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Drug quality analysis through high performance liquid chromatography of isometamidium chloride hydrochloride and diminazene diaceturate purchased from official and unofficial sources in Northern Togo

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ABSTRACT

Trypanocidal drugs remain the most accessible and thus commonly used means of controlling tsetse transmitted animal African trypanosomosis. In Togo, trypanocides are sold on official as well as unofficial markets, but the quality of these trypanocides is undocumented so a drug quality assessment study was conducted from May 2013 to June 2014. Trypanocides supplied by European, Indian and Chinese pharmaceutical companies and sold on official and unofficial markets in Togo were purchased. In total fifty-two trypanocides were obtained, 24 of these samples from official markets and 28 from unofficial markets made up of a total of 36 diminazene diaceturate and 16 isometamidium chloride hydrochloride samples. The samples were analysed in the reference laboratory of the OIE (World Organisation for Animal Health), Laboratory for the Control of Veterinary Medicines (LACOMEV) in Dakar which uses galenic testing and high performance liquid chromatography (HPLC) testing as standard reference analysis methods. The results revealed a high proportion of trypanocides of sub-standard quality on the Togolese market: 40% were non-compliant to these quality reference standards. All of the HPLC non-compliant samples contained lower amounts of active ingredient compared to the concentration specified on the packaging. Non-compliance was higher in samples from the unofficial (53.57%) than from the official markets (25%; $p = 0.04$).The main drug manufacturers, mostly of French origin in the study area, supply quality drugs through the official legal distribution circuit. Products of other origins mostly found on illegal markets present a significantly lower quality.

1. Introduction

Animal African trypanosomosis control is targeting either the vector or the parasite or both, respectively. Despite the existence of ambitious programs in sub-Saharan Africa such as the Pan African Tsetse and Trypanosomosis Eradication Campaign

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(PATTEC) and numerous governmental initiatives in different countries to achieve elimination of the vector, tsetse flies are still omnipresent. *Glossina* spp. are resilient vectors whose populations can restore quickly after control operations cease. Even though many efficient techniques are available for tsetse control, such as traps and targets (Esterhuizen et al., 2011), insecticide treated cattle (Bauer et al., 1995; Vale et al., 1999; Shaw et al., 2015), ground/aerial spraying, and sterile insect technique (Bouyer et al., 2014), elimination or even eradication of tsetse is unlikely to succeed in the near future because such interventions must be tediously planned at a continental scale in order to prevent tsetse re-infestation (Schofield and Kabayo, 2008). This is not possible for small-scale livestock owners in tsetse-infested areas who rely on access to trypanocidal drugs and self-organised or community-based vector control activities to decrease the negative impacts of the disease on livestock production (Affognon et al., 2010; Clausen et al., 2010; Muhanguzi et al., 2015). Ideally, trypanocidal drugs should be limited to use in treating clinical cases but in areas with high cattle densities under tsetse pressure, the restricted use of insecticides applied to the cattle's legs, lower belly, udder and the perianal region offers a much higher cost/benefit ratio (Shaw et al., 2013, 2014, 2015). Despite this and increasing drug resistance, animal trypanosomosis are still largely controlled by using trypanocides (Clausen et al., 2010; Mungube et al., 2012; Shaw et al., 2015).

Three compounds are in use, either diminazene diaceturate (DA) as a curative treatment, or as prophylaxis both isometamidium chloride hydrochloride (ISM) and homidium salts (homidium bromide and homidium chloride ethanoate). However, the use of homidium salts is no longer advisable due to their mutagenic effects (Sutcliffe et al., 2014). Because of their extensive and wide-spread use, resistance to DA and ISM has been increasingly reported in African countries such as Togo (Delespaux et al., 2008; Tchamdja, 2013), and this threatens the sustainability of trypanosomosis prevention and control. The poor quality of these drugs is often cited as contributing to both the development and spread of trypanocidal drug resistance (Geerts et al., 2001; Grace, 2003; Clausen et al., 2010).

Studies conducted in 2003 in Togo and Benin (Teko-Agbo et al., 2003) and in 2007 in Senegal (Walbadet, 2007) showed that a high proportion of trypanocidal drugs circulating in the region were of poor quality. In 2013, the trypanocides DA and ISM accounted for the largest proportion of sales of veterinary medicines in Togo, at 38% of the 1.13 million euros declared in the official market (Kombiagou, 2013). This relatively high value trypanocide market encourages the maintenance of a large unofficial trade network, often operated by untrained people in weekly livestock or food markets, which in turn can lead to poor treatment outcomes if drugs are of sub-standard quality.

