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Counterfeit medicines in Peru: a retrospective review (1997–2014)

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ABSTRACT

Objective: To consolidate and assess information on counterfeit medicines subject to pharmaceutical alerts issued by the Peruvian Medicines Regulatory Authority over 18 years (1997–2014) of health monitoring and enforcement.

Design: A retrospective review of drug alerts.

Setting: A search of the website of the General Directorate of Medicines, Supplies and Drugs (DIGEMID) of the Ministry of Health of Peru for drug alerts issued between 1997 and 2014.

Eligibility criteria: Drug alerts related to counterfeit medicines.

Results: A total of 669 DIGEMID alerts were issued during the study period, 354 (52.91%) of which cover 1738 cases of counterfeit medicines (many alerts deal with several cases at a time). 1010 cases (58.11%) involved pharmaceutical establishments and 349 (20.08%) involved non-pharmaceutical commercial outlets. In 126 cases (7.25%), counterfeit medicines were seized in an unauthorised trade (without any marketing authorisation); in 253 cases (14.56%) the type of establishment or business associated with the seized product was not identified.

Conclusions: Counterfeit medicines are a serious public health problem in Peru. A review of the data cannot determine whether counterfeit medicines in Peru increased during the study period, or if monitoring by different government health agencies highlighted the magnitude of the problem by providing more evidence. The problem is clearly structural, since the majority of cases (58.11% of the total) were detected in legitimate supply chains. Most counterfeit medicines involve staple pharmaceutical products and common dosage forms. Considerable work remains to be done to control the serious problem of counterfeit medicines in Peru.

Strengths and limitations of this study

- General Directorate of Medicines, Supplies and Drugs (DIGEMID) alerts are published systematically, are organised by date, and are readily available on the DIGEMID open access website.
- The information they provide is not entirely homogenous or standardised, which limits overall analysis.
- In most cases, the DIGEMID alerts do not provide full information, thereby hindering overall evaluation.
- The possible health effects resulting from the use of counterfeit medicines are not addressed in the alerts.
- Graphics, which can be very informative, are only provided in three alerts (DIGEMID Alerts 17-2006, 35-2005 and 40-2005).

INTRODUCTION

The WHO has been receiving reports of counterfeit medicines since 1982.[1] The phenomenon was first referred to as a problem at the WHO Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, in 1985. Since then, public awareness of counterfeit medicines has grown,[2] and it has become a major public health issue, as reflected by government initiatives worldwide in response to the problem.

The issue of counterfeit medicines is so complex that different definitions are still used, or a counterfeit medicine is confused with one of poor quality (substandard), a serious mistake that hampers the exchange of information between countries, and makes it difficult to grasp the true scale of a global problem. The WHO defines counterfeit medicines as those whose labels include, intentionally and fraudulently, false information about their identity and origin. Falsification can affect both branded and generic products, and may include products with the correct or wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.[2]

According to the WHO, the highest rates of medicine falsification in the world occur in regions with the weakest regulatory and control systems, such as many African, Asian and Latin American nations and countries in transition. In most industrialised nations, regulatory systems and market control are effective and thus the incidence of spurious/falsely labelled/falsified/counterfeit medicines is low, and estimated to be less than 1% of the market value.[3] Medicine falsification involves manufacturing and distribution networks

related to organised crime,[4] with annual turnovers of between US$75 and US$200 billion,[5 6] and has a significant impact even in large economies like the USA.[7]

In general, the deregulation of any trade or business and the existence of uninformed consumers facilitate the criminal activities of those whose sole purpose is to obtain illegitimate profits at the expense of harming consumers and the health system. This is the case in the medicine market in Peru (according to the World Bank, an upper-middle income country with a gross national income per capita of US$4126–US$12 745).[8]

In Peru, in the early 1990s, during an economic crisis, the regulated market for medicines was replaced with an open market, in line with the neoliberal economic model of the time. Ownership of community pharmacies was no longer the exclusive right of pharmacists, and anyone with enough capital could open a store dispensing and selling pharmaceuticals and related products in any location and without rigorous controls in place. *Boticas*, where the owner is not a pharmacist and pharmacies, where the owner is a pharmacist, provided the same service. This change was based on a political decision without preliminary analysis of the possible consequences, such as the chaotic growth in the number of pharmaceutical establishments, which currently stands at 23 527[9] (259 in 1980–1989, 3335 in 1990–1999 and 17 071 in 2000–2008),[10] rendering effective control by the authorities impossible. This is arguably one of the main causes of the high number of cases of counterfeit medicines found in the legal supply chain today. Attempts to resolve this problem include Law No. 26842 of 2009, which stipulates mandatory sanitary authorisation for the operation of pharmaceutical establishments, with prior verification of compliance,[11] and more recently a process of registration or special registration under the Temporary Supplementary Provisions of the Supreme Decree No. 033-2014-SA.[12]

This situation has caused serious public health problems, including treatment failure, possible cases of added contaminants[13] and even death. It has also resulted in the deployment and disbursement of often scarce resources, a loss of faith in health systems, distrust of medications and even the failure of major global health initiatives such as the fight against malaria.[14]

The regulatory authority for medicines in Peru is the General Directorate of Medicines, Supplies and Drugs (DIGEMID), created by Legislative Decree No. 584 of 16 April 1990,[15] as a dependent institution of the Ministry of Health of Peru. In May 1998, the Alerts Committee was established by Directorial Resolution No. 367-98-DG-DIGEMID to evaluate and define what action should be taken in response to alerts or communications about the safety and/or efficacy of pharmaceuticals and related products.[16]

Inspectors from DIGEMID and regional health institutions carry out inspections and spot checks of pharmaceutical products (in pharmaceutical and non-pharmaceutical establishments), and also receive counterfeit drugs seized by other regulatory authorities (the national police, customs, etc). Any suspected deficiency or observable abnormality in a product leads to its seizure, and its authenticity is then verified with the holder of the relevant marketing authorisation. If the suspected counterfeiting is confirmed, samples are transferred to an official control laboratory for completion of the relevant physical, chemical and microbiological analyses. All documentation and the case history is referred to the DIGEMID Alerts Committee so they can approve the publication of an alert on the institutional web page and initiate internal and external dissemination of information.[17]

OBJECTIVE

This work seeks to consolidate and assess information on counterfeit medicines referred to in pharmaceutical alerts issued by the Peruvian Medicines Regulatory Authority in 18 years (1997–2014) of health monitoring and enforcement. The ultimate aim is to draw attention to the situation of counterfeit medicines in Peru and highlight the efforts of various state institutions headed by DIGEMID.

