



Intestinal Helminth Infections, Compliance and Effectiveness of Albendazole Treatment among CDC Workers (18-45 Years) in Tiko, South-West Region, Cameroon

Judith Lum Ndamukong-Nyanga^{1*}, Diah Njanakea Owah²,
Nyanga Bernard Yunga³, Desdemona Njabi Nji⁴ and Changsen Jacqueline²

¹Department of Biological Sciences, Higher Teacher Training College, University of Yaounde 1, Cameroon.

²Medical Laboratory Science, Department of Allied Health, Biaka University Institute, Buea, Cameroon.

³Department of Physics, Faculty of Science, University of Buea, Cameroon.

⁴Department of Biochemistry, Faculty of Science, University of Buea, Cameroon.

Authors' contributions

This work was carried out in collaboration among all authors. Author JLNN designed the work, wrote the protocol, supervised the field and laboratory work, participated in the data analysis and wrote the first draft of the manuscript. Author CJ did the laboratory work, participated in the data analysis and edited the manuscript. Author NBY did the statistical analysis and participated in drafting of the manuscript. Author DNO participated in the design of the work, the field and laboratory work and the drafting of the manuscript. Author DNJ did the final editing of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ACRI/2020/v20i330181

Editor(s):

(1) Amal Hegazi Ahmed Elrefaei, Hot Lab and Waste Management Center, Atomic Energy Authority, Egypt.

Reviewers:

(1) Pr Blaise Nguendo Yongsi, University of Yaounde II, Cameroon.

(2) Nuhu Sambo, Federal University Dutse, Nigeria.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/56422>

Received 18 February 2020

Accepted 24 April 2020

Published 02 May 2020

Original Research Article

ABSTRACT

Intestinal helminthes infections are among the most prevalent of chronic human infections worldwide. These infections are common among people who work under very poor conditions most of the time without protective hand gloves, shoes and uniforms in the field. A cross-sectional study was done to determine the prevalence of intestinal helminthes among Cameroon Development

*Corresponding author: Email: ndamju@yahoo.com;

Cooperation (CDC) workers and their compliance to anti-helminthic treatment from November 2017 to April 2018. It involved 102 workers aged 18-45 years attending CDC cottage Hospital in Tiko. A cross-sectional study was done in which demographic data and data related to predisposing factors and preventive measures was collected using a simplified questionnaire, stool samples were collected pre and post treatment. Macroscopic and microscopic examination of stool samples was carried out in the hospital laboratory. Out of 102 people, a total of 81 (79.4%) people were infected with one or more species of intestinal helminthes and there was significant difference in the infection with respect to various helminthes species (0.004). Among the 81 infected cases, 58(71.6%) were infected with single helminth species and 23 (28.4%) were infected with more than one species (coinfection). Intestinal helminths varied significantly among the participants with prevalences of 24.5% for *T. trichuris*, 6.9% for Hookworm, 0.9% for *S. japonicum*, 24.5% for *S. haematobium*, 34.3% for *A. lumbricoides* and 7.8% for *S. mansoni* (P<0.004). Out of the 40 participants who took the drug (albendazole), 32 (80%) came for retesting and disappointingly, 8 (20.00%) of the treated participants did not come. A majority of the 32 people retested were negative (28, 87.5%) for all species of intestinal helminth parasites, 4 (12.5%) still tested positive for the parasite presence in their stool among which 2 had *schistosoma haematobium*, one had *schistosoma mansoni* and one had *Ascaris lumbricoides*. Workers were recommended to wear protective hand gloves, and proper working shoes in line with their work description.

Keywords: *Helminths; anti-helminthic treatment; albendazole; predisposing factors; preventive measures.*

1. INTRODUCTION

Intestinal helminthes are among the most prevalent of chronic human infections with an estimated 2 billion people infected worldwide [1]. The major public health significance and economic impact of this group of pathogens is hard to quantify, although the World Health Organization (WHO) has estimated that more than 1000 million people worldwide are infected with one or more of the major pathogenic species of human: *Ascaris lumbricoides*, *Trichuris trichiura*, Hookworms (*Necator americanus*, and *Ancylostoma maduodenale*), 39 million disability adjusted life years are attributed to this four Nematodes and an estimated 836 million were predisposed to these infection in 2016 [2,3]. The greatest number of infection occurs in Sub Saharan Africa where 89.9 million of school age children are infected [4]. Chronic and intense intestinal helminthes infection can contribute to malnutrition and iron deficiency anemia, and can adversely affect physical and mental growth in children [5].