Experts agree that the use of sub-standard or counterfeit trypanocides has severe implications for animal health, public health and the local economy (Van Gool and Mattioli, 2009; Sutcliffe et al., 2014). Even though the true proportion of such medicines is difficult to ascertain at a global scale, some research indicates that substandard drugs are being sold in significant numbers, generating a multi-billion dollar industry. The International Federation for Animal Health reports for example that the trade in unregistered and substandard veterinary drugs is worth $400 million annually (Kingsley, 2015). At the same time, a sociological survey conducted in Nigeria states that farmers themselves identified poor quality trypanocides as a negative impact on their livestock (Kingsley, 2015). Industry representatives on the other hand emphasized that the large market for substandard or fake products acted as a major disincentive for the development of new products, whereby the direct damage of sub-standard drugs was held responsible for treatment failure (Kingsley, 2015).

The objectives of this study were thus to assess the quality of trypanocidal drugs sold in official and unofficial markets by different suppliers from different countries and to discuss the results within the framework of the rules and regulations for veterinary pharmaceuticals in Togo.

This study is part of a joint initiative for trypanocidal drug quality control in Africa whose partners include the Global Alliance for Livestock Veterinary Medicines (GALVmed), the Food and Agriculture Organization of United Nations (FAO), the International Federation of Animal Health (IFAH), the International Atomic Energy Agency (IAEA) and the EC-funded Trypanosomosis Rational Chemotherapy program (TRYRAC).

2. Materials and methods

2.1. Study site and period

The study was conducted in Northern Togo in Kara and Savannah regions (Fig. 1), where 71% of the country's livestock production is concentrated (Ministère de l'Agriculture Elevage et Pêche, 2013). Drugs were purchased from two wholesalers and from four veterinary pharmacies, owned and run by veterinarians (official market) as well as from six weekly markets (unofficial). The trypanocidal drugs were collected in May 2013 and analysed at the Laboratory for the Control of Veterinary Medicines (LACOMEV) in Dakar, Senegal from July 2013 until July 2014.

2.2. Purchase of medicines

The protocol for purchasing DA and ISM was developed by LACOMEV, one of the reference laboratories of the World Animal Health Organisation (OIE). The products were purchased from the sellers (official and unofficial) and then sealed in plastic bags identified by a unique ID number. Information about (i) the trade name, (ii) the supplier, (iii) the place and date of manufacture, (iv) the expiry date and finally (v) the place of purchase were recorded on a standardised form.

To ensure sufficient sample quantity for analysis, 5 sachets of 10.5 g and 10 sachets of 1.05 g as well as 5 sachets of 1 g and 10 sachets of 125 mg were purchased for each DA and ISM sample, respectively.

In total, 52 samples (36 of DA and 16 of ISM) representing 25 different trade names were purchased (24 and 28 from the official and unofficial market respectively), and analysed at LACOMEV prior to the expiry date. The distribution of the samples according to active ingredient and marketing channel (official versus unofficial) is provided in Table 1.

2.3. Identification and storage of samples

The samples received at LACOMEV were entered into a Microsoft Access database. Identification codes were assigned to each sample and samples were stored in the sample laboratory where temperature is maintained at 22° +/− 2 °C.

2.4. Quality assessment

Quality was assessed by (i) galenic tests, (ii) identification and (iii) measure of the concentration of the active ingredient. The galenic test included pH measurement, the solubility of ready-made solutions as well as solutions prepared from DA granules or ISM powder according to the manufacturer's recommendations. The pH was measured using a Mettler-Toledo MP 230 pH meter with a pH between 4 and 7 considered as compliant. The solubility of solutions (ready-made or reconstituted) was assessed