METHODS

Inclusion and exclusion criteria

A counterfeit medicine is a product improperly manufactured, in a deliberate and fraudulent manner with respect to its identity or its origin. Counterfeit medicines may include products with the correct ingredients or the wrong ingredients, without active pharmaceutical ingredients, with insufficient or incorrect active pharmaceutical ingredients, or with falsified packaging or labelling.[18]

A DIGEMID alert is a document issued by the National Authority of Pharmaceutical Products and Medical Devices, as a health safety measure, through which regulatory actions and other actions regarding safety, falsification and critical quality results related to pharmaceutical products and medical devices are made known to the national scientific community and to the public in general, with the ultimate objective of controlling and minimising the risk related to the sale of the product and its use.[17]

To be eligible for inclusion in this retrospective review, DIGEMID alerts had to refer to counterfeit medicines. Medical devices, herbal products and cosmetic products were excluded, as were cases related to quality, general safety or regulation (eg, products without sanitary registration).

Data sources and searches

A search for DIGEMID alerts related to counterfeit medicinal products was carried out through the official DIGEMID website using the section allocated to DIGEMID alerts.[19] All drug alerts issued between 1997, when the first DIGEMID alert was published on the DIGEMID website, and 2014 were included.

Data collection

All available DIGEMID alerts were assessed for inclusion in the review. A structured Excel spreadsheet was used to record relevant information and ensure uniformity of the evaluation of each DIGEMID alert. The following data were extracted from the alerts:

- Publication date of the DIGEMID alert: so that the date of each counterfeiting case could be identified and its impact over time determined.
- Medicinal product: this allowed the identification of medical products being counterfeited, if it was on a regular basis, to which therapeutic group it belonged, etc.
- Batch number: this detected if the same batches of medicinal product were seized more than once.
- Pharmaceutical dosage form: so that it could be determined which pharmaceutical dosage forms were being regularly falsified.
- Establishment or place where seizure took place: this identified the types of establishments involved in the sale of counterfeit medicinal products and the geographical spread of cases across Peru.
- Seizure promoter: this indicated which authority assisted the seizure of the counterfeit medicinal product.
- Assessment result: this indicated the type of falsification of the medicinal product.

Data analysis

Based on the collected data, the total number of DIGEMID alerts issued per year, the number of DIGEMID alerts about counterfeit medicines and the number of cases of counterfeit medicines were determined (some DIGEMID alerts refer to more than one case of counterfeit medicinal product as we shall see later in the Results section) and indicate the magnitude of the problem.

Examination of data concerning the establishment where the counterfeit medicine was found allowed the type of establishment to be categorized into one of three groups as follows:

1. Pharmaceutical establishments (pharmaceutical offices (pharmacies and *boticas*), pharmacies of healthcare facilities, *botiquínes*, *droguerías*, specialty stores and laboratories):[18]
   - Pharmaceutical offices (pharmacies and *boticas*):
     - Pharmacy: a pharmaceutical store dispensing and selling pharmaceuticals and related products and owned by a pharmacist
     - *Botica*: a pharmaceutical store dispensing and selling pharmaceuticals and related products and not owned by a pharmacist
   - Pharmacy of a public or private healthcare facility
   - *Botiquín*: sells a restricted range of pharmaceuticals and related products as listed by the health authority
   - *Droguería*: engaged in the import, export, marketing, storage, quality control and/or distribution of pharmaceuticals and related products
   - Specialty stores: connected to a public health establishment for the storage and distribution of pharmaceuticals and related products
   - Laboratory: engaged in manufacturing, packaging, bottling, conditioning, reconditioning, quality control, storage and export of pharmaceuticals and related products
2. Non-pharmaceutical commercial establishments: any authorised commercial establishment that is not a pharmaceutical establishment
3. Informal, unauthorised commercial establishments or places

The results are distributed across the 24 regions of Peru and Callao (Constitutional Province) so the geographical spread of the falsification of medicinal products can be determined.

The various authorities initiating the seizure of counterfeit medicinal products are mentioned in the DIGEMID alerts: DIGEMID itself, health directorates (DISAs), regional health directorates (DIRESAs), the national police of Peru, public prosecutors, customs authorities, etc. This information was included in the analysis.

All counterfeit medicines were classified according to the WHO Anatomical Therapeutic Chemical Classification System (ATC), where medicines are grouped into five different levels; the first three levels were used in this review. The first level classifies the medicine according to the system or organ on which it acts, the second level classifies the medicine according to its therapeutic subgroup and the third level classifies the medicine according to its pharmacological subgroup.[20] The dosage form was taken as that given in the DIGEMID alert or the database for the registration of pharmaceutical products of the regulatory authority of medicinal products of Peru (PERUDIS).[21] This was done to determine the most frequent therapeutic classes and dosage forms affected by counterfeit drugs. The type of counterfeiting was classified according to the assessment provided by the alerts: features and/or information that do not match the product specifications, contains no active ingredient, contains an active ingredient other than that stated on the label, or contains the correct active ingredient but not in the authorised concentration. Medicines with the same batch number as a previous alert are not taken into account so as not to bias results.

Each counterfeit medicinal product was categorized into one of four groups: does not contain any active ingredient, contains active ingredients other than those stated on the label, contains the active ingredient at a different dosage to that claimed on the label claims or DIGEMID assessment result missing in the alerts.

Quality assessment

All authors had access to the primary information (DIGEMID alerts) for the study period and the

evaluation tables (Excel). Analysis and drafting the work was carried out by the first author, followed by verification and reconciliation of the results by the other authors.

RESULTS

In the 18-year period covered by this study (1997–2014), DIGEMID issued a total of 669 alerts, 354 of which (52.91%) concerned counterfeit medicine. There is no direct relationship between the number of DIGEMID alerts and the number of cases, since several alerts referred to more than one medicine or different batches of the same product, for instance, DIGEMID alert No. 27 issued in 2012[22] particularly stands out as it referred to 74 cases of counterfeit medicines. Thus, the 354 DIGEMID alerts concerning counterfeit medicines covered 1738 reported cases (figures 1 and 2).

