RESEARCH ARTICLE

Serious adverse reactions associated with ivermectin: A systematic pharmacovigilance study in sub-Saharan Africa and in the rest of the World

Jérémie T. Campillo1,2*, Michel Boussinesq1, Sébastien Bertout1,3, Jean-Luc Faillie2,4, Cédric B. Chesnais1☯

1 TransVIHMI, Université Montpellier, Institut de Recherche pour le Développement (IRD), INSERM, Montpellier, France, 2 Department of medical pharmacology and toxicology, CHU Montpellier, Montpellier, France, 3 Laboratoire de Parasitologie et Mycologie Médicale, Université de Montpellier, Montpellier, France, 4 EA 2415, IDESP, University of Montpellier, Montpellier, France

☯ These authors contributed equally to this work.
* jeremy.campillo@ird.fr

Abstract

Background

Ivermectin is known to cause severe encephalopathies in subjects infected with loiasis, an endemic parasite in Sub-Saharan Africa (SSA). In addition, case reports have described ivermectin-related serious adverse drug reactions (sADRs) such as toxidermias, hepatic and renal disorders. The aim of this study was to identify suspected sADRs reported after ivermectin administration in VigiBase, the World Health Organization’s global individual case safety reports database and analyze their frequency relative to the frequency of these events after other antinematodal drugs reported in SSA and other areas of the world (ROW).

Methods

All antinematodal-related sADRs were extracted from VigiBase. Disproportionality analyses were conducted to investigate nervous, cutaneous, psychiatric, respiratory, renal, hepatic and cardiac suspected sADRs reported after ivermectin administration in VigiBase, the World Health Organization’s global individual case safety reports database and analyze their frequency relative to the frequency of these events after other antinematodal drugs reported in SSA and other areas of the world (ROW).

Principal findings

2041 post-ivermectin or post-benzimidazole suspected sADRs were identified including 667 after ivermectin exposure (208 in SSA and 459 in the RoW). We found an increased reporting for toxidermias, encephalopathies, confusional disorders after ivermectin compared to benzimidazole drug administration. Encephalopathies were not only reported from SSA but also from the RoW (adjusted reporting odds ratios [aROR] 6.30, 95% confidence interval: 2.68–14.8), highlighting the fact these types of sADR occur outside loiasis endemic regions.
Conclusion
We described for the first time suspected sADRs associated with ivermectin exposure according to geographical origin. While our results do not put in question ivermectin’s excellent safety profile, they show that as for all drugs, appropriate pharmacovigilance for adverse reactions is indicated.

Author summary
Ivermectin is a drug used worldwide for various indications: onchocerciasis, lymphatic filariasis, strongyloidiasis, human sarcoptic scabies, acarodermatitis and rosacea. In the early 1990s, it was discovered that ivermectin could induce severe encephalopathies in some patients with high parasite loads of *Loa loa*, a filarial nematode. This objective of this pharmacovigilance study is to summarize serious neurological and non-neurological post-ivermectin adverse drug reactions reported in the World Health Organization database called VigiBase. This study shows that reported serious adverse drug reactions associated with ivermectin are fairly consistent with those mentioned in the official product information of ivermectin but also provides some new signals. Serious post-ivermectin encephalopathies can also occur outside of *Loa loa* endemic regions but the understanding of the mechanism by which it occurs requires further studies. A new signal concerning two serious toxidermias (DRESS syndrome and acute generalized exanthematous pustulosis) is also described. A lack of reporting of adverse drug reactions is noticeable in some Sub-Saharan African countries, and actions are needed to increase the reporting rates of these adverse effects in these countries.

Introduction
Ivermectin is included in the World Health Organization (WHO) list of essential medicines and is commonly used worldwide. Stromectol (ivermectin 3 mg) and its generics (Arrow Lab, Biogaran, Gerda, Mylan, Pierre Fabre, Sandoz, Zentiva) are mainly distributed in Europe and North America. In Europe, ivermectin is labeled for the treatment of strongyloidiasis, diagnosed or suspected infection with *Wuchereria bancrofti* (the filarial nematode causing lymphatic filariasis) or *O. volvulus* (the filarial nematode causing onchocerciasis), and human sarcoptic scabies. In North America, ivermectin is labeled for the treatment of strongyloidiasis and onchocerciasis. Ivermectin is also used off-label in certain cases of acarodermatitis (skin inflammation due to bites of parasitic mites), rosacea and loiasis (the disease caused by the filarial nematode *Loa loa*) [1,2]. In African countries, ivermectin is distributed at single oral doses of 150–200 μg/kg as part of onchocerciasis and lymphatic filariasis elimination programs (the drug, registered under the name of Mectizan for these indications, is donated by Merck & Co., Inc.). It is used as preventive chemotherapy, i.e. distributed annually (sometimes biannually) using a mass drug administration strategy, i.e. to the entire eligible population of the target communities without individual diagnosis.

Ivermectin is a derivative of avermectins. It acts mainly by binding to the glutamate-dependent chloride channels of invertebrate nerve and muscle cells, causing an increase in membrane permeability leading ultimately to neuromuscular paralysis and death of certain parasites. In subjects with high densities of microfilariae (mf, the larval stages of the filarial
parasites) in the skin or the blood, ivermectin is able to induce complex inflammatory reac-
tions called Mazzotti reactions which include pruritus, rash, fever, malaise, lymphadenopathy, 
arthralgia, tachycardia, hypotension, edema and abdominal pain [3,4]. These reactions reflect 
the inflammatory phenomena associated with the destruction of mf by the drug. Since the 
early 1990, ivermectin has been known to cause potentially fatal encephalopathies in individu-
als with very high microfilarial density of L. loa in the blood (loiasis is endemic only in Central 
Africa) [5,6], also referred to as “Possible/Probable L. loa encephalopathy temporally related to 
Mectizan” (PLERM). PLERM can occur in subjects with L. loa microfilarial density >10,000 
ml/mL if measured before treatment or >1,000 mf/mL if measured after treatment [7]. Since 
then, few studies have been conducted to investigate the frequency of these Loa-related adverse 
drug reactions (ADR) and the mechanisms by which they occur [8].