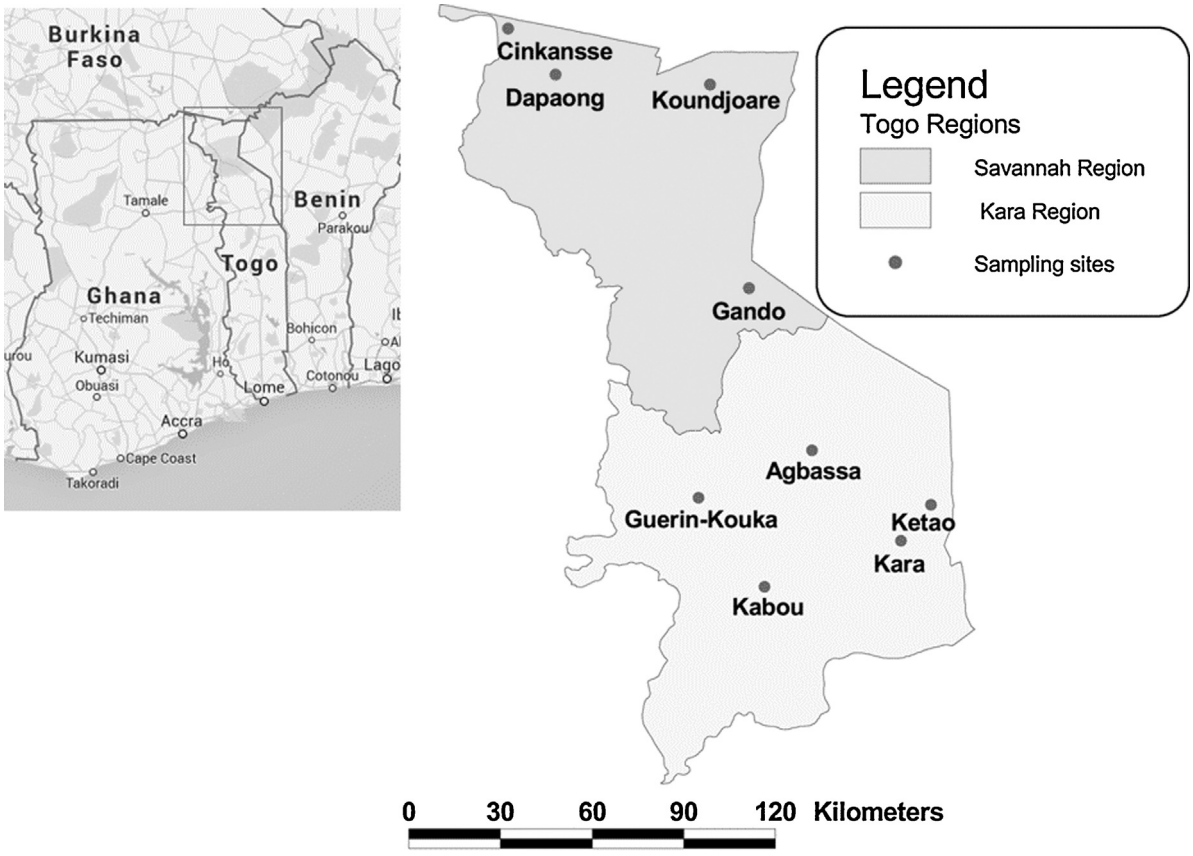
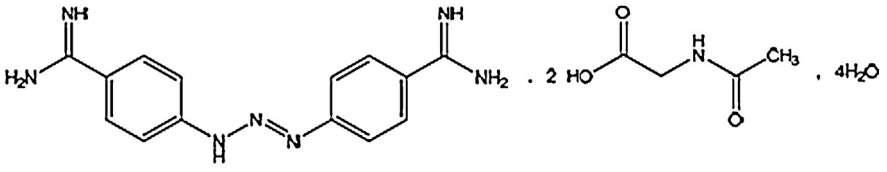


Fig. 1. Sites of purchase of trypanocidal medicines in Northern Togo.

Table 1
Proportion of compliant ISM and DA drugs sampled from official and illegal outlets (number compliant/number tested).

