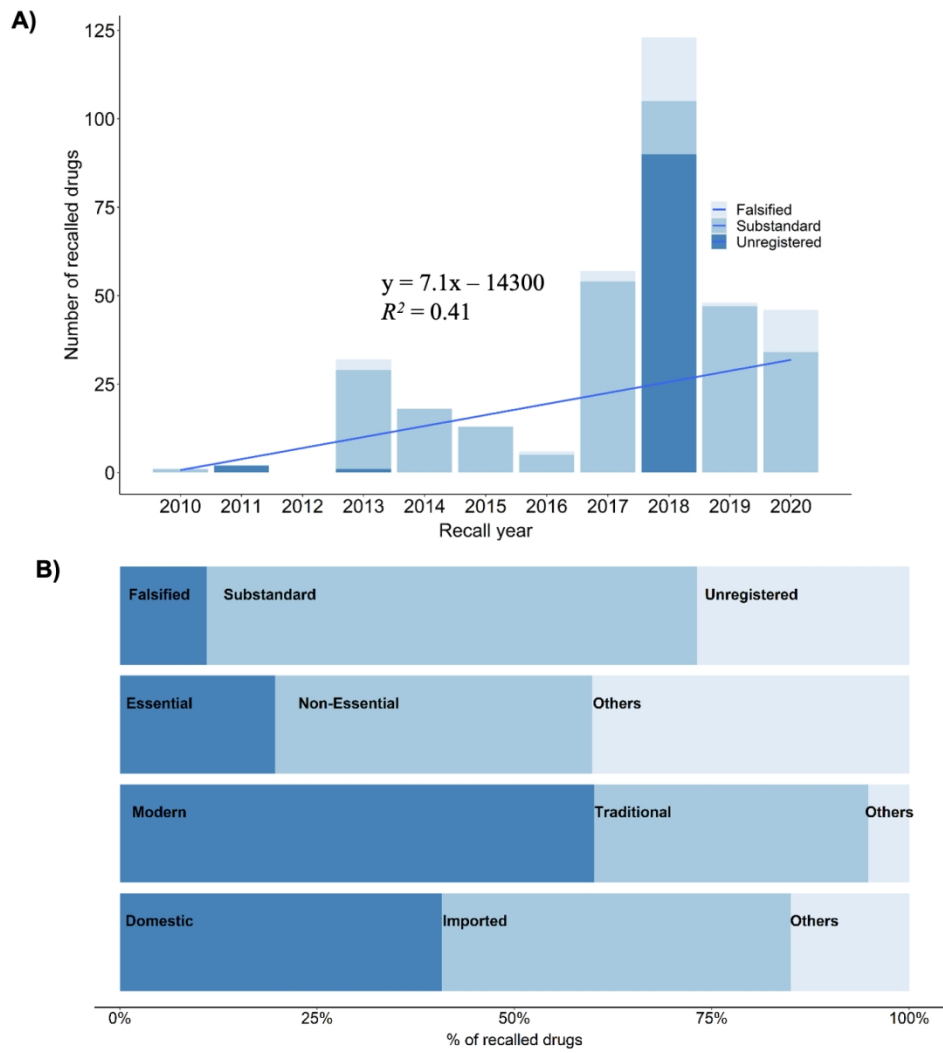


Figure 2: (A) Temporal trend of recalled pharmaceutical products in Nepal. (B) Contribution of different categories of pharmaceutical products in the recall list.

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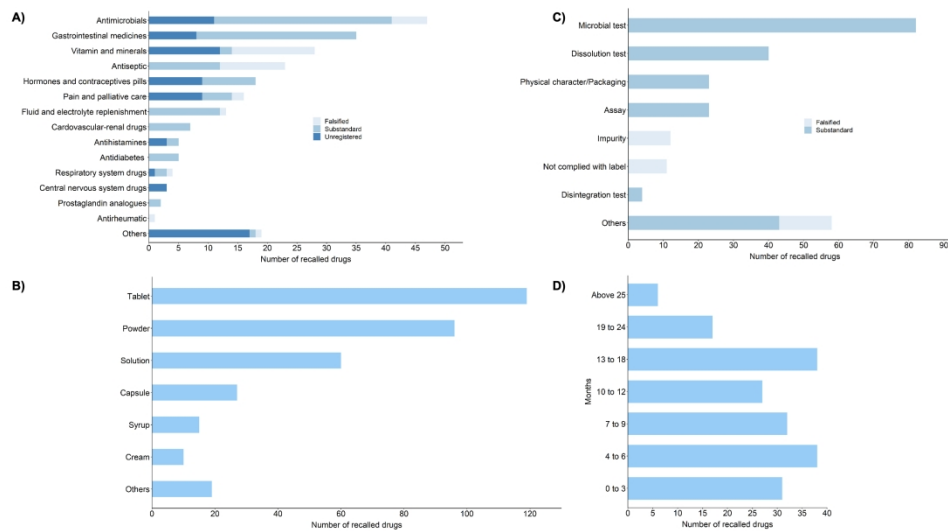


Figure 3: (A) Categories of recalled drugs based on their therapeutics, (B) Types of dosage forms of recalled drugs, (C) Major reasons for recalling the pharmaceutical products, (D) Self life of recalled pharmaceutical products after the recall (in months).

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Pattern of drug recalls and quality of pharmaceutical products in

Nepal

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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. https://www.bmj.com/lookup/other-materials-used-in-the-review-guidelines.xhtml	Data used for analysis



PRISMA 2020 Checklist

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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/>

For peer review only