In Cameroon, these infections are prevalent all over the country and most people are co-infected with two or more species of intestinal helminths [5] although prevalence values vary from one locality to another.

In an attempt to control this public health problem, several forms of therapy have been

used over the decades to get a better anti-helminthic drug to properly take care of these human challenges. This study was based on the anti-helminth Albendazole, which is the agent of choice and a broad spectrum anthel anti-helminthic drug [4].

Action of these parasites on man can be translated by the alteration of their health state and the reduction of the productive success. Helminths are in dying need of a secondary host to fully complete their life cycle so as to survive [6]. Scientific studies have shown that all age and sex groups in poorly managed and less sanitary facilities like, prisons, factories mostly suffer from gastrointestinal helminthes infections and other diseases [6]. Infections are high among populations who are heavily exposed in low income countries as well as under developed countries such as Romania, Bulgaria [5].

Humans can become infected by either eating eggs or larvae, or by skin penetration of larvae. The human activities and life style predispose people to repeated infections. According to the chief of bureau of Tiko health district, the problem most at times boil downs to sanitation that is greatly lacking from CDC workers, since they do not know that helminthes infections can result from their lifestyle and most of them are unwilling to take prescribed medications [7]. The objective of this study was therefore to determine the prevalence of Intestinal Helminth infections

among CDC workers (18-45 years), their compliance to treatment and the effectiveness of albendazole in the treatment of intestinal helminthes in Tiko, South-west Region, Cameroon.

2. METHODS

2.1 Study Area

This research was carried out in CDC Cottage Hospital in Tiko. This hospital is a referral hospital for CDC workers in thole of the S.W. Region. The town of Tiko is geographically located in Fako-subdivision, in south-west region of Cameroon Africa with its population solely dependent on Cameroon Development Cooperation (CDC) Public Plantation Limited for job employment. Tiko (-5m.a.s.l to 74 m.a.s.l., 04°07'N, 09°36'E) is situated east of Buea and is a settlement in the heart of the rain forest. The population is made of Cameroonian (Anglophone and Francophones) and foreigners from Nigeria and other African countries involved in Trade and fishing. About One-third of the population is made up of CDC workers living in Camp houses provided by the corporation.

2.2 Study Population and Study Design

The target population for this study involved only CDC workers who came to the hospital for consultation. The study was a cross sectional one in two phases. Phase one involved recruiting and screening participants for helminth infection and treating the infected cases with albendazole and phase two involved re-testing of participants for infections three to four weeks post treatment.

2.3 Sample Size

The sample size for this study was calculated using the formula of Lorentz which states that

$$n = Z^2P(1-P)/e^2.$$

Where: n - Maximum Sample size of the study population. Z – a constant corresponding to the confidence level for example (1.65 for 90% confidence, 1.95 for 95% confidence, and 2.575 for 99% confidence). In this study, 1.96 for 95% confidence interval was used). P – Estimated value or percentage of a sample that has similar condition of interest, and e – The margin of error or precision of the event of interest (0.05). With P = 6.5% (Ndamukong-Nyanga et al., 2014, for intestinal helminthes prevalence in Tole, SW Cameroon) [5].

$$Z = 1.95, e = 0.05$$

$$\text{It implies that } n = \{(1.95)^2(0.065)(1-0.065)\}/(0.05)^2 = 88 .$$

A minimum of 88 workers were to be recruited for the study. However, twice the calculated sample size (160 workers) was issued consent forms. One hundred and two people (102) signed the forms indicating their willingness to participate in the study. Thus the study involved 102 CDC workers.

2.4 Study Period, Informed Consent, Data Collection and Analysis

The research was conducted from the month of November, 2017 to April, 2018.