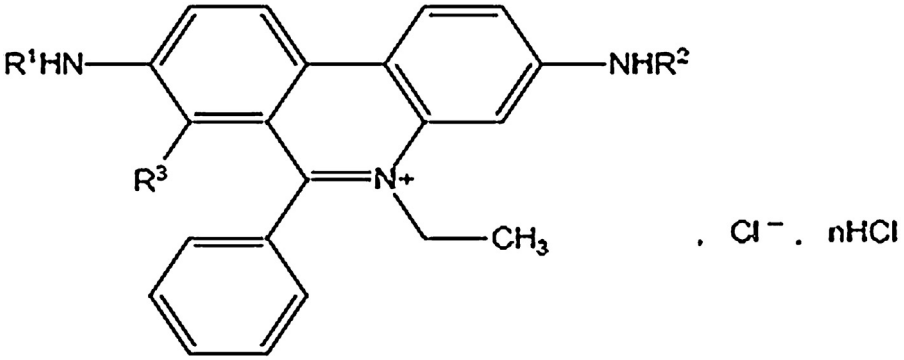
Compound	Official circuit		Open market (unofficial)	Total
	Pharmacy	Wholesaler		
ISM	5/6	3/4	5/6	13/16
DA	4/4	6/10	8/22	18/36
Total	9/10	9/14	13/28	31/52



$C_{14}H_{15}N_7.2C_4H_7NO_3.4H_2O$

Fig. 2. Molecular structure of diminazene diaceturate (Sutcliffe et al., 2014).

visually with the naked eye for the absence of visible solid particles. Identification and concentration of the active ingredient were assessed using high performance liquid chromatography (HPLC) according to the OIE's monograph prepared by GALVmed, FAO and IFAH in collaboration with Manchester Metropolitan University and IAEA (Sutcliffe et al., 2014). The reference substances were provided to LACOMEV by the consortium GALVmed/FAO/IAEA/IFAH. The reference substances for diminazene diaceturate (Fig. 2) and isometamidium chloride hydrochloride (Fig. 3) (Igoli et al., 2014; Sutcliffe et al., 2014) were manufactured by VETOQUINOL and CEVA, respectively. For DA, a measured concentration within ±10% of the manufacturer's label claim was considered as compliant according to the threshold applied by LACOMEV (Tettey et al., 2002). For ISM, the following criteria according OIE monograph were used: (i) presence of the four isomers (I, II, III, IV), (ii) a proportion of isomer I (principal component) equal to or greater than 55%, (iii) a proportion of isomers II, III and IV was equal to or less than 40% and (iv) a proportion of the four isomers between 95–102%.



	R¹	R²	R³	n
I	X	H	H	1
II	H	X	H	1
III	H	H	X	1
IV	X	X	H	2

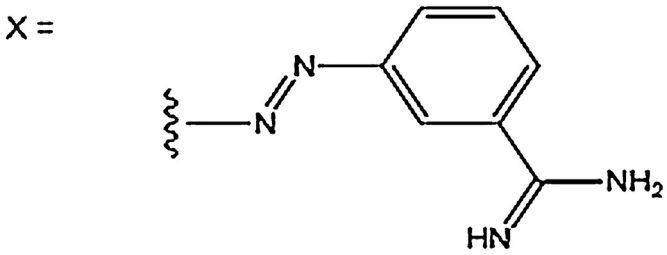


Fig. 3. Molecular structure of isometamidium chloride hydrochloride (Sutcliffe et al., 2014).

Pharmaceutical companies of the purchased test samples have been anonymised. Full details about the HPLC method i.e. specificity, robustness, precision, linearity as well as the limit of detection and quantification were described by Atsriku et al. (2002).

2.5. Data analysis

First, the binary compliance data was analysed in a logistic regression using drug (DA or ISM), circuit (official or not) and the interaction between the two as explanatory variables. To investigate the causes of the lack of compliance, the proportion of compliant samples and exact 95% confidence intervals were calculated for the main manufacturers individually and for the grouped smaller manufacturers (manufacturers with 1 or 2 samples only). Finally, a backward stepwise logistic regression with origin (French, European or Asian), drug (ISM and DA) and circuit (official or not) or seller (veterinary pharmacies, wholesalers or unofficial as open markets) as explanatory variables was used to evaluate their respective statistical significance.

3. Results

Only two samples, diminazene diaceturate samples, were non-compliant, based on the galenic test. HPLC analysis showed that all of the non-compliant trypanocides contained insufficient active ingredient. The proportions of compliant samples according to galenic testing, identification of the active ingredients and determination of their concentration are presented in Table 1. The results showed that overall 40% were non-compliant; 50% for DA and 19% for ISM. In the official circuit, 25% of the samples were found non-compliant, whereas 54% of the drugs from illegal markets were non-compliant. The logistic regression using the drug (ISM or DA), the distribution circuit (official or unofficial) and the interaction between the two revealed no statistical effect of the drug (Fig. 4). Using the distribution circuits (official or not) as only explanatory variable, it appeared that a significant higher proportion of drugs distributed in unofficial markets were non-compliant ($p = 0.04$). This is particularly true for DA (64% vs 19% in official circuit; $p = 0.05$).