A total of 1738 cases of counterfeit medicines were identified (see online supplementary table S1). Of these, 1010 cases (58.11%) involved pharmaceutical establishments (pharmaceutical offices, *droguerías*, *botiquines* and laboratories) and 349 (20.08%) involved non-pharmaceutical establishments (non-pharmaceutical commercial outlets). In 126 cases (7.25%), counterfeit medicines were seized in an unauthorised trade (without any marketing authorisation), including 10 cases of clandestine laboratories. In the remaining 253 (14.56%) cases there was insufficient information to clearly identify the type of establishment or business involved. Overall, 850 (84.16%) cases of counterfeit medicines involved *boticas* and 130 (12.87%) involved pharmacies (table 1).

Regarding the region where counterfeit medicines were seized, Lima province had the highest number of cases with 562 (32.34%), far outstripping La Libertad, which had 315 (18.12%). Interestingly, no cases were reported in the Huanuco or Tumbes regions. The province with the highest number of cases of counterfeit

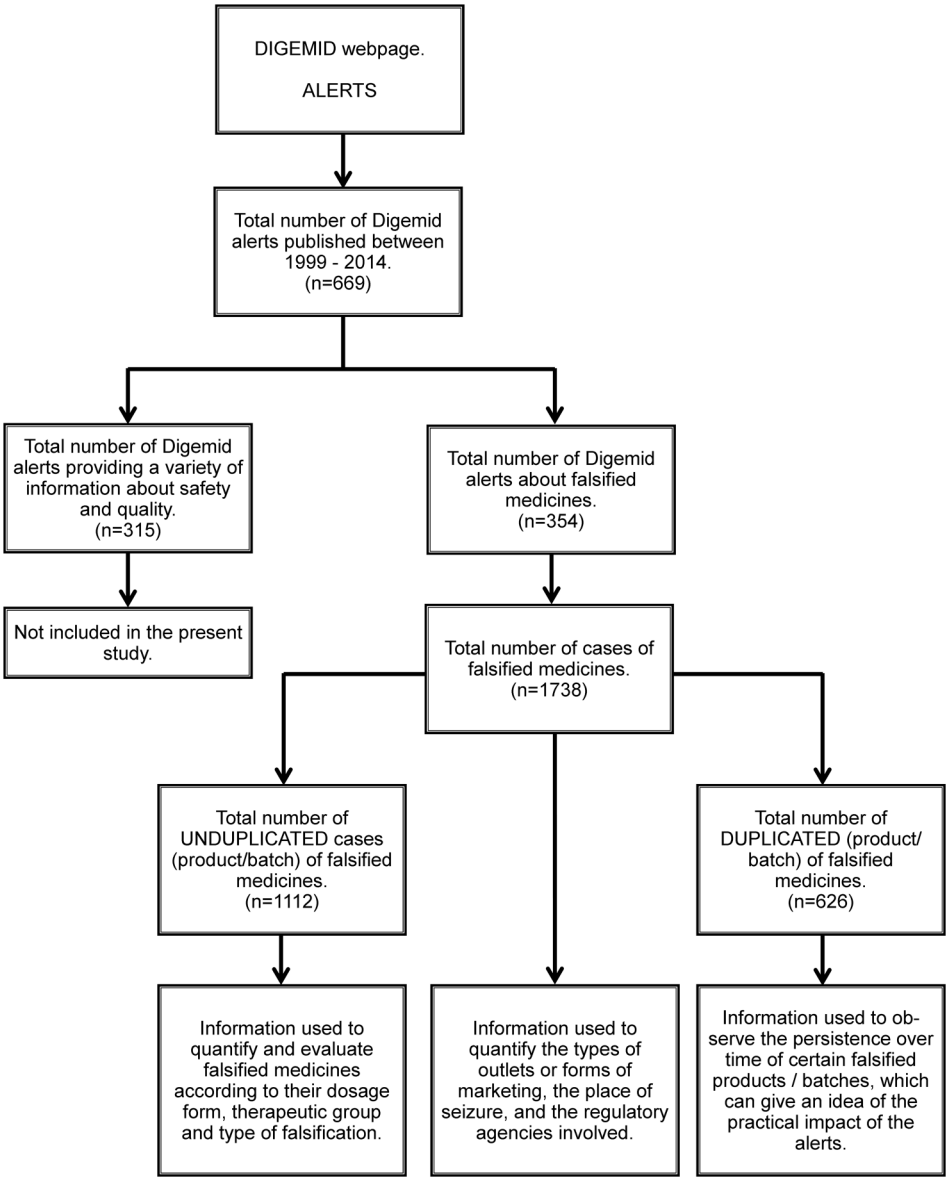

Figure 1 Flow diagram showing the types of General Directorate of Medicines, Supplies and Drugs (DIGEMID) alerts and overall results.

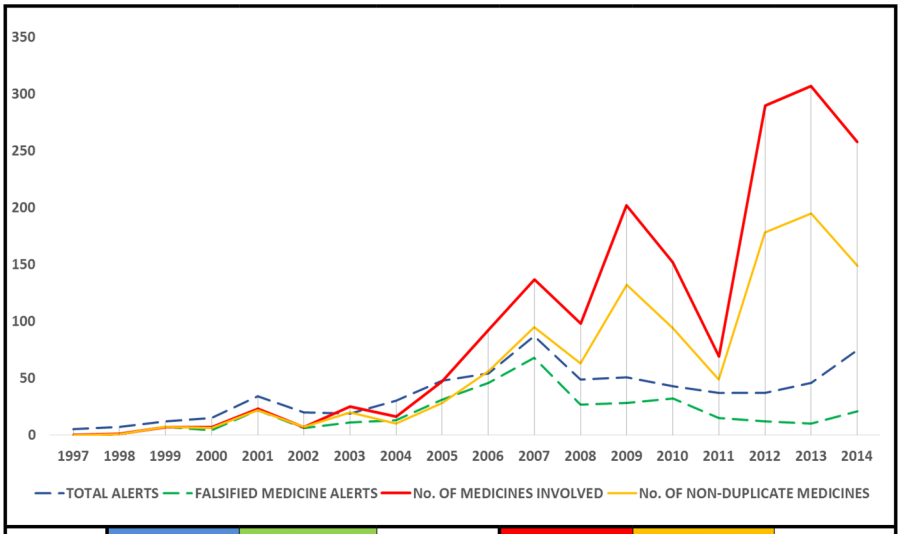

Figure 2 General Directorate of Medicines, Supplies and Drugs (DIGEMID) alerts and counterfeit medicines by year.