Consent forms with attached questionnaire were given to all prospective participants. The forms were read out for those who did not understand and explanations were given in pidgin English. The explanations included all the phases of the work (Screening Treatment and rescreening). All those who agreed to participate in the study read and signed the consent forms, then, answered the questionnaire with the assistance of members of the research team. The questionnaire was designed to gather demographic data and data on the predisposing factors for helminthes. Where consent was given, sterile stool containers were given to the participants. The sample bottles (with stool) were returned with the answered questionnaires and the participant was asked to wait for one hour for results and treatment of positive cases. All those who refused to sign the consent form were excluded from the study.

Two wet mounts were prepared per sample using normal saline and iodine. Microscopy of stool samples were done using X10 and X40 objective of the microscope. All positive participants were given albendazole treatment (400 mg oral treatment). After three weeks all those that were positive and were treated were again tested for intestinal helminthes using fresh stool samples. The results obtain were analysed using SPSS version 20.0.

3. RESULTS

3.1 Demographic Data

A total of 102 CDC workers from 18 - 45 years participated in the study. Males were significantly less (35, 34.31%) than females (67, 65.69%)

($P < 0.012$). A majority of the participant had completed primary school (38, 37.25%), some (8, 7.84%) had done Vocational Training, some (27, 26.47%) had completed secondary education and a few had completed high school (29, 28.43%). In relation to the participants job description, 22 (21.57%) were rubber tapper, 27 (26.47%) were Grass-cutters, 30 (29.41%) were Banana workers, 20 (19.64%) were Cleaners, and only 3 (2.94%) were health care workers.

3.2 Knowledge on Transmission and Prevention of Intestinal Helminth

The results showed that all 102 (100%) of the participants knew what a worm looks like and could differentiate between intestinal worms (such as *Ascaris*) excreted by humans and earth worms (annelids). Most of the participants (94, 92.16%) said they excreted worms either through their anus, mouth or nostrils. In relation to hand washing practices, most participants (97.1%) washed their hands after using the toilet and before eating. A few participants indicated their awareness to eating undercooked meat (51%), poorly washed fruits and vegetables (53%), drinking water from doubtful sources (60.8%), lack of good toilets (53.9%) and lack of protective clothing (70.6%) as predisposing factors to intestinal helminths (Table 2).

3.3 Knowledge of Some Antihelminthic Drugs Commonly Used

The question on the drug of choice that participants often take for the treatment of intestinal helminthes infection was challenging. The difference in the responses with respect to the different types of drugs was non-significant.

From the answered questionnaires 56.9% (the valid majority) used Albendazole as seen in the Table 3.

3.4 Phase One of the Participants Stool Analysis

3.4.1 Macroscopy of stool

The physical examination of the stool shows the variation of Consistency, color and odor of the stool by 102 participants. These variations can be seen in Table 4.

3.4.2 Microscopy of stool

Out of the 102 participants 81 (79.4%) were infected with one or more species of intestinal helminthes and there was significant difference in the infection with various helminthes species ($P < 0.004$). Among the 81 infected cases, 58(71.6%) were infected with one helminth species only and 23 (28.4%) were infected with more than one species (coinfection). Most of the participants were infected with *A. lumbricoides* (35, 34.3%) followed with *Schistosoma haematobium* 25 (24.5%) and *Trichuris trichiura* 25 (24.5%). A minority (21, 20.6%) were completely free from intestinal helminthes as seen in Table 5.

3.5 Administration of Drugs: 400 mg of Albendazole

The tablet form of the drug was given to the participant orally with clean water. Out of the 81 positive cases, 40 accepted to take the drug and the remaining participant didn't take the treatment.

Table 1. Demographic characteristics of the study population

Demographic characteristic	Category	Number examined	Percentage
Gender	Males	67	65.6
	Females	35	34.3
Total		102	
Level of education	Primary	38	37.25
	Vocational training	8	7.64
	Secondary	27	26.47
	High school	29	28.43
	University	00	00
Total		102	100
Job description	Rubber tappers	22	21.57
	Grass cutters	27	26.47
	Banana workers	30	29.41
	cleanners	20	19.64
	Health workers	3	2.94
Total		102	100

Table 2. Knowledge on macroscopic identification, transmission and prevention of intestinal helminth