The 52 samples were produced by a total of 16 manufacturers. Most samples were produced by five of them (4–10 samples from each) whereas 14 samples were produced by 11 other companies. Fig. 5 displays the proportions of non-compliant samples for the main manufacturers and the 95% confidence intervals.

Most of the brands of the 52 samples were supplied by French companies (32). Other countries of origin included India (11), Holland (2), Belgium (2), Spain (2), UK (2) and China (1). For further analysis, samples were grouped as French samples (32), samples of other origin (8) or Asian samples (12). In a backward stepwise logis-

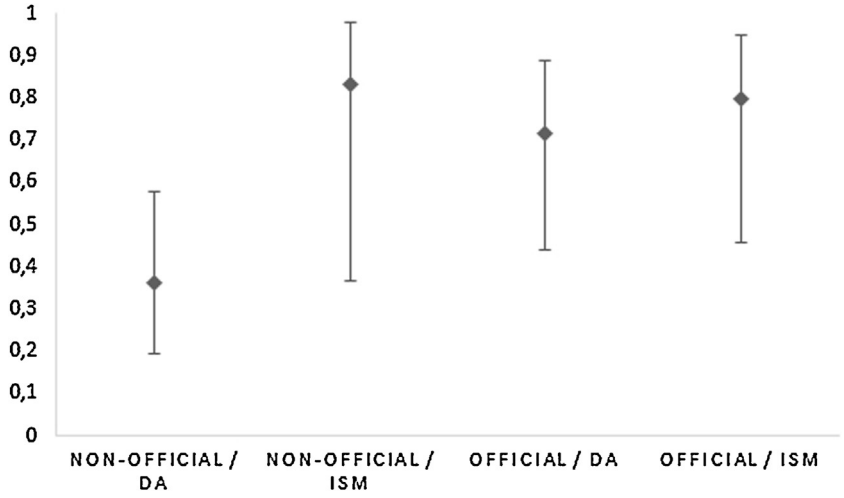


Fig. 4. Proportion of compliant samples in function of the drug (ISM or DA) and the distribution circuit (official or not) with 95% confidence intervals.

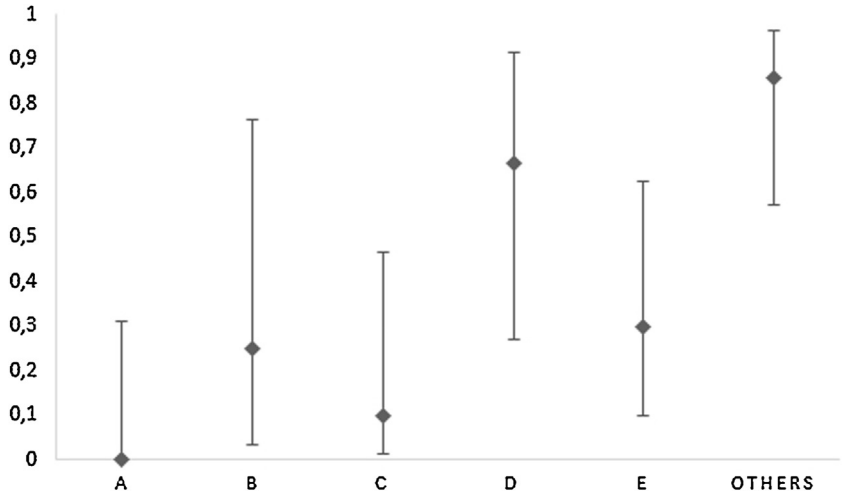


Fig. 5. Proportion of non-compliant drugs by manufacturer with 95% confidence intervals With A, B, C, D and E as anonymised pharmaceutical companies; others as grouped pharmaceutical companies.

tic regression using origin (French, European or Asian), drug (ISM and DA) and circuit (official or not) or seller (veterinary pharmacy, wholesaler or unofficial) as explanatory variables, France was the only significant variable with $p < 0.1$ ($p < 0.001$; $p = 0.001$ for DA on its own). A total of 82% of the French samples met the quality standards (95% CI: 57–94%) while 13% (95% CI: 2–54%) and 27% (95% CI: 9–59%) of other European and Asian samples were compliant, respectively.