YEAR	TOTAL ALERTS	FALSIFIED MEDICINE ALERTS	%	No. OF MEDICINES INVOLVED	No. OF NON-DUPLICATE MEDICINES	%
1997	5	0	0.00%	0	0	0.00%
1998	7	1	14.29%	1	1	100.00%
1999	12	7	58.33%	7	7	100.00%
2000	15	4	26.67%	7	6	85.71%
2001	34	22	64.71%	23	22	95.65%
2002	20	6	30.00%	7	7	100.00%
2003	19	11	57.89%	25	20	80.00%
2004	30	13	43.33%	16	10	62.50%
2005	48	31	64.58%	47	28	59.57%
2006	54	46	85.19%	92	56	60.87%
2007	87	68	78.16%	137	95	69.34%
2008	49	27	55.10%	98	63	64.29%
2009	51	28	54.90%	202	132	65.35%
2010	43	32	74.42%	152	94	61.84%
2011	37	15	40.54%	69	49	71.01%
2012	37	12	32.43%	290	178	61.38%
2013	46	10	21.74%	307	195	63.52%
2014	75	21	28.00%	258	149	57.75%
TOTAL	669	354	52.91%	1 738	1 112	63.98%

medicines per 100 000 inhabitants was Madre de Dios, with 19.33 cases, followed by La Libertad with 16.94 cases. More details are shown in table 2.

Regarding the institutions whose actions ultimately resulted in the counterfeit medicine alerts, 1006 cases (57.88%) followed initiatives by local decentralised health institutions (DISAs or DIRESAs), 168 (9.67%) were due to the actions of various agencies (national police, public prosecutors, etc) and 151 (8.69%) to DIGEMID itself. In 413 (23.76%) cases the initiators of the seizure were not specified.

Interestingly, monitoring activity increased with decentralisation, resulting in greater effectiveness, as can be seen in figure 3.

To obtain more precise results regarding the counterfeit medicines themselves, identical batches (duplicate product/batch number) seized in more than one place or mentioned in earlier alerts were excluded, ultimately resulting in a total of 1112 counterfeit medicines with different batch numbers (see online supplementary table S2), the details of which are shown in figures 1 and 2. A total of 626 cases of counterfeit medicines had batch numbers included in more than one alert, many of them in different years.

The numbers of cases of counterfeit medicines classified according to the organ or system on which they act, and the therapeutic and pharmacological subgroups of the ATC code are detailed in table 3. Among the therapeutic subgroups, painkillers were the most frequent counterfeit medicines, representing 22.57% of all cases, followed by systemic antibacterials at 19.78%.

Table 1 Type of establishment or business associated with the possession or sale of counterfeit medicines

Type of establishment/outlet	Total	Per cent
Pharmaceutical	1010	58.11
Pharmacy	130	7.48
Pharmaceutical store dispensing and selling pharmaceuticals and related products, owned by a pharmacist		
Botica	850	48.91
Pharmaceutical store dispensing and selling pharmaceuticals and related products, not owned by a pharmacist		
Botiquín	4	0.23
Sells pharmaceuticals and related products included in a restricted list issued by the health authority		
Droguería	23	1.32%
Engaged in the import, export, marketing, storage, quality control and/or distribution of pharmaceuticals and related products		
Laboratory	3	0.17
Engaged in manufacturing, packaging, bottling, conditioning, reconditioning, quality control, storage and export of pharmaceuticals and related products		
Non-pharmaceutical	349	20.08
Unauthorised trade	126	7.25
Without information	253	14.56
Total	1738	100.00

Twenty-six different dosage forms were identified in the study period, the most common being tablets (including coated and chewable), with a total of 816 cases (73.38%), followed by injectable dosage forms (injectable solution, powder for injectable suspension, injectable suspension and powder for injectable solution), with a total of 111 cases (9.98%), and 76 cases involving capsules (6.83%).

A total of 164 cases (14.75%) had characteristics and/or information that did not correspond to product specifications, 100 (8.99%) did not contain an active ingredient, 12 (1.08%) had a different active ingredient to that on the label, and 7 (0.63%) had the correct active ingredient but not at the authorised concentration. It is noteworthy that in most cases (829, 74.55%) no information about the type of counterfeit was provided in the alert, which prevents proper overall assessment.

DISCUSSION

Regarding the type of establishment involved in the possession or sale of counterfeit medicines, 1010 cases (58.11%) involved pharmaceutical establishments, 349 cases (20.08%) involved non-pharmaceutical commercial outlets, in 126 cases (7.25%) the medicines were seized in an unauthorised trade (without any marketing authorisation), and in 253 cases (14.56%) the type of establishment or business associated with the seized product was not identified.

DIGEMID alerts are a valuable resource for warning the general public about the safety of some supposed medicines and related products. To be effective and efficient, the alerts should provide detailed, homogenised and standardised data. It is worthwhile assessing the impact of the alerts on efforts to control and minimise the risks associated with the use of counterfeit medicines.

