The health consequences of falsified medicines- A study of the published literature

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Abstract

OBJECTIVES To analyse and present the literature describing the health consequences of falsified medicines, focusing on mortality and morbidity, as well as the scale of the issue, the geographic extent, the medicines affected, and the harm caused at both the individual and population levels.

METHODS We searched for articles in PubMed, using pre-optimized keywords ‘(counterfeit OR fake OR bogus OR falsified OR spurious) AND (medicine OR drug)’. Searches up to February 2017 yielded 2006 hits, of which 1791 were full-length articles in English. Among them, we found 81 papers that qualitatively or quantitatively described 48 incidents in which falsified medicines caused patients to suffer serious adverse effects, injury, symptoms or death.

RESULTS The distribution of incidents was examined according to the economic status of the countries involved, regional location in the world, therapeutic category of the medicines, number of incidents and victims by year, and characteristics of the falsified medicines. Among the 48 reported incidents, 27 (56.3%) occurred in developing countries and 21 (43.7%) in developed countries. These incidents involved a total of approximately 7200 casualties including 3604 deaths.

CONCLUSIONS Despite the poor quality of much of the reported data, the results of this study indicate that all types of medications have been targeted for falsification, and falsified medicines have had a serious impact on the health of both adults and children worldwide, with similar numbers of incidents in developing and developed countries.

keywords falsified medicine, counterfeit medicine, spurious medicine, fake medicine, bogus medicine, health effect, adverse effect, death

Introduction

Falsified medicines may lead to avoidable morbidity, mortality, drug resistance, early death or treatment failure, as well as loss of faith in health systems, especially in low-income and middle-income countries, and therefore a reliable supply of good-quality medicines is essential for public health [1–4]. However, it has been difficult to quantify the impact on patients’ health, because of fragmented and incomplete reporting of incidents and the consequences of falsified medicines range from no effect at all to enabling disease progression [5], or to lethal toxicity, as in the case of diethylene glycol-containing cough syrup [6,7]. Also, inadequate doses of anti-infectives may lead to drug resistance [8,9]. With the exponential increase in internet connectivity, those engaged in distribution of falsified medical products have gained access to a global market place [10], and the growth of a culture of self-diagnosis and self-prescribing has led to the emergence of thousands of unregulated websites providing unsupervised access to medical products with no guarantee of authenticity [11]. Thus, what was once considered a problem suffered by developing and low-income countries has now become an issue for all, although low- and middle-income countries and areas of conflict or unrest are still most vulnerable to falsified medical products owing to inadequate health-related regulatory systems.

The purpose of this research is to study the literature describing the health consequences of falsified medicines, focusing on mortality and morbidity, as well as the scale of the issue, the geographic extent, the medicines affected and the harm caused at both the individual and population levels. We do not attempt to present an exhaustive analysis of every health consequence of substandard or falsified drugs, but aim to give an overview of the actual
Impact of these products on public health. It should be noted that this article deals only with falsified drugs and not with substandard drugs resulting from inadequate quality control during manufacture or distribution, although such drugs are also likely to have a substantial impact on public health.

Methods

This study is based on searches performed in PubMed. Four authors independently performed the literature search, selection of relevant articles and data extraction. Initially, we searched in several databases using different combinations of keywords to identify relevant articles, aiming to optimize keyword and source selection. Keywords were extracted from the abstracts of the identified articles using IBM SPSS Text Analytics (IBM Japan, Tokyo, Japan), and we finally selected ‘counterfeit OR fake OR bogus OR falsified OR spurious’ AND (medicine OR drug’). Searches of Google Scholar, Scopus, Web of Science and PubMed using these keywords showed that the PubMed database search gave the most comprehensive result, whereas searches of the other databases missed some articles. Therefore, PubMed was selected as the preferred database for the present purpose.