Characteristic	Frequency n (%)	
	No	Yes
Macroscopic identification, transmission, prevention		
Differentiation of human intestinal worm from earthworms.	00	102 (100)
Experience of worm defecation through the anus, mouth or nostrils.	8(7.84)	94 (92.16)
Frequent hand washing practice after using the toilet and before eating.	3(2.9)	99 (97.1)
Eating of undercooked meat as a means of transmission of helminths.	50 (49.0)	52(51.0)
Drinking of water from streams, rivers and wells without disinfecting as a means of transmission of helminths.	40 (39.2)	62(60.8)
Consumption of fruits and vegetables from the farms and markets without proper washing as a means of transmission of helminths.	47(46.1)	55(53.9)
Use of toilets in defecating as a preventive measure for intestinal helminthiasis.	44 (43.1)	58(56.9)
Wearing of protective shoes, clothes and gloves as a means of protection when working in the farms.	30 (29.4)	72(70.6)

Table 3. Knowledge on some types of anthelmintic drugs

	Anthelminthes	Frequency	Percentage	P value
1	Albendazole	65	63.72%	0.3
2	Mebendazole	11	16.67%	
3	Ivermectine	0	0.00%	
4	Praquantel	0	0.00%	
5	No idea	26	25.50%	

Table 4. Macroscopic stool analysis

No	Property	Frequency	Valid percentage	P value	
1	Consistency of stool	Formed	58	56.9%	0.002
		Semiformed	30	29.4%	
		Mucous	14	13.7%	
2	Colour of Stool	Brownish	67	65.5%	
		Yellowish	22	21.6%	
		Other	13	12.7%	
3	Odour of Stool	Offensive	85	83.3%	
		Non offensive	17	16.6%	

Table 5. Microscopy of stool analysis (phase one)

No	Parasites	Frequency (no. of people)	Valid percentages	P value
1	<i>T. trichiura</i>	25	24.5%	0.004
2	Hookworm	7	6.9%	
3	<i>H. fluke</i>	0	0.0%	
4	<i>F. buski</i>	0	0.0%	
5	<i>S. japonicum</i>	1	0.9%	
6	<i>S. makongi</i>	3	2.9%	
7	<i>S. haematobium</i>	25	24.5%	
8	<i>A. Lumbricoides</i>	35	34.3%	
9	<i>S. mansoni</i>	8	7.8%	
10	Tapeworm	0	0.0%	
11	Total positive	104 positive parasite species in 81 people		
12	No parasite seen (Negative)	21	20.8%	
Total	no of people Sampled	102	100%	

3.6 Phase Two of Participants Stool Analysis

The second phase of this study involved the microscopic examination of previously infected and treated participant. Out of the 40 participants who took the drug, 32 (80%) showed up for retesting and 8 (20.00%) of the treated participants did not show up for retesting. Out of the 32 people retested 28 (87.5%) were negative for all species of intestinal helminth parasites, 4 (12.5%) still tested positive for the parasite presence in their stool. Among the four cases that re-tested positive, 2 had *schistosoma haematobium*, one had *schistosoma mansoni* and one had *Ascaris lumbricoides*.

4. DISCUSSION, CONCLUSION AND RECOMMENDATION

4.1 Discussion

All of the participants (100%) involved in this study were fully aware of the existence of intestinal helminthes infections in the Tiko municipality. Despite this awareness, some of them were reluctant to accept screening while others who tested positive did not wait to collect their drugs. Most (70.58%) of the participants said that they have being practicing good hand washing habits before eating and after using the pit toilets in the camps. Which show their level of awareness on infections transmission and control? Most of the workers have a low level of education (about 37.25% for those that had attained primary education). Participating in Anthelminthic campaigns and Health talk organized by health centers are of very little interest to the works.

Prevalence values in this study (79.4%) were very high compared to previous studies in South West Cameroon and other parts of Cameroon. Ndamukong Nyanga et al. [5] reported a prevalence of 6.5% in Tole, S.W, Cameroon in 2014. In other parts of the country and beyond, lower prevalence values have been recorded by Tchuem Tchuenté [8] who worked in Loum Littoral Region, Njunda et al. [9] in Buea, Ndamukong K.N. et al. [10] in Kumba, Cameroon and Thomas et al., in Nigeria [11]. These high prevalence values could be due to the fact that in this study the participants were adults unlike the other studies that involved children. Free deworming by mass distribution of albendazole in Cameroon targets only children from 0-5 years. Adults need to take initiative and go for screening