This review demonstrates that there is a substantial problem regarding counterfeit medicines in Peru. The findings suggest the country has a serious public health problem, particularly if these results are compared with similar studies in other countries considered to have better health surveillance,[24] such as the UK, which had seven cases of counterfeit medicines in 11 years (2001–2011)[25] or Canada with four cases in 9 years (2005–2013).[26]

A troubling finding in this study is the extent to which the medicine supply chain in Peru is compromised, with the highest rate of counterfeit drugs found in pharmaceutical establishments (pharmacies and *boticas*): 980 (56.39%) of a total of 1738 cases. This situation is particularly worrying since, according to the Institute of Statistics and Informatics of Peru (INEI), the Peruvian population mainly relies on pharmacies or *boticas* for healthcare.[27] Consumer confidence in the legal supply chain is being damaged, and efforts promoting the responsible acquisition of safe medicines in legally established pharmaceutical establishments are also being undermined. This situation requires the active and joint participation of regulatory authorities and institutions representing the pharmaceutical establishments. Ways to solve the problem would be to: (i) grant a leading role to the pharmacist, who should procure medicines from recognised and reliable sources; (ii) warn patients against acquiring medicines from informal establishments or places (including the internet); (iii) ensure that distributors buy products from approved suppliers; (iv) check the alerts on counterfeit medicines issued by health authorities; (v) be vigilant for products with suspicious features; (vi) collaborate with the pharmaceutical industry, distributors and health authorities to establish safety procedures to prevent violations of the legal supply chain; (vii) make use of available technology for the safe management and traceability of medicines; and (viii) provide training and safety refresher courses in the workplace, with any suspicious activity or product reported to health authorities.[28] Pharmacists must confront the challenge of counterfeit medicines.

No less worrying are the 349 cases involving non-pharmaceutical outlets, and the 126 cases of unauthorised trade, which included 10 cases related to clandestine laboratories.

Lima is home to 31.57% of Peru's 31 151 643 inhabitants[23] and was the location of 562 cases (32.34%) subject to counterfeit medicine alerts, followed by La Libertad with 315 cases (18.12%). As indicated by the WHO, there can be enormous variation in the incidence of counterfeit medicines within the same country, whether between

Table 2 Number of cases of counterfeit medicines according to the geographical location where they were seized and regional population

Region	No. of cases of counterfeit medicines	Per cent	Population in 2015[23]	No. of cases per 100 000 inhabitants
Amazonas	1	0.06	422 629	0.24
Ancash	53	3.05	1 148 634	4.61
Apurimac	1	0.06	458 830	0.22
Arequipa	93	5.35	1 287 205	7.22
Ayacucho	26	1.50	688 657	3.78
Cajamarca	123	7.08	1 529 755	8.04
Callao	20	1.15	1 013 935	1.97
Cusco	68	3.91	1 316 729	5.16
Huancavelica	3	0.17	494 963	0.61
Huánuco	0	0.00	860 548	0.00
Ica	12	0.69	787 170	1.52
Junín	146	8.40	1 350 783	10.81
La Libertad	315	18.12	1 859 640	16.94
Lambayeque	56	3.22	1 260 650	4.44
Lima	562	32.34	9 834 631	5.71
Loreto	146	8.40	1 039 372	14.05
Madre de Dios	27	1.55	137 316	19.66
Moquegua	24	1.38	180 477	13.30
Pasco	3	0.17	304 158	0.99
Piura	7	0.40	1 844 129	0.38
Puno	18	1.04	1 415 608	1.27
San Martín	3	0.17	840 790	0.36
Tacna	4	0.23	341 838	1.17
Tumbes	0	0.00	237 685	0.00
Ucayali	11	0.63	495 511	2.22
Without information	16	0.92		

rural and urban areas or between different cities.[29] This is an important factor for planning appropriate strategies to combat the problem.

It is especially interesting to note the effect of the decentralisation of public health surveillance powers as reflected in our findings. In 1999, Ministerial Resolution

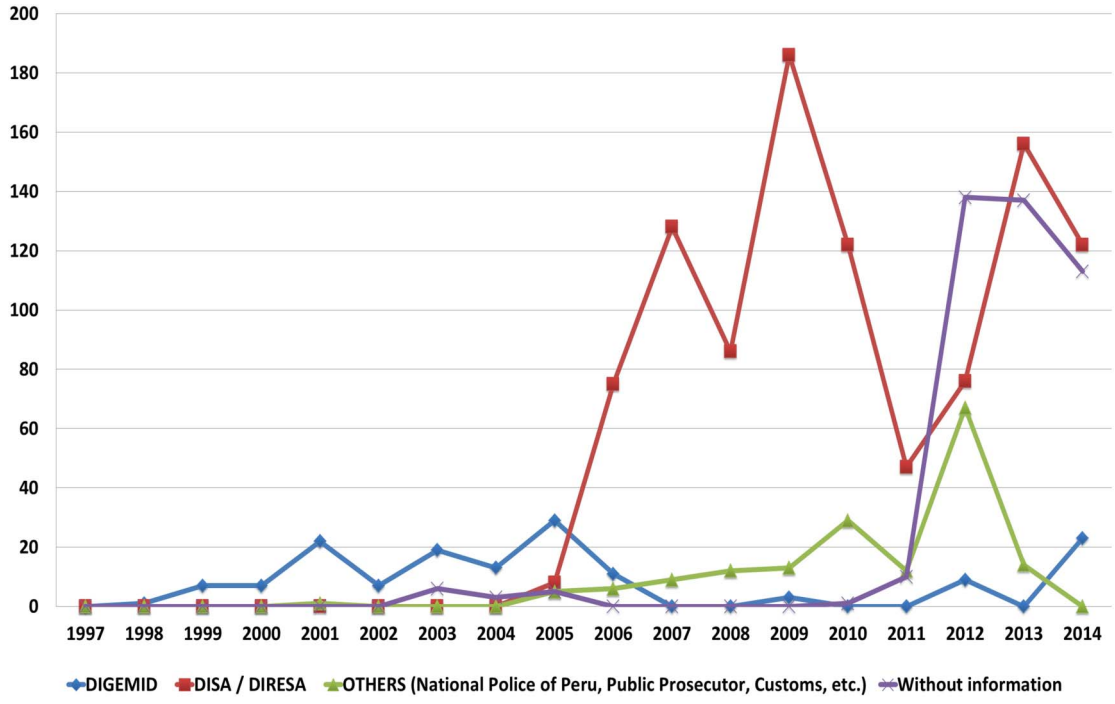

Figure 3 Evolution of inspections according to the initiating authority.