In 2017, an analysis of the WHO Global individual case safety report (ICSR) database (Vigi-
Base) for serious neurological adverse events was conducted [9]. The search identified 52 iver-
mectin-related ICSRs entered into VigiBase by the pharmacovigilance system of the 
Democratic Republic of the Congo (DRC) between 2009 and 2013. All patients had central 
and peripheral nervous system disorders. The mean L. loa microfilarial density measured after 
treatment in these patients was 2149.1 mf/mL, and 61% of them had microfilarial density 
below 1000 mf/mL, suggesting the possible occurrence of PLERM at low microfilarial density. 
Another search of the VigiBase was conducted in 2016 to identify serious neurological adverse 
events other than PLERM after ivermectin administration. The authors found 28 cases of sus-
ppected neurological serious ADRs (sADRs) following ivermectin treatment for diseases other 
than onchocerciasis (10 for scabies, 8 for acarodermatitis, 3 for strongyloidiasis, 5 for lym-
phatic filariasis, 1 for myiasis and 1 for taeniasis) [10]. This study raised questions about the 
mechanisms underlying the appearance of these neurological effects. To our knowledge, these 
studies are the only two that have used a pharmacovigilance database to evaluate the occur-
rence of post-ivermectin ADRs and they have focused exclusively on neurological events.

Our systematic search of the literature for non-neurological adverse events found 10 cases 
where ivermectin was associated with cutaneous reactions [11–15], nephropathy [16], psychi-
atric disorders [17,18], hepatic disorders [19,20] and multiorgan dysfunction syndrome [21]. 
Clinical trials and observational studies have reported common adverse events such as head-
ache, pruritus, muscle pain, cough, dyspnea, nausea, vomiting, diarrhea, blurred vision, pos-
tural hypotension and confusion and more anecdotal effects such as serious skin reactions and 
edematous swelling [22–24].

In the present study, we searched VigiBase for all the suspected sADRs (not only the neuro-
logical ones) reported after ivermectin treatment and after treatment with other antinematodal 
drugs and conducted disproportionality analyses considering the geographical origin of the 
reported cases. More specifically, the aims of this study were to identify (i) possible non-neuro-
logical pharmacovigilance signals (increased reporting of serious suspected adverse reactions 
after treatment with ivermectin compared to treatment with other antinematodal drugs), and 
(ii) possible neurological signals related to indications other than onchocerciasis.

Methodology

Data source

Data were extracted from the WHO Global Individual Case Safety Report (ICSR) database, 
VigiBase [25] which includes more than 20 million cases of suspected ADRs reported by 
national pharmacovigilance centers in more than 130 countries participating in the WHO Pro-
gram for International Drug Monitoring [26]. An ICSR is an anonymized report for a single 
individual who experienced adverse event(s) that may be linked to the use of one or more
drugs. ICSR contains sociodemographic information (age, sex, reporter qualification, country of origin, year of report), information about the drug administration (frequency, dosage, co-medication) and information about the reported adverse event. The latter include the seriousness according to the criteria of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [27], adverse event verbatim description and associated terms from the Medical Dictionary for Regulatory Activities (MedDRA) developed by the ICH. All reports of suspected sADRs associated with antinematodal drugs (Anatomical Therapeutic Chemical [ATC] code P02C) from December 2003 (first ever report of ivermectin-associated suspected sADR recorded) up to July 15, 2020 were extracted. Antinematodal drugs included ivermectin, benzimidazole drugs (mebendazole, tiabendazole, albendazole, ciclobendazole, flubendazole, fenbendazole), levamisole, pyrantel, piperezine, diethylcarbamazine, and pyrvinium. Prior to analysis, suspected duplicate reports identified by an automated screening were excluded [28]. When ivermectin had been administered in combination with a benzimidazole or another antinematodal drug, the report was excluded from the analysis. Suspected sADRs were classified following the MedDRA [29], grouped at the System Organ Class (SOC) level and at the individual preferred term (PT) level.

Study design

We performed disproportionality analyses using the case/non-case method which allows to identify disproportionate reporting, i.e., a higher than expected number of adverse reaction reports compared to other reactions recorded in the database by calculating Reporting Odds Ratios (ROR). ROR compares the odds of exposure to ivermectin between cases and non-cases [30,31].

Cases were defined as reports of each suspected sADR of interest identified by a MedDRA PT for severe headache, encephalopathies, confusional disorders, seizures, toxidermias (drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis), psychiatric disorders, suicidal behavior, severe acute respiratory syndrome (SARS), renal disorders, hepatic disorders, cardiac failure, rhythm disorders and Mazzotti reaction. For specific syndromes of interest, we mapped the PTs for the most common symptoms to one variable and used that in the analyses instead of the individual PTs (Table 1).

Non-cases were defined as reports of any other suspected sADR occurring after administration of the same drug.

Exposure definition

Exposure to ivermectin was identified in the ICSR by the use of ivermectin (ATC code P02CF01) preceding the onset of the serious adverse reaction. Only oral administration of ivermectin was included (topical formulations were excluded).

Statistical analysis

Descriptive statistics were used to summarize the basic characteristics according to the origin of the ICSR: sub-Saharan Africa (SSA) or the rest of the world (RoW).

Among all suspected sADR reports associated with antinematodal drugs, our primary analyses consisted in calculating the ROR of each suspected sADR of interest (and corresponding 95% confidence interval [95% CI]) for ivermectin compared to benzimidazole drugs using logistic regression models adjusted for age groups, date of the ICSR publication, and origin of the notification (SSA or RoW). The latter can additionally be used as a proxy for ivermectin indication since >99% of subjects with onchocerciasis live in SSA, and ivermectin is usually
not used for lymphatic filariasis control/elimination outside SSA. To explore a potential effect modification by origin, we performed secondary analyses with stratification according to the origin of the notification (SSA and RoW).

Sensitivity analyses were performed using all antinematodal drugs (including benzimidazoles) as the control group instead of benzimidazoles alone and using the same statistical methods.