Collinearity was observed between countries of origin and distribution circuits (Table 2). Whereas French and Asian drugs are distributed in equivalent quantities through unofficial channels (44 and 50% respectively), drugs of European origin other than French were only found in open markets (unofficial circuit).

3.1. Non-compliance at different thresholds

The proportions of non-compliant samples were computed using different thresholds of percentage deviance from stated amounts of active ingredients. Increasing thresholds of +/−5, 10, 15 and 20% gave non-compliance results of 46; 40; 19 and 10% respectively.

4. Discussion

4.1. Overall results and study limitations

Quality assessment of trypanocides is a prerequisite to ensure good quality drugs for the management of trypanosomoses and the prevention of drug resistance (Clausen et al., 2010). This study focused on the identification of the active ingredients, the determination of their concentration, galenic testing of solubility and pH testing of the reconstituted solutions but the assessment of contaminants, impurities and/or degradation products was not performed. However, since this study did not verify the authenticity of samples, as LACOMEV did not have samples of packaging from pharmaceutical companies for comparison, the place of manufacture and the name of the supplier were simply recorded from the packaging.

Results for non-compliance depended on the threshold that is used. The threshold recommended by OIE for DA is +/−5% (Sutcliffe et al., 2014). However, for purposes of comparison with previous studies conducted by LACOMEV we used the threshold of +/−10%. This threshold is the current standard applied by LACOMEV and is based on studies of Tettey et al. (2002). In this work the rate of non-compliance for the tested 52 samples was 40% using the threshold

Table 2
Proportion of compliant ISM and DA drugs according to regions of origin (number compliant/number tested).

Origin	Official circuit		Open market (unofficial)	Total
	Pharmacy	Wholesaler		
France	9/10	7/8	11/14	27/32
Europe	0/0	0/0	1/8	1/8
Asia	0/0	2/6	1/6	3/12
Total	9/10	9/14	13/28	31/52

of +/−10%. Obviously, this rate would increase to 46% if the OIE threshold of +/−5% had been used. Thresholds of +/−20%, classified as extremely deviating by the World Health Organization in a study on anti-malarial medicine (World Health Organization, 2011) would have resulted in this case of an only 10% non-compliance.

The rate of non-compliant trypanocides of 40% in this study is well below the detected 71% in Ivory Coast (Assoumy et al., 2010), 100% in Cameroon (Teko-Agbo et al., 2009) and 70% in Senegal (Akoda et al., 2008). However, it is equivalent to the level of 42% which was observed in Burkina Faso by Teko-Agbo et al. (2011). This study provides information about the quality of trypanocidal drugs available to farmers in Togo but it is not really possible to link non-compliance to the quality of the original product or to poor conditions of storage leading to a chemical degradation. All of the trypanocides that qualified as non-compliant by HPLC analysis contained less active ingredient than indicated. The result is particularly concerning in a country where resistance to DA and ISM has been detected (Tchamdja, 2013) and where the development of resistance is very likely being linked to under-dosing (Grace, 2003).

4.2. Non-compliance according to active ingredient

In total, DA samples showed greater non-compliance (50%) than ISM samples (19%). This high proportion of non-compliance for DA could be explained by the fact that the molecule is easier to synthesize, has a larger market and is therefore produced by several companies. This explains the wide range of sources for products containing DA compared to ISM which in turn increases the probability of poor quality and even falsification.

4.3. Non-compliance related to the marketing channel

Surprisingly, non-compliant trypanocides in Togo were found in both the official (25%) and unofficial markets (54%). The same observations have been made in studies in Burkina Faso (42%/43%) Cameroon (100%/100%), Ivory Coast (46%/30%) and Senegal (60%/80%) for the official and unofficial markets, respectively (Akoda et al., 2008; Assoumy et al., 2010; Teko-Agbo et al., 2011,2009). It is unlikely that the 54% of non-compliance observed within the unofficial market is solely due to poor conditions of storage, transport and/or handling. This situation is more likely to be linked to the source of supply and to a lack of quality control during manufacture. In addition to the poor quality of trypanocides, these medicines are often administered by untrained livestock keepers who may not accurately measure the weight of their cattle when treating and will thus fail to administer correct dosages as described Grace et al. (2008). Prices of trypanocides sold on unofficial markets are considerably lower than those from the official sector which may encourage livestock keepers to buy these products. The problem is complicated by the fact that people who illegally practice veterinary medicine often act as trypanocide wholesalers bringing even more confusion about what is official and what is not (Pissang and Faye, 2012; Hoppenheit et al., 2014). This results in reduced drug efficacy, poor treatment outcomes, increased drug resistance and thereby negatively impact the livestock economy in Togo.