Table 3 Classification of the counterfeit medicines according to the Anatomical Therapeutic Chemical Classification System (ATC) code

		No.	Per cent
Main anatomical group			
N	Nervous system	297	26.71
J	Anti-infectives for systemic use	220	19.78
G	Genito-urinary system and sex hormones	217	19.51
A	Alimentary tract and metabolism	188	16.91
R	Respiratory system	90	8.09
M	Musculo-skeletal system	32	2.88
D	Dermatologicals	25	2.25
H	Systemic hormonal preparations, excl. sex hormones and insulins	15	1.35
B	Blood and blood forming organs	15	1.35
C	Cardiovascular system	9	0.81
P	Antiparasitic products, insecticides and repellents	3	0.27
S	Sensory organs	1	0.09
L	Antineoplastic and immunomodulating agents	0	0.00
V	Various	0	0.00
Total		1 112	100.00
Therapeutic subgroup			
N02	Analgesics	251	22.57
J01	Antibacterials for systemic use	220	19.78
G02	Other gynaecologicals	178	16.01
R06	Antihistamines for systemic use	68	6.12
A11	Vitamins	65	5.85
A04	Antiemetics and antinauseants	40	3.60
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	36	3.24
M01	Anti-inflammatory and antirheumatic products	28	2.52
G03	Sex hormones and modulators of the genital system	24	2.16
N05	Psycholeptics	21	1.89
A03	Drugs for functional gastrointestinal disorders	20	1.80
	Others	161	14.48
Total		1 112	100.00
Pharmaceutical subgroup			
N02B	Other analgesics and antipyretics	232	20.86
G02C	Other gynecologicals	178	16.01
J01E	Sulfonamides and trimethoprim	102	9.17
J01C	Beta-lactam antibacterials, penicillins	71	6.38
R06A	Antihistamines for systemic use	68	6.12
A04A	Antiemetics and antinauseants	40	3.60
A11J	Other vitamin products, combinations	39	3.51
A07D	Antipropulsives	36	3.24
M01A	Anti-inflammatory and antirheumatic products, non-steroids	28	2.52
N03A	Antiepileptics	17	1.53
N05B	Anxiolytics	17	1.53
	Others	284	25.54
Total		1 112	100.00

No. 150-99/DM[30] decreed that regional and sub-regional health directorates assume the functions of health control and monitoring, although the rules of procedure and operation were not approved until Ministerial Resolution No. 573-2003-SA/DM of 2003.[31] After a period of implementation, results began to be seen in 2005, when the regional directorates participated in 8 cases of counterfeit medicines, which grew to 75 in 2006 and 128 in 2007, reaching a total of 1006 cases over the study period, representing 57.88% of all cases. In parallel, the operational role of the centralised body, DIGEMID, was reduced, as it concentrated more on other functions including coordination.

In the period covered by this review, the alerts referred to 1112 cases of counterfeit medicines (product/batch). Analysis of the pharmacological/therapeutic subgroups (second level) of the ATC code[20] assigned to registered products in the DIGEMID database,[21] showed the most common counterfeit medicines in Peru were analgesics (251, 22.57%), followed by systemic antibacterials (220,

19.78%), other gynecologicals (178, 16.01%), systemic antihistamines (68, 6.12%) and vitamins (65, 5.85%). These results partly reflect the most frequently consumed medicines in Peru, as reported in the 2008 study by Meza-Cornejo *et al*,[32] which according to the IMS Health is likely to remain the same in the near future.[33] Modern technologies should be employed to detect counterfeit medicines[34] and procedures should be developed to trace pharmaceutical products, including radio frequency technology[35–40] and two-dimensional codes such as the Data Matrix system. Modern analytical methods have already been adapted to identify counterfeit medicines, leading to faster and more effective results and more timely action and communication by health authorities. In this way, the alert system is not only informative, but also becomes an effective tool.[41–49]

The liberalisation of the world economy, with fewer commercial borders and a growing impact of the internet on medicine advertising and trade, demands global measures against counterfeit medicines. Solutions include an internationally accepted standard terminology for improved information management, transparency surrounding and identification of brokers and commercial intermediaries, legislative and regulatory harmonisation and the implementation of tracing systems. Although the DIGEMID alerts do not provide data on the issue, trade in counterfeit medicines over the internet is a major global problem (particularly in developed countries).[50 51] Criminal gangs involved in medicine counterfeiting will be aware that the global pharmaceutical market is forecast to grow by around 4% per year (21% between 2012 and 2017).[52] Concern about counterfeit medicine is increasing worldwide, in developed as well as developing countries; its impact on public health and the economy, although quantitatively different, is similar in both.

Continuing the work of inspection is vital. The magnitude and nature of the problem require a thorough analysis within regions or countries as well as globally. It is necessary to evaluate the measures, activities and behaviours (WHO guidelines)[53] responsible for the high levels of counterfeit medicines in the pharmaceutical market in Peru, with an obvious and worrying violation of the legal supply chain.[54] It is necessary to understand why the situation persists, despite the corrective measures in place. All aspects of the problem need to be addressed, from health to economic,[7] legal,[55] technological, social and cultural perspectives, which could lead to more viable, effective and efficient strategies to combat this scourge.[56—60]

The finding of 626 duplicate products/batches during the study period highlights the persistence of counterfeit medicines on the market, and suggests that the impact of the alert system needs to be re-assessed.

A review based only on data from alerts cannot indicate the extent to which counterfeit medicines have penetrated the Peruvian pharmaceutical market, or their typology. Nevertheless, the results of this study give an idea of the magnitude of the problem, and suggest that a rethinking of strategies is required to effectively combat the trade in counterfeit medicines in Peru. Moreover, it is important to recognise that the situation could worsen, as is occurring in many African countries.[61]

CONCLUSIONS

In light of the results, it is clear that the falsification of medicines in Peru is currently a serious public health problem. It cannot be determined from a review based only on the data provided by alerts whether the amount of counterfeit medicines increased in Peru during the study period, or whether the magnitude of the problem was merely highlighted by the increased activity of different public health surveillance bodies. The types of counterfeit medicines found in Peru are characteristic of developing countries. The problem is clearly either structural or due to pharmaceutical policy, since the highest incidence of cases of counterfeit medicines leading to DIGEMID alerts involve legal supply chains. Most cases of counterfeit medicines were found in large cities, and the decentralisation of health management has had a significant impact on inspections. It is necessary to establish systems of analysis and risk management related to the counterfeit medicine trade as part of a regional, national and global plan, in which pharmaceutical alerts form part of the communication process and whose impact should be evaluated. Much work remains to be done to address this serious public health concern, both in Peru and worldwide.