Table 1. Mapping of the PTs for the most common symptoms of syndrome of interest to a new variable.

| New variable                      | Algorithm                                                                 |
|-----------------------------------|---------------------------------------------------------------------------|
| Encephalopathies                  | At least one of the following PTs                                         |
|                                   | - Confusion                                                               |
|                                   | - Aphasia                                                                 |
|                                   | - Loss of consciousness                                                  |
|                                   | - Coma                                                                    |
| Confusional disorders             | At least one of the following PTs                                         |
|                                   | - Confusion                                                               |
|                                   | - Agitation                                                               |
|                                   | - Disorientation                                                         |
| Toxidermias                       | At least one of the following PTs                                         |
|                                   | - Drug reaction with eosinophilia and systemic symptoms syndrome         |
|                                   | - Stevens-Johnson syndrome                                               |
|                                   | - Toxic epidermal necrolysis                                              |
|                                   | - Acute generalized exanthematous pustulosis                             |
| Psychiatric disorders             | At least one of the following PTs                                         |
|                                   | - Delusion                                                                |
|                                   | - Hallucination                                                           |
|                                   | - Delirium                                                                |
|                                   | - Depersonalization                                                       |
|                                   | - Derealization                                                           |
| Renal disorders                   | At least one of the following PTs                                         |
|                                   | - Renal failure                                                           |
|                                   | - Renal impairment                                                        |
|                                   | - Renal pain                                                              |
|                                   | - Renal injury                                                            |
| Hepatic disorders                 | At least one of the following PTs                                         |
|                                   | - Hepatitis                                                               |
|                                   | - Hepatic failure                                                         |
|                                   | - Hepatocellular injury                                                   |
|                                   | - Jaundice                                                                |
|                                   | - Liver injury                                                            |
|                                   | - Hepatic function abnormal                                               |
| Mazzotti reaction                 | At least two of the following PTs                                         |
|                                   | - Headache                                                                |
|                                   | - Asthenia or Fatigue                                                     |
|                                   | - Pyrexia or Chills                                                       |
|                                   | - Arthralgia or Myalgia                                                   |
|                                   | - Edema or Swelling                                                       |

https://doi.org/10.1371/journal.pntd.0009354.t001
For all analyses, the p-values in the Tables are indicated by asterisks: ***: p<0.01; **: p≥0.01 to <0.05; *: p≥0.05 to <0.10. For all analyses, "N/A" means that the category is not available or non-applicable.

Analyses were conducted using STATA v.15.1 software (StatCorps, LP, College Station, TX, USA). Maps were created using the mapCountryData package from R statistical software v. 3.5.0.

Results

Descriptive analysis of the sADRs reported after treatment with ivermectin

After elimination of duplicates, 2041 suspected sADRs occurring after administration of antihelminthic agents were reported between December 2003 and July 2020, of which 209 (10.2%) resulted in death. A total of 667 suspected sADRs were reported after ivermectin administration: 208 cases in SSA and 459 in the RoW. Table 2 shows the distribution of cases between SSA and RoW by age, gender, who reported the case, brand name, fatality, reporting period, and indication.

Most cases concerned people aged 18–44 years old (43.7%) and were reported by healthcare professionals (90.0%). Mean age (44.7 ± 22.9 years for all cases) was significantly lower for SSA (32.3 ± 14.6 years) than for RoW cases (51.1 ± 23.8 years). Sex distribution was also significantly different between SSA cases (female: male ratio 1:1.96) and RoW cases (1:1). Stromectol, the most frequently brand name reported in the RoW (62.0%), was not reported at all in SSA. Suspected sADRs were more frequently fatal in the RoW (67 deaths; 14.6%) than in SSA (9 deaths; 4.3%). Onchocerciasis was the most frequently reported indication for ivermectin use and this was particularly the case in SSA. Scabies was the second most frequently reported indication for ivermectin use, all cases being from the RoW (96; 28.0%). The reported SOC are presented in Table 3, the three most reported SOC were "General disorders and administration site conditions" (44.4%), "Nervous system disorders" (31.3%) and "Skin and subcutaneous tissue disorders" (30.4%).

The three countries that reported the highest number of cases were the United States of America (152 ICRS, 22.8%), France (151, 22.6%) and the DRC (115, 17.2%). Distributions by country for the 6 most frequently reported SOC (excluding the SOC "Infections and Infestations" and "Injury, poisoning and procedural complications" for which a causal relationship to drug administration is extremely unlikely) are presented across the world in Fig 1 and across Africa and Europe in Figs 2 and 3, respectively.

The most frequently reported suspected sADRs are presented by SOC in S1A, S1B and S1C Table. The ten most frequently reported suspected sADRs of interest are reported in Table 4.

The syndromes of interest which occurred after ivermectin intake and described in Table 1 are reported in Table 5.

Ivermectin indications for the 23 serious encephalopathies which occurred outside SSA were scabies (8), acarodermatitis (4), strongyloidiasis (4), rosacea (1), onchocerciasis (1) and unknown indications (5). Ivermectin indications for the 32 serious encephalopathies which occurred in SSA were onchocerciasis (30), unspecified filariasis (1) and unknown (1). Indications for ivermectin treatment in cases of serious toxidermia were scabies (9), unknown (12), strongyloidiasis (3), lice (3), acarodermatitis (2), cysticercosis (1), onchocerciasis (1), unspecified filariasis (1) and in one case ivermectin had been administered erroneously. Ivermectin indications for cases of serious Mazzotti reactions were onchocerciasis (28), lice (3), parasitosis (1), strongyloidiasis (1), worms (1), filariasis (1) and not reported (7).
Disproportionality analysis

The results of the disproportionality analyses of sADRs of interest as well as non-cases after administration of ivermectin compared to benzimidazole drugs are presented in Table 6. After
adjustment, the relative frequency of serious headaches reported after treatment with ivermectin and with benzimidazole drugs was similar (adjusted ROR [aROR]: 1.22, 95% CI: 0.83–1.78). This was also the case in origin-stratified analysis (aROR: 1.16, 95% CI: 0.68–1.98 and aROR: 1.39, 95% CI: 0.76–2.53 in SSA and RoW, respectively). In contrast, serious encephalopathies were much more frequently reported after ivermectin than benzimidazole treatment, globally (aROR: 9.23, 95% CI: 4.56–18.61), in SSA countries (aROR: 27.1, 95% CI: 6.34–116.1) and in the RoW (aROR: 6.30, 95% CI: 2.68–14.8). Reports of confusional disorders were strongly associated with ivermectin use globally (aROR: 4.05, 95% CI: 1.81–9.09), in the RoW (aROR: 3.66, 95% CI: 1.49–8.87) but not in SSA (aROR: 3.87, 95% CI: 0.76–19.6). Serious seizures were not more frequently reported after ivermectin than after benzimidazole drugs (aROR: 0.49, 95% CI: 0.49–0.97).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was more frequently reported with ivermectin than with benzimidazole drugs (aROR: 8.59, 95% CI: 1.85–39.9). No adjustments were possible for the analysis of DRESS because of the low number of cases. Serious toxidermias (DRESS, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis) were more frequently reported with ivermectin than with benzimidazole drugs globally (aROR: 4.43, 95% CI: 2.07–9.47) and in the RoW (aROR: 6.05, 95% CI: 2.76–13.3), but not in SSA countries (aROR: 0.52, 95% CI: 0.05–5.01). It is
noticeable that eight cases of toxidermia were excluded from the analyses because ivermectin was co-administered with albendazole.