and for deworming and they have to buy albendazole. Even though the cost is highly subsidized [12], most adults neglect treatment of intestinal worms because the pathological consequences are not as obvious and life threatening as in children [13]. Thus, adults can harbor intestinal worm without obvious signs and symptoms and will only show signs and symptoms when the parasite load is high [6]. Most of the participants were infected with *A. lumbricoides* *Schistosoma haematobium* and with *Trichuris trichiura*. These results agree with results by Njunda et al., [9] highlighting these parasites as the most common helminth infections in SW, Cameroon [14]. Gastrointestinal nematodes such as Hookworm, *Ascaris lumbricoides* have also been shown to be among the most prevalent infection among human populations especially in areas where hygienic practices are poor [15,16]. A minority were completely free from intestinal helminthes. This could be as a result of the fact that they had earlier accepted and received ivermectin during the mass distribution phase that took place four months before the start of this study. It could also be because some of them (6workers) were health workers (who had awareness on preventive measures) and some (8workers) were administrative staff whose job description was limited to office work and not fields work. Following treatment with albendazole, most of the participants had complete worm-eradication. Indicating the effectiveness of albendazole in the treatment of intestinal helminthes. This agrees with studies by Albonico et al. [17] and Schmidt and Larry [6] who indicated that albendazole is effective in the treatment of helminth infections.

The few cases that tested positive after albendazole treatment could be as a result of re-infection (for the person with *Ascaris*) and drug resistance/ineffectiveness for the cases with Schistosomiasis considering that the drug of choice for schistosomiasis is praziquantel (that was not administered). There is lack of effective counseling to working aged group population, since public health official are most concerned with school-aged children forgetting that adults are not immune to this infections especially the plantation field and factory workers in CDC. Most of the CDC workers in the field are in constant risk of acquiring geohelminthes infections because of the nature of their jobs. Their working condition is a great call for concern and improvements are needed at all level since most of this field work is done with bare hands. Most

often, workers are not provided with proper working materials, protective clothings, shoes and gloves. From this study, we can see the need for improvement in the working conditions of the CDC workers in order to prevent infections from soil-transmitted helminthes.

4.2 Conclusion

Following the objective of this study, it was concluded that.

- All (100.00%) of the participants had knowledge of what an intestinal worm (Ascaris) looks like.
- Most of the participants had defecated *Ascaris* worm at one point in their lives and can distinguish it from other soil worms.
- Most of the study participants were infected with one or more species of intestinal helminthes and there was significant difference in the infection with various helminthes.
- Intestinal helminths varied significantly among the participants with prevalences of 24.5% for *T. trichuris*, 6,9% for Hookworm, 0.9% for *S. japonicum*, 24.5% for *S. haematobium*, 34.3% for *A. lumbricoides* and 7.8% for *S. mansoni* ($P < 0.004$).
- Compliance to therapy was poor because out of the 40 participants who took the drug (albendazole), 32 (80%) came for retesting and disappointedly, 8 (20.00%) of the treated participants did not come.
- A majority of the 32 people retested were negative (28, 87.5%) for all species of intestinal helminth parasites indicating that the drug was effective.
- A small number of the participants were resistant to the drug or had some form of reinfection within the period of treatment and retesting.
- The low educational level of the workers is a hindrance to control of infections because stigmatization among the workers is a serious problem. The CDC Tiko camps (Sostain, Watertank, and Army Camp) sanitary conditions and drainage systems of standing water are really poor and in need of efficient drainage system, gutters and bridges.

4.3 Recommendation

The Cameroon Development Corporation (CDC) should use its resources in Health Care to organize community campaigns to create more

awareness about the transmission of geohelminthic infection in their camps.

The company should provide good protective uniforms and hand gloves to its labourers working in the field, because the best way to fight these infections is to cut off the route of transmission from the soil.

CONSENT

However, twice the calculated sample size (160 workers) was issued consent forms. One hundred and two people (102) signed the forms indicating their willingness to participate in the study. Thus the study involved 102 CDC workers.