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REFERENCES

1. Organización Panamericana de la Salud—OPS. Combate a la Falsificación de Medicamentos. http://www.paho.org/HQ/index.php?option=com_docman&task=doc_download&gid=20060&Itemid=+&lang=es (accessed 5 Aug 2014).
2. WHO. Programmes—Essential medicines and health products. General information on counterfeit medicines. http://apps.who.int/medicinedocs/en/d/Jh1456e/2.html (accessed 4 Jul 2014).
3. OMS. Medicamentos espurios, de etiquetado engañoso, falsificados o de imitación. Nota descriptiva N°275. Mayo de 2012. http://www.who.int/mediacentre/factsheets/fs275/es/ (accessed 5 Aug 2014).
4. Dégardin K, Roggo Y, Margot P. Understanding and fighting the medicine counterfeit market. *J Pharm Biomed Anal* 2014;87:167–75.

5. World Health Organization. Growing threat from counterfeit medicines. *Bull World Health Organ* 2010;88:247–8.
6. Customs group to fight $200 bln bogus drug industry. http://www.reuters.com/article/2010/06/10/us-customs-drugs-idUSTRE65961U20100610 (accessed 24 Sep 2014).
7. Blackstone EA, Fuhr JP Jr, Pociask S. The health and economic effects of counterfeit drugs. *Am Health Drug Benefits* 2014;7:216–24.
8. The World Bank. Data. Updated Income Classifications. Posted on 07/03/2014. http://data.worldbank.org/news/2015-country-classifications (accessed 12 Aug 2014).
9. Dirección General de Medicamentos, Insumos y Drogas (DIGEMID). Registro Nacional de Establecimientos Farmacéuticos. http://observatorio.digemid.minsa.gob.pe/PortalConsultas/Consultas/ConsultaEstablecimientos.aspx?over=1 (accessed 12 Dec 2015).
10. Víctor Dongo. Simposio: Política de Medicamentos. LEY N.° 29459—ley de los productos farmacéuticos, dispositivos médicos y productos sanitarios. *Rev Peru Med Exp Salud Pública* 2009;26:517–29.
11. Ley No 29459. Ley de los productos farmacéuticos, dispositivos médicos y productos sanitarios, del 26 de noviembre de 2009. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/Ley29459.pdf (accessed 26 Nov 2015).
12. Decreto Supremo No. 033-2014-SA que Modifica el Reglamento de Establecimientos Farmacéuticos aprobado por Decreto Supremo No. 014-2011-SA, modificado por Decreto Supremo No 002-2012-SA. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/Normatividad/2014/DS_014-2014.pdf (accessed 26 Nov 2015).
13. Pullirsch D, Bellemare J, Hackl A, *et al*. Microbiological contamination in counterfeit and unapproved drugs. *BMC Pharmacol Toxicol* 2014;15:34.
14. Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. *Br J Clin Pharmacol* 2014;78:218–43.
15. DECRETO LEGISLATIVO No. 584 del 16 de abril de 1990, Ley de Organización y Funciones del Ministerio de Salud. ftp://ftp.minsa.gob.pe/intranet/leyes/DL-584_LOF-MINSA.pdf (accessed 11 Aug 2014).
16. RESOLUCION DIRECTORAL No. 367–98—DG-DIGEMID del 26 de mayo de 1998. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/Normatividad/RD_367-1998.pdf (accessed 11 Aug 2014).
17. Resolución Directoral No. 082-2015-DIGEMID-DG-MINSA del 09 Junio de 2015. Procedimiento para la Emisión de Alertas DIGEMID. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/Normatividad/2015/RD_082-2015.pdf (accessed 24 Nov 2015).
18. Decreto Supremo No. 014-2011-SA. Reglamento de establecimientos farmacéuticos. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/DS014-2011-MINSA.pdf (accessed 24 Jan 2016).
19. Dirección General de Medicamentos, Insumos y drogas (DIGEMID)—ALERTAS—DIGEMID. http://www.digemid.minsa.gob.pe/Main.asp?Seccion=371 (accessed 6 Jan 2015).
20. WHO Collaborating Centre for Drug Statics Methodology. ATC/DDD Índex 2014. http://www.whocc.no/atc_ddd_index/ (accessed 12 Aug 2014).
21. Dirección General de Medicamentos, Insumos y Drogas (DIGEMID). Registro Sanitario de Productos Farmacéuticos—Base de datos online de productos. http://www.digemid.minsa.gob.pe/indexperudis.ASP?seccion=448 (accessed 6 Jan 2015).
22. ALERTAS-DIGEMID. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/Alertas/2012/ALERTA_27-12.pdf (accessed 24 Aug 2014).
23. National Institute of Statistics and Informatics of Peru. Population in 2000 to 2015. http://proyectos.inei.gob.pe/web/poblacion/ (accessed 26 Nov 2015).
24. Decreto Supremo N° 029-2015-SA. Modifican Reglamento para el Registro, Control y Vigilncia Sanitaria de Productos Farmacéuticos, Dispositivos Médico y Productos Sanitarios. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/Normatividad/2015/DS_029-2015.pdf (accessed 26 Nov 2015).
25. Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). *BMJ Open* 2013;3:pii: e002924.
26. Almuzaini T, Sammons H, Choonara I. Quality of medicines in Canada: a retrospective review of risk communication documents (2005-2013). *BMJ Open* 2014;4:e006088.
27. Instituto de Estadística e Informática—INEI. Condiciones de vida en el Perú Enero—Febrero—Marzo 2014. Informe Técnico No 2—Junio 2014.
28. Chambliss WG, Carroll WA, Kennedy D. Role of the pharmacist in preventing distribution of counterfeit medications. *J Am Pharm Assoc* 2012;52:195–9.
29. Medicamentos espurios, de etiquetado engañoso, falsificados o de imitación. http://www.who.int/mediacentre/factsheets/fs275/es/ (accessed 11 Aug 2014).
30. RESOLUCION MINISTERIAL No 150-99-SA/DM del 26 de marzo de 1999. Dispone que las Direcciones Regionales y Subregionales de Salud asuman las funciones de control y vigilancia de los productos farmacéuticos y afines. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/RESOLUCIONMINISTERIALN150-99-SA_DM.pdf (accessed 12 Oct 2014).
31. RESOLUCION MINISTERIAL N° 573-2003-SA/DM del 27 de mayo de 2003. Aprueba Reglamentos de Organización y Funciones de las Direcciones de Salud y de las Direcciones de Red de Salud. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/RESOLUCIONMINISTERIALN573-03-SA_DM.pdf (accessed 13 Oct 2014).
32. Meza-Cornejo E. Valor terapéutico de los medicamentos más vendidos en el Perú. Acción Internacional para la Salud Oficina de Coordinación América Latina y el Caribe. Lima—Perú 2010.
33. Global Outlook for Medicines Through 2018 Exhibits. http://www.imshealth.com/portal/site/imshealth/menuitem.762a961826aad98f53c753c71ad8c22a/?vgnextoid=6011f106fe3c9410VgnVCM10000076192ca2RCRD (accessed 2 Feb 2014).
34. Kovacs S, Hawes SE, Maley SN. Technologies for detecting falsified and substandard drugs in low and middle-income countries. *PLoS ONE* 2014;9:e90601.
35. Taylor D. RFID in the pharmaceutical industry: addressing counterfeits with technology. *J Med Syst* 2014;38:141.
36. Bansal D, Malla S, Gudala K, *et al*. Anti-counterfeit technologies: a pharmaceutical industry perspective. *Sci Pharm* 2013;81:1–13.
37. Hall C. Technology for combating counterfeit medicine. *Pathog Glob Health* 2012;106:73–6.
38. Bussy U, Thibaudeau C, Thomas F, *et al*. Isotopic finger-printing of active pharmaceutical ingredients by 13C NMR and polarization transfer techniques as a tool to fight against counterfeiting. *Talanta* 2011;85:1909–14.
39. Sacré PY, Deconinck E, Daszykowski M. Impurity fingerprints for the identification of counterfeit medicines--a feasibility study. *Anal Chim Acta* 2011;701:224–31.
40. Nityanand Zadbuke, Sadhana *et al*. Recent trends and future of pharmaceutical packaging technology. *J Pharm Bioallied Sci* 2013;5:98–110.
41. Ranieri N, Tabernero P, Green MD, *et al*. Evaluation of a new handheld instrument for the detection of counterfeit artesunate by visual fluorescence comparison. *Am J Trop Med Hyg* 2014;91:920–4.
42. Koesdjojo MT, Wu Y, Boonloed A, *et al*. Low-cost, high-speed identification of counterfeit antimalarial drugs on paper. *Talanta* 2014;130:122–7.
43. Lebel P, Gagnon J, Furtos A. A rapid, quantitative liquid chromatography-mass spectrometry screening method for 71 active and 11 natural erectile dysfunction ingredients present in potentially adulterated or counterfeit products. *J Chromatogr A* 2014;1343:143–51.
44. Custers D, Canfyn M, Courselle P. Headspace-gas chromatographic fingerprints to discriminate and classify counterfeit medicines. *Talanta* 2014;123:78–88.
45. Anzanello MJ, Ortiz RS, Limbergerb RP, *et al*. A multivariate-based wavenumber selection method for classifying medicines into authentic or counterfeitclasses. *J Pharm Biomed Anal* 2013;83:209–14.
46. McCarthy M. Handheld device for counterfeit drug detection to be tested in Africa. *BMJ* 2013;346:f2732.
47. Deconinck E, Sacré PY, Courselle P. Chromatography in the detection and characterization of illegal pharmaceutical preparations. *J Chromatogr Sci* 2013;51:791–806.
48. Mbinze JK, Lebrun P, Debrus B. Application of an innovative design space optimization strategy to the development of liquid chromatographic methods to combat potentially counterfeit nonsteroidal anti-inflammatory drugs. *J Chromatogr A* 2012;1263:113–24.
49. Debrus B, Lebrun P, Kindenge JM, *et al*. Innovative high-performance liquid chromatography method development for the screening of 19 antimalarial drugs based on a generic approach, using design of experiments, independent component analysis and design space. *J Chromatogr A* 2011;1218:5205–15.