Serious psychotic disorders and suicidal disorders were not more frequently reported with ivermectin than with benzimidazole drugs (aROR: 1.78, 95% CI: 0.70–4.53 and aROR: 7.67, 95% CI: 0.85–69.0, respectively).

Only 5 cases of Severe Acute Respiratory Syndrome (SARS) were reported, and no significant associations were found. aROR values did not indicate any associations for serious hepatic disorders or serious renal disorders either (aROR: 0.51, 95% CI: 0.36–0.74 and aROR: 1.36, 95% CI: 0.66–2.85, respectively).

Serious cardiac failures were significantly associated with ivermectin compared to benzimidazole drug intake (ROR: 11.4, 95% CI: 1.37–94.9, no adjustment possible). Serious rhythm disorders were not found to be associated with ivermectin compared to benzimidazole drugs.

Finally, serious Mazzotti reactions were strongly associated with ivermectin compared to benzimidazole drugs both in SSA (aROR: 1.95, 95% CI: 1.09–3.52) and in the RoW (aROR: 19.7, 95% CI: 2.20–175.5).

**Sensitivity analyses**

Disproportionality analyses were repeated with all antinematodal drugs rather than only benzimidazole drugs as control group (S2 Table). Associations for reports of serious headache in RoW (aROR: 1.82, 95% CI: 1.01–3.28) and serious rhythm disorders in RoW (aROR: 3.45, 95% CI: 1.02–11.7) were strengthened in these sensitivity analyses. No changes were found for encephalopathies, confusional disorders, DRESS, toxidermias, seizures, renal disorders, suicidal disorders, psychiatric disorders, SARS, hepatic disorders and Mazzotti reactions. In
contrast to the primary analysis, the sensitivity analysis identified no association for cardiac failures.

**Discussion**

Our study used a case-non-case approach to assess the association between the use of ivermectin and the reporting of neurological as well as non-neurological suspected sADRs, recorded in the WHO drug adverse events database from 2003 to 2020 (see S3 Table for STROBE checklist of case-control studies). To our knowledge, it is the first to globally review the main serious ADRs reported with ivermectin. Some strong significant disproportionality signals were found, showing more frequent reporting of encephalopathies after ivermectin than after benzimidazoles, both in SSA countries and in the RoW. Disproportionality signals were also identified for serious toxidermias, serious confusional disorders and serious Mazzotti reactions with ivermectin when compared with benzimidazole drugs or all non-ivermectin antinematodal drugs. A less consistent signal was found for cardiac failures and further studies are needed to confirm this result.
Some of these results were expected, given the different mechanisms of action of ivermectin and benzimidazoles on the various targeted parasites. Ivermectin exerts a strong microfilaricidal effect on filariae, leading to a destruction of mf within one week after treatment. In subjects

**Table 4. Frequency of ten most reported suspected sADRs by regions and in total.**

| Suspected sADRs, n (%) | Sub-Saharan sADRs | RoW sADRs | Total sADRs |
|------------------------|-------------------|-----------|-------------|
| Headaches              | 60 (73.2%)        | 22 (26.8%)| 82          |
| Asthenia               | 61 (78.2%)        | 17 (21.8%)| 78          |
| Pruritus               | 47 (61.8%)        | 29 (38.2%)| 76          |
| Pyrexia                | 42 (66.7%)        | 21 (33.3%)| 63          |
| Coma                   | 31 (86.1%)        | 5 (13.9%) | 36          |
| Dizziness              | 29 (67.4%)        | 14 (32.6%)| 43          |
| Vomiting               | 16 (50.0%)        | 16 (50.0%)| 34          |
| Rash                   | 9 (29.0%)         | 22 (71.0%)| 31          |
| Diarrhea               | 20 (66.7%)        | 10 (33.3%)| 30          |

https://doi.org/10.1371/journal.pntd.0009354.t004
infected with *Onchocerca volvulus*, the destruction of mf in the skin is associated with inflammatory processes leading to the so-called Mazzotti reaction. In those infected with *L. loa*, the drug probably induces a paralysis of the *L. loa* mf, which are then drained passively in the blood circulation. If the microfilarial density is high, the process can lead to an embolization of mf in the brain capillaries, to inflammatory reactions at the cerebral level, and to an encephalopathy. In contrast, benzimidazoles have little short-term effect on the mf of any filarial species, and thus do not induce Mazzotti reactions, but impair the production of new mf by the adult female worms.

The US Food and Drug Administration (FDA) approved product information for ivermectin mentions that “Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide.” [2] In our study, we confirmed the findings of a previous analysis of the data in VigiBase [10] which identified encephalopathies reported with ivermectin also outside of SSA where *L. loa* is not endemic. In addition, we quantified this association by estimating aRORs for ivermectin-induced encephalopathy. aROR was higher in the SSA countries than in the RoW but both were significant, demonstrating a strong global safety signal. Another recent publication described the case of a 13 years old boy presenting a progressive encephalopathy after a single oral dose of ivermectin given at 230 $\mu$g per kg, i.e. only slightly higher than the dose used for ivermectin mass drug administration for onchocerciasis (150 $\mu$g/kg) and lymphatic filariasis (200 $\mu$g/kg) control or to prevent scabies infection (200 $\mu$g/kg). The authors found that the patient was a carrier of non-sense mutations in the gene coding for the ATP-binding cassette subfamily B member 1 (ABCB1) transporter which is known to efflux ivermectin from the brain. These mutations can lead to neurological adverse reactions induced by ivermectin [32]. Our results are therefore consistent with the literature and support the evidence of post-ivermectin serious neurological ADRs in some people not infected with *L. loa*. The clinical presentations of *Loa*-related and non-*Loa*-related post-ivermectin neurological ADRs are summarized in Table 7.