ETHICAL APPROVAL

Administrative and ethical and authorizations were obtained from the Regional Delegation of Public Health in Buea, the CDC Health office in Bota Limbe and Biaka University Institute of Buea Cameroon. Strict confidentiality was maintained in handling the data.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Albonico M, Shamlaye N, Shamlaye C, Savioli L. The control of intestinal parasitic infections in the Seychelles: A comprehensive and sustainable approach. Bulletin of the World Health Organization. 1996;74:577-86.
2. Chan MS. The global burden of intestinal nematode infections—fifty years on. Parasitology Today. 1997;13(11):438–443.
3. WHO. Soil-transmitted helminthes infections – World Health Organisation. WHO fact sheet on soil-transmitted helminth infections caused by different intestinal parasites, Includes key facts, definition, distribution, transmission, control and WHO response; 2019.
4. Cheesbrough M. District Laboratory Practice in Tropical Countries. 2nd Edition update, Part 1, Cambridge University Press, Cape, Town South Africa. 2006;246–255.
5. Ndamukong-Nyanga JL, Kimbi HK, Sumbele IUN, Nana Y, Sunjo CB, Ndamukong KJN, Lehman LG. A Cross-

- sectional Study on the Influence of Altitude and Urbanisation on Co-infection of Malaria and Soil-transmitted Helminths in Fako Division, South West Cameroon. *International Journal of Tropical Disease & Health*. 2015;8(4):150-164. [Article no.IJTDH.2015.088] [ISSN: 2278–1005]
6. Schmidt Gd, Larry RS. *Foundations of Parasitology* 6th Edition, U.S.A-Mac Graw Hill Publishers; 2000.
 7. Tiko district health service report to Bota personal communication; 2016.
 8. Tchuem Tchuente LA, Behnke JM, Gilbert FS, Southgate VR, Vercruysse J. Polyparasitism with *Schistosoma haematobium* and soil-transmitted helminth infections among school children in Loum, Cameroon. *Tropical Medicine and International Health*. 2004;9(2):314.
 9. Njunda AL, Fon SG, Assob JCN, Nsagha DS, Kwenti TDB, Kwenti TE. Coinfection with malaria and intestinal parasites, and its association with anaemia in children in Cameroon. *Infectious Diseases of Poverty*. 2015;4(43).
 10. Ndamukong KJ, Ayuk MA, Dinga JS, Akenji TN, Ndiforchu VA. The pattern of soil transmitted nematode infections in primary school children of Kumba Health district, south- West Cameroon. *Afr J Health Sci*. 2000;7:103-106.
 11. Thomas HZ, Jatau ED, Inabo HI, Garba DD. Prevalence of intestinal helminths among primary school children in Chikun and Kaduna South Local Government areas of Kaduna state, Nigeria. *Journal of Medicine and Medical Research*. 2014; 2(2):6-11.
 12. MINSANTE Cameroon (27 juil. 2018). 8^{ème} Réunion statutaire du comité national de lutte contre la Schistosomiase et les Helminthiases *Intestinales* au Cameroun; 2018. Available:https://www.minsante.cm/site/?q=fr/content/8%C3%A8me-r%C3%A9union-statutaire-du-comit%C3%A9-national-de-lutte-contre-la-schistosomiase-et-les
 13. De Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D. Soil-transmitted Helminth infections: Updating the global picture. *Trends Parasitolol*. 2003; 19(N0.12):547-551.
 14. Njunda AL, Fon SG, Assob JCN, Nsagha DS, Kwenti TDB, Kwenti TE. Coinfection with malaria and intestinal parasites, and its association with anaemia in children in Cameroon. *Infectious Diseases of Poverty*. 2015;4(43).
 15. Crompton DW. How much human helminthiasis is there in the world? *Journal of Parasitology*. 1999;85:397-403.
 16. Eze CN, Nzeako SO. Intestinal Helminths amongst the Hausa and Fulani settlers at Obinze, Owerri, Imo State, Nigeria. *Nigeria Journal of Parasitology*. 2011;32(2):225-229.
 17. Albonico M, Smith PG, Hall A, Chwaya HM, Alawi KS, Savioli L. A randomised controlled trial comparing Mebendazole and Albendazole against *Ascaris*, *Trichuris*, and the hookworms. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1994; 88:585-9.

© 2020 Ndamukong-Nyanga et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/56422>