Based on the above findings, a comprehensive search was conducted in all articles listed in PubMed up to Feb. 2017; the earliest identified publication dated from 1972. From the hits, we selected English language articles describing damage to patients’ health due to falsified medicines. Among the 2006 articles hit in the final search using the selected key words, full-length English language articles amounted to 1791. These articles were manually searched to find those that contained a description of casualties related to falsified medicines; finally, 81 publications were selected as meeting this criterion. Publication year was not taken into consideration. Data from publications were included and tabulated if they provided examples of serious health hazards, adverse reactions, injury or deaths. When possible, primary sources (reporting the outbreak or case studies) have been cited and the references were divided into primary and secondary sources. There were some articles among the searched articles in which the terms false, deliberate contamination or adulteration were used to describe apparently falsified drugs. Incidents described in these articles were judged as falsified medicine incidents and data from these articles were included.

Statistical analysis

Results are summarised as descriptive statistics and expressed as number and percent. Graphs were prepared using Microsoft Excel 2010. IBM SPSS Text Analytics (IBM Japan, Tokyo, Japan), 2013 version was used for the keyword selection.

Results and discussion

We identified 81 articles describing 48 incidents related to falsified drugs (Table 1), resulting in approximately 7200 casualties including 3604 deaths. Among the articles identified, several are not listed in Table 1, and the data are not included in the figures, because these reports were considered incorrect or unreliable, as described below. For example, there have been several reports that in 2001 alone, a total of 192 000 people died due to fake medicines in China [5,12–15]. However, the original article by Cockburn et al [16], incorporated translational mistakes by the San Francisco Examiner, which were traced to the Shenzhen Evening News in Fackler's article [17] and corrected later by Cockburn et al [18]. There was another report in which diethylene glycol contamination of paracetamol syrup was claimed to have been responsible for the death of the same number of people in China [19], but it seems possible that this refers to the same incident. Other reports mentioned the death of 700 000 people due to fake antimalarial and tuberculosis drugs, but gave no details as to the country involved, or the year [8,9].

Geographical distribution of incidents

Among the total reported incidents involving health damage due to falsified medicines \( n = 48 \), 27 (56.3%) occurred in developing countries and 21 (43.7%) in developed countries, as classified according to the World Bank country and lending groups country classification [20]. The distribution of these incidents among regions is shown in Figure 1.

The 2006 estimate of falsified medicines by WHO indicated that the prevalence of falsified medicines ranged from less than 1% in developed countries to over 10% in developing countries [3,4,21]. But, it is noteworthy that our results show that the difference between developing and developed countries is quite small in terms of the number of incidents where falsified pharmaceuticals actually impacted on human health. What was once regarded a problem mostly affecting developing and low-income countries now seems a serious issue for all [22,23]. Surprisingly, the USA alone accounted for around 25% of the total incidents reported. Since 2001, at least 10 drug falsification incidents affecting patients were reported, although the US-FDA suggests that drug falsifying occurs less frequently in the U.S. than in other countries due to
Table 1  Summary of incidents of falsified medicines causing health damage, including deaths or adverse reactions