50. Benton D, Williamson L, Stodart K. Buying medicine online is risky business. *Nurs N Z* 2014;20:27.
51. Mackey TK, Liang BA. Pharmaceutical digital marketing and governance: illicit actors and challenges to global patient safety and public health. *Global Health* 2013;9:45.
52. EAE Business School: El Gasto Farmacéutico 2014. http://www.eae.es/news/2014/07/14/el-gasto-farmaceutico-publico-por-habitante-cae-un-7-2-y-se-situa-en-196-52 (accessed 15 Jan 2015).
53. Tremblay M. Medicines counterfeiting is a complex problem: a review of key challenges across the supply chain. *Curr Drug Saf* 2013;8:43–55.
54. OMS. Consejo Ejecutivo 134° reunión (EB134/25) del 3 de enero de 2014. Productos médicos de calidad subestándar, espurios, de etiquetado engañoso, falsificados o de imitación. Informe de la Directora General. http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_29-sp.pdf (accessed 13 Jan 2015).
55. Lai CW, Chan WK. Legislations combating counterfeit drugs in Hong Kong. *Hong Kong Med J* 2013;19:286–93.
56. Gostin LO, Carpenter D, Hogerzeil H, *et al*. IOM (Institute of Medicine). Countering the problem of falsified and substandard drugs. Washington, DC: The National Academies Press, 2013.
57. Mackey TK, Liang BA. Improving global health governance to combat counterfeit medicines: a proposal for a UNODC-WHO-Interpol trilateral mechanism. *BMC Med* 2013;11:233.
58. Weigmann K. Elixirs of death. International organizations are working towards a global solution to address the problem of falsified and substandard medicines, but progress has stagnated. *EMBO Rep* 2013;14:597–600.
59. Seear M. The need for coordinated action against falsified and substandard medicines. *Int J Tuberc Lung Dis* 2013;17:286.
60. Attaran A, Barry D, Basheer S. How to achieve international action on falsified and substandard medicines. *BMJ* 2012;345:e7381.
61. Newton PN, Tabernero P, Dwivedi P. *et al*. Falsified medicines in Africa: all talk, no action. *Lancet Glob Health* 2014;2:e509–10.