The FDA-approved product information for ivermectin also includes the risk of toxic epidermal necrolysis and Stevens-Johnson syndrome as very rare events. By identifying a strong disproportionality signal between ivermectin and benzimidazole drugs or all other antinematodal drugs, our study suggests that ivermectin may be associated with a higher risk of toxidermias than other antinematodal drugs. We also found in VigiBase two types of toxidermia that were never mentioned in the literature: 9 cases of DRESS and 2 cases of acute generalized exantheme supr bulosis after ivermectin intake. These findings could be of great interest for clinicians considering ivermectin treatment in patients at risk for these sADRs or assessing the causality of ivermectin in the development of a toxidermia.

Our study has several strengths. First, we used the global ADRs database VigiBase intended to collect information on suspected ADRs from nearly all national pharmacovigilance centers

| Suspected syndromes, n (%) | Sub-Saharan cases | RoW cases | Total cases |
|---------------------------|------------------|-----------|-------------|
| Encephalopathy            | 32 (58.2%)       | 23 (41.8%)| 55          |
| Confusional disorders     | 6 (27.3%)        | 16 (72.7%)| 22          |
| Toxidermia                | 8 (24.2%)        | 25 (75.8%)| 33          |
| Psychotic disorders       | 1 (9.1%)         | 10 (90.9%)| 11          |
| Renal disorders           | 1 (5.3%)         | 18 (94.7%)| 19          |
| Hepatic disorders         | 2 (3.8%)         | 51 (96.2%)| 53          |
| Mazzotti reaction         | 34 (81.0%)       | 8 (19.0%) | 42          |

https://doi.org/10.1371/journal.pntd.0009354.t005
in the world, allowing us to estimate ROR for rare events with sufficient statistical power and
to stratify on geographical origin (SSA vs. RoW). Second, analyses were performed with
adjustment for several potential confounders such as origin, gender, age and period of notifica-
tion. Third, nearly all results of our principal analysis were confirmed in our sensitivity analy-
ses considering all antinematodal agents. Fourth, our results are consistent with already
known risk associated with ivermectin (encephalopathy in SSA and Mazzotti reactions).

Limitations of this study include the concern about under-reporting of suspected ADRs
and differences in the under-reporting between different countries as well as the lack of infor-
mation on the number of drug administrations, which is a major disadvantage inherent in
studies using pharmacovigilance databases [33,34]. Although under-reporting may be less
important since we focused on serious ADRs (which are more likely to be reported) [35], our

| Serious adverse drug reaction | Drugs     | Cases | Non-cases | Crude ROR (95% CI) | Adjusted ROR * (95% CI) | Adjusted ROR b in Sub-Saharan Africa (95% CI) | Adjusted ROR b in RoW (95% CI) |
|------------------------------|-----------|-------|-----------|--------------------|------------------------|---------------------------------------------|---------------------------------|
| Headache                     | Ivermectin| 71    | 502       | 1.40 ** (1.01–1.93) | 1.22 (0.83–1.78)       | 1.16 (0.68–1.98)                            | 1.39 (0.76–2.53)                |
|                             | Benzimidazoles | 99   | 980       | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Encephalopathy               | Ivermectin| 55    | 518       | 10.3 *** (5.35–19.9) | 9.23 *** (4.56–18.6)   | 27.1 *** (6.34–116.1)                        | 6.30 *** (2.68–14.8)             |
|                             | Benzimidazoles | 11   | 1068      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Confusional disorders        | Ivermectin| 22    | 551       | 3.88 *** (1.87–8.05) | 4.05 *** (1.81–9.09)   | 3.87 (0.76–19.6)                            | 3.66 *** (1.49–8.97)             |
|                             | Benzimidazoles | 11   | 1068      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Seizure                      | Ivermectin| 11    | 562       | 0.49 (0.25–0.97)   | 0.83 (0.40–1.72)       | N/A                                         | N/A                             |
|                             | Benzimidazoles | 41   | 1038      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| DRESS *                      | Ivermectin| 9     | 564       | 8.59 *** (1.85–39.9) | N/A                    | N/A                                         | N/A                             |
|                             | Benzimidazoles | 2    | 1072      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Toxidermia                   | Ivermectin| 25    | 548       | 3.47 *** (1.79–6.73) | 4.43 *** (2.07–9.47)   | 0.52 (0.05–5.01)                            | 6.05*** (2.76–13.3)             |
|                             | Benzimidazoles | 15   | 1065      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Psychotic disorders          | Ivermectin| 10    | 563       | 1.72 (0.73–4.08)   | 1.78 (0.70–4.53)       | N/A                                         | 1.62 (0.62–4.23)                |
|                             | Benzimidazoles | 11   | 1068      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Suicidal behavior            | Ivermectin| 4     | 569       | 7.58 * (0.84–68.0)  | 7.67 * (0.85–69.0)     | N/A                                         | N/A                             |
|                             | Benzimidazoles | 1    | 1078      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| SARS **                      | Ivermectin| 4     | 569       | 7.58 * (0.84–68.0)  | N/A                    | N/A                                         | N/A                             |
|                             | Benzimidazoles | 1    | 1078      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Renal disorders              | Ivermectin| 17    | 556       | 2.03 ** (1.02–4.05) | 1.36 (0.66–2.85)       | N/A                                         | N/A                             |
|                             | Benzimidazoles | 16   | 1063      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Hepatic disorders            | Ivermectin| 50    | 523       | 0.61 (0.44–0.86)   | 0.51 (0.36–0.74)       | 1.36 (0.08–21.9)                            | 0.50 (0.35–0.73)                |
|                             | Benzimidazoles | 145  | 934       | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Cardiac failure              | Ivermectin| 6     | 567       | 11.4 ** (1.37–94.9) | N/A                    | N/A                                         | N/A                             |
|                             | Benzimidazoles | 1    | 1078      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Rhythm disorders             | Ivermectin| 7     | 566       | 3.32 * (0.97–11.40)| 3.18 * (0.86–11.7)     | N/A                                         | 3.18 * (0.86–11.7)              |
|                             | Benzimidazoles | 4    | 1075      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |
| Mazzotti’s reaction          | Ivermectin| 36    | 537       | 2.94 *** (1.74–4.99)| 2.16 ** (1.16–4.03)    | 1.95 ** (1.09–3.52)                         | 19.7 *** (2.20–175.5)           |
|                             | Benzimidazoles | 24   | 1055      | Ref.               | Ref.                   | Ref.                                         | Ref.                            |