| S.N | Occurrence Year | Country     | Health Impact | Cause                                                                                     |References |
|-----|-----------------|-------------|---------------|-------------------------------------------------------------------------------------------|-----------|
| 01  | 1969            | South Africa| Seven children died | Diethylene glycol poisoning from sedative mixtures                                         | [27] [25,26] |
| 02  | 1982            | USA         | Seven people died  | Cyanide-laced paracetamol                                                                | - [16] |
| 03  | 1986            | India       | 14 patients died  | Receiving doses of impure glycerin contaminated with diethylene glycol                   | [28] [29] |
| 04  | 1988            | Nigeria     | A 21 year old woman died | Hyperglycaemia due to fake insulin                                                          | - [5] |
| 05  | 1989            | Haiti       | 89 people died    | Paracetamol cough syrup prepared with diethylene glycol                                   | - [30] |
| 06  | 1990            | Nigeria     | 109 children died | Acute renal failure from diethylene glycol contaminated syrup/elixir                       | [32,33] [8,12,16,25,26,29,31,34–40] |
| 07  | 1990            | Bangladesh  | 236 patient died including 51 children | Paracetamol syrup tainted with diethylene glycol                                           | [7] [13,16,25,26,29,39–41] |
| 08  | 1992            | Argentina   | 26 people died    | Consumption of a propolis syrup with high level of diethylene glycol                      | - [13,16,25,29,39,40,42] |
| 09  | 1995            | Haiti       | 85 children died  | Ingestion of paracetamol syrup adulterated with diethylene glycol                           | [43,44] [8,12–16,25,26,34,38–40,42,45–49] |
| 10  | 1995            | Niger       | 2500 people died  | Falsified meningitis vaccine                                                              | - [8,14,15,34,45–48,50–53] |
| 11  | 1998            | Brazil      | 200 unwanted pregnancies | Falsified contraceptive pill                                                             | - [12,14,15,34,39,46,54] |
| 12  | 1998            | India       | 36 children were suffering from acute renal failure, 33 of them died | Falsified antirheumatic drug                                                             | [55,56] [12,13,16,25,26,29,36,38–40,45,50,57] |
| 13  | 1998            | Brazil      | Several people died | Falsified antirheumatic drug                                                             | - [39,54] |
| 14  | 1998            | Russia      | 1000 patients were hospitalized | Falsified insulin                                                                       | - [14] |
| 15  | 1999            | Cambodia    | 30 people died    | Falsified artemisin prepared with sulphadoxine-pyrimethamine                             | - [40,45,50] |
| 16  | 1999            | USA         | 17 deaths and 254 occurrence of adverse effects | Injection of fake growth hormone                                                        | [59] - |
| 17  | 2001            | USA         | Several patients were suffering from tissue swellings or skin rashes in seven states of USA | Injection of fake growth hormone                                                        | - [59] |
| 18  | 2002            | USA         | A 16 year old boy was suffering from painful spasms | Injection of diverted drug containing very low amount of erythropoietin hormone          | - [60] |
| 19  | 2002            | USA         | A cancer patient died | Falsified erythropoietin hormone                                                          | - [61] |
| 20  | 2004            | Nigeria     | Three hospitals reported cases of adverse reaction | Infusion contaminated with microorganism                                                  | - [35] |
| 21  | 2004            | Canada      | Four people died  | Heart attacks and strokes after taking falsified amlodipine made from talc               | - [62] |
| S.N. | Occurrence Year | Country        | Health Impact                                    | Cause                                                                 | References                  |
|------|-----------------|----------------|-----------------------------------------------|----------------------------------------------------------------------|----------------------------|
| 22   | 2004            | Argentina      | Two woman died and one gave premature birth to 26 week premature baby | Falsified iron injection for anaemia                                | - [63]                     |
| 23   | 2005            | USA            | Five men died                                 | Ingestion of misbranded dextromethorphan                               | - [14]                     |
| 24   | 2005            | USA            | Respiratory paralysis of several people       | Fake version of Botox                                                | - [64]                     |
| 25   | 2005            | Myanmar        | A 23 year old man died from cerebral malaria  | Artesunate tablet containing paracetamol as a main ingredient         | [65] [66]                  |
| 26   | 2006            | Canada         | Four people died                             | Unauthorized substitution of Falsified viagra containing talcum powder | - [67]                     |
| 27   | 2006            | Panama         | 200 people died including more than 100 children | Paracetamol cough syrup contaminated with diethylene glycol          | [6] [8,53,68,69]           |
| 28   | 2007            | Canada         | A 58 year old woman died                     | Falsified zolpidem and acetylsalicylic acid                          | - [61,67,70]               |
| 29   | 2007            | Hong Kong      | 10 non-diabetic patients were hospitalized due to hypoglycaemia including one death and another taken to ICU | Herbal drug for erectile dysfunction; (yellow capsules labelled as 假偉哥 and red/pink capsules named as “Nangen”) containing glibenclamide | [71] -                     |
| 30   | 2008            | China          | 12 patient died                              | Armillarisin manufactured with diethylene glycol as a solvent        | [72] [26]                  |
| 31   | 2008            | USA            | 785 adverse reaction reports including 81 deaths | Falsified heparin contaminated with oversulphated chondroitin sulphate | [73] [8,74,75]            |
| 32   | 2008            | Singapore      | 150 patients were hospitalized, seven remained comatose and four subsequently died | Falsified Cialis (tadalafil), three herbal preparations and sildenafil | [71] [36,76–78]           |
| 33   | 2008            | Norway         | 44 people were suffering from poisoning      | Fake flunitrazepam tablets containing scopolamine                     | [79] -                     |
| 34   | 2008            | Nigeria        | 118 children died                            | Paracetamol teething mixture containing diethylene glycol            | - [25,26,37,53,68]         |
| 35   | 2009            | China          | Two people died                              | Falsified glibenclamide six times more potent than normal           | - [5,74,80]                |
| 36   | 2010            | Australia      | A 54 year old man was suffering from severe hypoglycaemia | Ingestion of Falsified tadalafil                                    | [81] -                     |
| 37   | 2010            | China          | 81 patients were suffering from intraocular inflammation | Endotoxin-contaminated falsified Bevacizumab                         | [82,83] -                  |
| 38   | 2013            | Guinea-Bissau  | 74 patients had recurrence or increased frequency of seizures, two subsequently died | Falsified Phenobarbital                                            | [84] -                     |
their strict regulatory framework [24]. However, this strict framework may mean that incidents are reported in the US that would have been overlooked or not reported in other countries with less well-developed heath systems. Incidents were also reported in other developed countries: Australia, Canada, Singapore, UK, Japan, Russia and Norway. Among developing countries, Nigeria was the victim of repeated incidents of harm caused by falsified drugs, with the latest (falsified phenobarbital) being reported in 2014 (Table 1). Among other developing countries, 2500 people died in Niger after receiving fake meningitis vaccine.