4.4. Non-compliance according to supplier's company and country

When looking at the results for compliance assorted by places of origin of the supplier, products from Asian companies were significantly more likely to be non-compliant (75%) compared to those from France (14%). For both countries, the proportions of samples collected from the unofficial and official sectors were similar (50 and 44% unofficial from Asia and France respectively). Trypanocides supplied by other companies (Holland, Belgium, Spain, UK and China) were all found and purchased from the unofficial market and were mostly non-compliant.

Comparable results were demonstrated in a study of anti-malarial medicine in six African countries. Among products that were imported from China, India, Vietnam and Bangladesh, the rates of non-compliance were 24, 33, 50 and 100% respectively compared to 2% in medicines that were imported from South Africa and the United States (World Health Organization, 2011). All of the brand names were anonymised in this study but the respective companies will be contacted individually to inform them about the outcomes of these quality tests.

4.5. Non-compliant medicines and veterinary pharmaceutical legislations in Togo

Togo has established a legal framework to resolve the problem of unregulated trade in veterinary medicines, including trypanocides: a law, a decree and two orders dictate the importation and supply of veterinary medicines (Ministère de l'Agriculture Elevage et Pêche, 1998, 2005, 2010, 2012). It is essential to effectively implement these rules and to raise awareness among the principal stakeholders of the official and unofficial trade of veterinary medicines in order to combat the high prevalence of poor quality trypanocides in Togo. It will be necessary to thoroughly control unofficial trade and to enforce the quality control of suppliers, ensuring that the trypanocides imported into Togo meet quality standards to obtain a marketing authorisation from the West African Economic and Monetary Union (UEMOA). Among the 25 analysed trypanocide brands, only five possessed a legal marketing authorisation allowing their sale in Togo and in the UEMOA, all of which were manufactured in France (UEMOA, 2012a, 2012b, 2012c, 2013a, 2013b). All five legally marketed brands were compliant.

It is the responsibility of the relevant authorities in collaboration with the National Association of Veterinarians in Togo to apply the legal framework for veterinary pharmaceuticals in order to reduce illegal trade of poor quality veterinary medicines in Togo because trypanocides of good quality are a prerequisite to control animal African trypanosomosis and minimise the emergence of drug resistance (Clausen et al., 2010).

Registered veterinarians in Togo are mostly situated in the south of the country which is the administrative centre, whereas the cattle population is concentrated in the northern regions (Pissang and Faye, 2012; Hoppenheit et al., 2014). Thus, small-scale farmers are often struggling to receive state of the art veterinary care for their animals which makes them vulnerable to purchases of low priced and poor quality products on the unofficial market. Only if

the existing laws of Togo are enforced in the northern region, with for instance the support of yet to be legalised animal health workers, will a reduction in poor quality trypanocides in this market be addressed.

5. Conclusions

The main drug manufacturers, mostly of French origin in the study area, supply quality drugs through a legal distribution circuit. Products of other origins mostly found on illegal markets present a significantly lower quality. The results of this study on the quality of trypanocides demonstrate a high proportion of non-compliant products used for the treatment of animal African trypanosomosis. This non-compliance compromises the efficacy of the treatment as well as boosts the development of drug resistance, which is already suspected to exist in Togo (Tchamdja, 2013). The first step to the solution to this problem will be the enforcement of national and sub-regional laws (UEMOA) on the quality control, importation, supply and utilisation of veterinary medicines. Furthermore, high quality veterinary products should not be in competition with products of unknown or sub-standard quality. Low priced products will always be more attractive to cattle breeders with limited financial resources but no way of reliably testing for quality and effectiveness. This is why it is of utter importance to ensure a legal framework that is enforced, quality controlled and supported by skilled veterinary personal at the field level in order to practice and communicate state of the art veterinary care where it is needed most.

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