* Adjusted for origin (Sub-Saharan Africa or RoW), gender, age and period of notification
b Adjusted for gender, age and period of notification
DRESS Drug reaction with eosinophilia and systemic symptoms
SARS Severe Acute Respiratory Syndrome

https://doi.org/10.1371/journal.pntd.0009354.t006

Pharmacovigilance study of serious adverse reactions after ivermectin
analyses cannot measure the real risk of ADR but only the differences in reported events. Indeed, subjects in the control group (non-cases) are not healthy controls but patients with other various reported ADRs and pharmacovigilance data do not consider the total amount of patients exposed to the drug. Nevertheless, there is no apparent reason that, in a specific region, ADRs would be more or less reported with ivermectin than those occurring after treatment with benzimidazole drugs or other antinematodal drugs. By analyzing real-life surveillance data, disproportionality analyses have demonstrated their usefulness for detecting drug risks [36,37]. Anyway, these results should be taken with caution because of potential missing information. Pharmacovigilance systems are not yet well established in SSA countries. In 2017, only 30% of these countries had specific procedures for the monitoring of ADRs and only 28% had a platform for coordinating pharmacovigilance activities at the national level [38]. Cases of serious adverse events occurring during the ivermectin mass drug administration organized by the onchocerciasis and LF control programs have to be reported by the countries to the Mectizan Donation Program, but the extent to which all relevant observations are recorded in the rural areas where onchocerciasis and LF are endemic and then passed on to the central level is unknown as is the extent to which they are reported into the WHO VigiBase. For example, we found no cases from Cameroon even though ivermectin mass drug administration programs have been ongoing there for 30 years, and many cases are known to have occurred since the early 1990s [39]. In addition, the first case of a post-ivermectin ADR was reported in VigiBase in December 2003 while the first reported death after ivermectin was reported by the WHO Drug Information in 1991 [40]. We consider it likely that availability of complete data from SSA would show more cases associated with ivermectin use and would increase the strength of the safety signals we identified.

In addition, a notoriety bias (selection bias in which a case has a greater chance of being reported if the drug is known to cause, thought to cause, or likely to cause the event of interest [41]) could be considered for reports of encephalopathy in SSA given that the first cases of encephalopathies involving ivermectin led to complications in the early mass drug administration campaigns for elimination of onchocerciasis. However it is unlikely that such bias exist for two reasons (i) in SSA countries, ivermectin is distributed as part of mass treatment organized by the Ministries of Health, and those of L. loa-endemic countries might be less inclined to report post-ivermectin sADRs because the cases are not regarded as exceptional and (ii) we also found a strong disproportionality signal in the RoW which is not being affected by this bias.

### Table 7. Possible/Probable Loa loa encephalopathy temporally related to Mectizan and other encephalopathies related to ivermectin: mains risk factors, symptoms and mechanisms involved.

| Possible/Probable Loa loa encephalopathy temporally related to Mectizan (PLERM) | Main risk factors | Main symptoms | Main mechanisms involved |
|---|---|---|---|
| - Intensity of the initial Loa microfilaremia | - 12-24h following treatment: fever, fatigue, arthralgia, agitation, mutism, incontinence | - Paralysis of the microfilariae due to the action of ivermectin resulting in embolisms in the brain capillaries |
| | - 24-72h following treatment: consciousness disorders including coma and extrapyramidal signs, typical hemorrhages in the palpebral conjunctiva, retinal lesions | - Inflammatory processes at the cerebral level |
| | - Existence of diffuse pathological process at electroencephalogram level | | |

Other encephalopathies related to ivermectin:
- Toxicosis due to an overdose
- Toxicosis due to a mutation

| Other encephalopathies related to ivermectin: |
|---|
| - Polymorphism of MDR1 gene |
| - Deficiency in P-glycoproteins |
| - Intentional or unintentional overdosing |

| Main risk factors | Main symptoms | Main mechanisms involved |
|---|---|---|
| - Few hours after administration: nausea, vomiting, abdominal pain, salivation, tachycardia, hypotension, ataxia, pyramidal signs, binocular diplopia | - Passage of ivermectin through the blood-brain barrier (due to overdose or mutation of transporters/metabolism actors) |
| - Normal paraclinical tests results | | |

[376x129] [376x129] L. loa-endemic countries might be less inclined to report post-ivermectin sADRs because the cases are not regarded as exceptional and (ii) we also found a strong disproportionality signal in the RoW which is not being affected by this bias.

[https://doi.org/10.1371/journal.pntd.0009354.t007](https://doi.org/10.1371/journal.pntd.0009354.t007)
Our analyses identified serious ADRs that can be associated with ivermectin use that to date have received little, if any attention. As ivermectin is currently widely used off label, especially in Latin America, to control COVID-19 without strong evidence for beneficial effect [42], this study is timely to describe the various suspected sADRs to which this population is potentially exposed even in the absence of onchocerciasis and loiasis endemicity. While ivermectin’s excellent safety profile is the basis for mass drug administration campaigns and progress towards elimination in particular of onchocerciasis, one must remain aware and vigilant about the sADRs it may possibly induce.

Supporting information

S1 Table. A. Most frequently reported serious ADRs for each System Organ Class (SOC). If several sADRs belonging to the same SOC are reported in a single patient (ICSR form), the SOC is counted only once in the total. B. Most frequently reported serious ADRs for each System Organ Class (SOC) in SSA. If several sADRs belonging to the same SOC are reported in a single patient (ICSR form), the SOC is counted only once in the total. C. Most frequently reported serious ADRs for each System Organ Class (SOC) in RoW. If several sADRs belonging to the same SOC are reported in a single patient (ICSR form), the SOC is counted only once in the total.