**Therapeutic categories of falsified drugs**

Among the categories of falsified drugs that caused health damage, sedatives, hypnotics, narcotics and drugs for sexual dysfunction were the most common in both

| S.N | Occurrence Year | Country | Health Impact | Cause | References |
|-----|----------------|---------|---------------|-------|------------|
| 39  | 2014           | USA     | A 65-year old male was suffering from Hepatotoxicity | Chinese Herbal Medicine Containing Sildenafil [85] | - |
| 40  | 2014           | Nigeria | 105 patients had increased frequency of seizures | Falsified Phenobarbital [84] | - |
| 41  | 2014           | Congo   | 930 people were suffering from dystonic reactions, 11 among them died | Falsified Diazepam containing haloperidol [86] | - |
| 42  | 2014           | USA     | 40 patients were suffering from adverse events including one death | Non-sterile simulated IV fluids containing large amounts of endotoxin and significant bacterial contamination [87] | - |
| 43  | 2015           | USA     | Eight people were suffering from adverse effects | Ingestion of Falsified alprazolam tablets found to contain fentanyl and, in some cases, etizolam [88] | - |
| 44  | 2015           | India   | 15 patients were suffering from intraocular inflammation | Injections of falsified bevacizumab [89] | - |
| 45  | 2016           | USA     | Seven people were suffering from adverse effects | Norco (acetaminophen and hydrocodone), containing fentanyl and promethazine [90] | - |
| 46  | Unknown        | UK      | Acute lead intoxication of a man | Falsified ayurvedic drug for erectile dysfunction (Kamagra) [91] | - |
| 47  | Unknown        | USA     | A child complains of burning sensation after injection with human growth hormone | Human growth hormone containing inexpensive insulin [92] | - |
| 48  | Unknown        | Japan   | A 39 year old man was suffering from hypoglycaemia | Sexual enhancement medication containing extremely large amount of glibenclamide and low amount of sildenafil [93] | - |