S2 Table. Disproportionality analysis of serious adverse reactions associated with ivermectin compared to other antinematodal drugs.

S3 Table. STROBE Statement—Checklist of items that should be included in reports of case-control studies.

Acknowledgments

The Uppsala Monitoring Centre has provided the data but the study results and conclusions are those of the authors and not necessarily those of the Uppsala Monitoring Centre, National Centers, or WHO.

Author Contributions

Conceptionalization: Jérémy T. Campillo, Michel Boussinesq, Jean-Luc Faillie, Cédric B. Chesnais.

Data curation: Jean-Luc Faillie.

Formal analysis: Jérémy T. Campillo.

Project administration: Jean-Luc Faillie, Cédric B. Chesnais.

Resources: Jean-Luc Faillie.

Supervision: Michel Boussinesq, Sébastien Bertout, Jean-Luc Faillie, Cédric B. Chesnais.

Validation: Michel Boussinesq, Sébastien Bertout, Jean-Luc Faillie, Cédric B. Chesnais.

Visualization: Jérémy T. Campillo.

Writing – original draft: Jérémy T. Campillo.
Writing – review & editing: Jérémy T. Campillo, Michel Boussinesq, Sébastien Bertout, Jean-Luc Faillie, Cédric B. Chesnais.

References

1. ANSM. STROMECTOL 3 mg, comprimé—Résumé des caractéristiques du produit. [cited 10 Nov 2020]. Available: http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?spced=61950360&typedoc=R

2. FDA. Ivermectin prescribing information. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050742s022lbl.pdf

3. Duke B. Human onchocerciasis—an overview of the disease. Acta Leiden. 1990; 59: 9–24. PMID: 2198761

4. Ackerman SJ, Kephart GM, Francis H, Awadzi K, Gleich GJ, Ottesen EA. Eosinophil degranulation: An immunologic determinant in the pathogenesis of the Mazzotti reaction in human onchocerciasis. J Immunol. 1990; 144: 3961–3969. PMID: 2332637

5. Boussinesq M, Gardon J, Gardon-Wendel N, Chippaux J-P. Clinical picture, epidemiology and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. Filaria J. 2003; 1 Suppl 1: S4. https://doi.org/10.1186/1475-2883-2-S1-S4 PMID: 14975061

6. Gardon J, Gardon-Wendel N, Demanga-Ngangue, Kamgno J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. Lancet. 1997; 350: 18–22. https://doi.org/10.1016/S0140-6736(96)11094-1 PMID: 9217715

7. Twum-Danso NAY, Meredith SEO. Variation in incidence of serious adverse events after onchocerciasis treatment with ivermectin in areas of Cameroon co-endemic for loiasis. Trop Med Int Heal. 2003; 8: 820–831. https://doi.org/10.1046/j.1365-3156.2003.01091.x PMID: 12950668

8. Chesnais CB, Pion SD, Boulé C, Gardon J, Gardon-Wendel N, Fokom-Domgue J, et al. Individual risk of post-ivermectin serious adverse events in subjects infected with Loa loa. EClinicalMedicine. 2020; 28. https://doi.org/10.1016/j.eclinm.2020.100582 PMID: 33294807

9. Nzolo D, Anto F, Hailemariam S, Bakajika D, Muteba D, Makenga JC, et al. Central and Peripheral Nervous System Disorders Following Ivermectin Mass Administration: A Descriptive Study Based on the Democratic Republic of Congo Pharmacovigilance System. Drugs—Real World Outcomes. 2017; 4: 151–158. https://doi.org/10.1007/s40801-017-0110-0 PMID: 28600751

10. Chandler RE. Serious neurological adverse events after ivermectin-do they occur beyond the indication of onchocerciasis? Am J Trop Med Hyg. 2018; 98: 382–388. https://doi.org/10.4269/ajtmh.17-0042 PMID: 29210346

11. Aroke D, Tchouakam DN, Awungia AT, Mapoh SY, Ngassa SN, Kadia BM. Ivermectin induced Steven-Johnsons syndrome: Case report. BMC Res Notes. 2017; 10: 5–8. https://doi.org/10.1186/s13104-016-2356-0 PMID: 28057060

12. Ngwasi CA, Abanda MH, Aminde LN. Ivermectin-induced fixed drug eruption in an elderly Cameroonian: A case report. J Med Case Rep. 2018; 12: 18–21. https://doi.org/10.1186/s13256-017-1526-6 PMID: 29373985

13. Mara C, Mallaret M, Raclot-Roy N, Massot C. Drug-induced eruption after treatment of hyperkeratotic crusted scabies with ivermectin. Rev Med Interne. 2004; 25: 476–77. https://doi.org/10.1016/j.revmed.2004.02.021 PMID: 15153234

14. Sanz-Navarro J, Feal C, Dauden E. Treatment of Human Scabies with Oral Ivermectin. Eczematous Eruptions as a New Non-Reported Adverse Event. Actas Dermo-Sifiliograficas English Ed. 2017; 108: 643–649. https://doi.org/10.1016/j.ad.2017.02.011 PMID: 28385424

15. Fujimoto K, Kawasaki Y, Morimoto K, Kikuchi I, Kawana S. Treatment for Crusted Scabies: Limitations and Side Effects of Treatment with Ivermectin. J Nippon Med Sch. 2014; 81: 157–63. https://doi.org/10.1272/jnms.81.157 PMID: 24998962

16. Cruel T, Arborio M, Schill H, Neveux Y, Neudec G, Chevalier B, et al. [Nephropathy and filariasis from Loa loa. Apropos of 1 case of adverse reaction to a dose of ivermectin]. Bull Soc Pathol Exot. 1997; 90: 179–181. PMID: 9410254

17. Kaur U, Chakrabarti SS, Gambhir IS. Delirium induced by albendazole–ivermectin combination: Report of the first case in an older patient. Geriatr Gerontol Int. 2017; 17: 2618–2620. https://doi.org/10.1111/jgl.13158 PMID: 29265756

18. Mohapatra S, Sahoo AJ. Drug-Induced Psychosis Associated with Albendazole-Ivermectin Combination Therapy in a 10-Year-Old Child. J Child Adolesc Psychopharmacol. 2015; 25: 817–818. https://doi.org/10.1089/cap.2015.0143 PMID: 26683000
19. Sparsa A, Bonnetblanc J, Peyrot I, Loustaud-Ratti V, Vidal E, Bédane C. Effets secondaires de l’ivermectine utilisée dans le traitement de la gale. Ann Dermatol Venereol. 2006; 133: 784–787. https://doi.org/10.1016/s0151-9638(06)71044-4 PMID: 17072195

20. Veit O, Beck B, Steuerwald M, Hatz C. First case of ivermectin-induced severe hepatitis. Trans R Soc Trop Med Hyg. 2006; 100: 795–797. https://doi.org/10.1016/j.trstmh.2006.02.003 PMID: 16682062

21. Choksi TT, Madison G, Dar T, Asif M, Fleming K, Clarke L, et al. Case report: Multorgan dysfunction syndrome from Strongyloides stercoralis hyperinfection in a patient with a human T-cell lymphotropic virus-1 coinfection after initiation of ivermectin treatment. Am J Trop Med Hyg. 2016; 95: 864–867. https://doi.org/10.4269/ajtmh.16-0259 PMID: 27527631

22. Budge PJ, Herbert C, Andersen BJ, Weil GJ. Adverse events following single dose treatment of lymphatic filariasis: Observations from a review of the literature. PLoS Negl Trop Dis. 2018; 12: 1–22. https://doi.org/10.1371/journal.pntd.0008454 PMID: 29768412

23. De Sole G, Remme J, Awadzi K, Accorsi S, Alley ES, Ba O, et al. Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: Combined results from eight community trials. Bull World Health Organ. 1989; 67: 707–719. PMID: 2633886

24. Burnham GM. Adverse reactions to ivermectin treatment for onchocerciasis. Results of a placebo-controlled, double-blind trial in Malawi. Trans R Soc Trop Med Hyg. 1993; 87: 313–317. https://doi.org/10.1016/0035-9203(93)90144-f PMID: 17072195

25. VigiBase. Uppsala Monitoring Centre. Available: https://www.who-umc.org/vigibase/vigibase/

26. Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic facts. Drug Inf J. 2008; 42: 409–419. https://doi.org/10.1177/009286150804200501

27. European Medicines Agency. ICH E2D Post-Approval Safety Data Management. 1998; 1–8.

28. Norén GN, Orre R, Bate A, Edwards IR. Duplicate detection in adverse drug reaction surveillance. Data Min Knowl Discov. 2007; 14: 305–328. https://doi.org/10.1007/s10618-006-0052-8

29. Brown E, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999; 20: 109–117. https://doi.org/10.2165/00002126-199920020-00002 PMID: 10082069

30. Moore N, Thiessard F, Begaud B. The history of disproportionality measures (reporting odds ratio, proportional reporting rates) in spontaneous reporting of adverse drug reactions. Pharmacoepidemiol Drug Saf. 2005; 14: 285–286. https://doi.org/10.1002/pds.1058 PMID: 15782397

31. Puijenbroek EP van, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection on adverse drug reaction spontaneous reporting data-base of Guangdong province in China. Pharmacoepidemiol Drug Saf. 2002; 11: 3–10. https://doi.org/10.1002/ps.668 PMID: 11998548

32. Eloise Baudou, Anne Lespine, Durrieu Geneviève, André François, Peggy Gandia, Clarisse Durand, et al. Serious ivermectin toxicity and human ABCB1 nonsense mutations. N Engl J Med. 2020; 383. https://doi.org/10.1056/NEJMc2001210 PMID: 31991079

33. Bégaud B, Martin K, Haramburu F, Moore N. Rates of Spontaneous Reporting of Adverse Drug Reactions in France. JAMA. 2002; 288: 1588. https://doi.org/10.1001/jama.288.13.1588 PMID: 12350188

34. Van Der Heijden PGM, Van Puijenbroek EP, Van Buuren S, Van Der Hofstede JW. On the assessment of adverse drug reactions from spontaneous reporting systems: The influence of under-reporting on odds ratios. Stat Med. 2002; 21: 2027–2044. https://doi.org/10.1002/sim.1157 PMID: 12111885

35. Martin RM, Kapoor K V., Wilton L V, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed (‘black triangle’) drugs in general practice: Observational study. Br Med J. 1998; 317: 119–120. https://doi.org/10.1136/bmj.317.7151.119 PMID: 9657787

36. Maciá-Martínez M-A, de Abajo F, Roberts G, Stalley J, Thakrar B, Wilsniewski A. An Empirical Approach to Explore the Relationship Between Measures of Disproportionate Reporting and Relative Risks from Analytical Studies. Drug Saf. 2016; 39: 29–43. https://doi.org/10.1002/dps.668 PMID: 26507885

37. Montastruc J-L, Sommet A, Bagheri H, Lapreyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol. 2011; 72: 905–908. https://doi.org/10.1111/j.1365-2125.2011.04037.x PMID: 21658002

38. Kaboré L, Yaméogo TM, Sombié I, Ouédraogo M, Fofana S, Berthé A, et al. Plaidoyer pour un renforcement du système de pharmacovigilance au Burkina Faso. Sante Publique (Paris). 2017; 29: 921–925. https://doi.org/10.3917/spub.176.0921 PMID: 29473406

39. Twum-Danso NA. Loa loa encephalopathy temporally related to ivermectin administration reported from onchocerciasis mass treatment programs from 1989 to 2001: implications for the future. Filaria J. 2003; 2 Suppl 1: 1–8. https://doi.org/10.1186/1475-2883-2-S1-57 PMID: 14975064

40. Anonymous. Ivermectin: a possible neurotoxicity. WHO Drug Inf. 1991; 5: 127–128.
41. Pariente A, Gregoire F, Fourrier-Reglat A. Impact of Safety Alerts on Measures of Disproportionality in Spontaneous Reporting Databases The Notoriety Bias. Drug Saf. 2007; 891–898. https://doi.org/10.2165/00002018-200730100-00007 PMID: 17867726

42. Mega ER. Embrace of unproven COVID treatment hinders drug trials. Nature. 2020. Available: https://www.nature.com/articles/d41586-020-02958-2