In some cases, different numbers of injuries in the same incident were given in different articles. In cases where multiple articles give the same number, that number is shown; otherwise the maximum reported number of injuries for each incident is shown. Some cases were regarded as duplicates, because health damage, occurrence year, country, drugs and cause were the same. Some cases are not included in the table because the reports gave very few details and could not be verified, and they were considered incorrect or unreliable (see text for details).
developing and developed countries. However, patients from developing or under-developed countries were mainly affected by falsified antipyretics, analgesics, and antitussives, such as paracetamol elixir, cough syrup, or teething mixture containing diethylene glycol [26,73]. Overall, the number of incidents by drug therapeutic category is illustrated in Figure 2.

**Annual trends in number of incidents and number of persons affected by falsified medicines**

According to the Pharmaceutical Security Institute (PSI), the global incidence of drug falsifying has increased by 51% between 2011 and 2015, with 2015 seeing the highest level of falsifying to date, a 38% increase compared with 2014. The Institute documented 3002 incidents of pharmaceutical crime during 2015 alone [94]. Regarding
health damage from falsified drugs, Figure 3 shows the numbers of incidents during various time periods. There is no clear trend to suggest that the number of incidents or the numbers of persons affected has been decreasing over time, although the number of victims is currently much smaller than in the 1990s (Table 1). The largest number of people seemed to have been affected during the period of 1992 to 1996 (more than 2500), followed by 1997 to 2001 (more than 1500) and 2012 to 2016 (more than 1000). Only 200 people were affected between 2002 and 2006. These figures exclude cases where insufficient information was available in published reports. However, it is possible that reporting of incidents of health damage due to falsified medicines has become more comprehensive.

Nature of drug falsification

The identified incidents involved many kinds of falsified drug products. Some did not contain any active ingredient (meningitis vaccine containing no active ingredient or just salt water) [8,14,53], or included the active ingredient in harmful amounts (traditional antidiabetic medicine containing six times the normal dose of glibenclamide) [5,74,80]. Others involved a completely different active ingredient or incorrect formulation, or contained unacceptably high levels of impurities (cyanide-laced paracetamol or zolpidem and acetaminophen laced with metal) [16,61,67,70].

Looking at the health damage caused by falsified drugs at Table 1, the most common category (nine cases) covered antipyretic, analgesics, (acetaminophen, paracetamol) antitussive medication (cough syrup, paracetamol, dextromethorphan), and in eight of them, diethylene glycol was present as a contaminant (either deliberate or accidental) in the drug. Mass poisoning incidents with diethylene glycol have occurred in a number of countries over a long period. Medicines containing an incorrect amount of API or a totally different kind of API appeared in at least 12 cases. Another common finding was endotoxin and microbial contamination of ophthalmic products or infusions.

Limitations of the study

This study has several limitations. Firstly, it covers only English language articles in the PubMed database. In some of the reported cases, there was no information about specific drug involvement, exact number of patients harmed, year of occurrence or the location of the incident. Also, for many of the incidents, there was no primary source of data but only a review(s) summarising the incident details. In particular, several incidents that were claimed to involve hundreds of thousands of people were very poorly described. It should also be borne in mind that the results might be biased by differences in the effectiveness of reporting systems among countries; for example, less serious incidents in under-developed countries might not have been reported. In addition, different reports sometimes gave conflicting information about the same incident. Thus, we cannot estimate the true extent of the problem.

Conclusion

It is clear from the results of this study that falsified medicines impact both directly and indirectly on global public health and remain a serious problem. A wide range of medicines has been falsified in a variety of ways, and our findings may be helpful to identify particular causes for concern, such as deliberate or accidental contamination with ethylene glycol. Although many of the reports identified in our study only provided seriously inadequate or even conflicting data, we believe this study of reported drug falsification incidents involving health damage will be useful to focus attention on the potential scale of the problem, and may provide a basis for further studies in the future. Recognition of the problem, coordination of responses and active engagement of key stakeholders will be essential in combating transnational pharmaceutical crime, and reducing the human cost of falsified medicines.

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