THERAPEUTIC ADVANCES in
Infectious Disease

Editorial

Marburg virus disease amid COVID-19 in West Africa: an emerging and re-emerging zoonotic epidemic threat, future implications and way forward

Stanley Chinedu Eneh, Osaretin Christabel Okonji, Anyike Goodness Chiburoma, Onukansi Francisca Ogochukwu, Levi Tuwleh, Inyangudo Gideon, Emeka Francis Okonji, Fidele Nyimi Bushabu and Osaro Mgbere

Keywords: emerging infectious diseases, Equatorial Guinea, West Africa, Ghana, Marburg virus disease, outbreak, public health

Received: 7 November 2022; revised manuscript; 6 March 2023; accepted: 22 March 2023.

Ther Adv Infect Dis

2023, Vol. 10: 1–7

DOI: 10.1177/20499361231168520

Correspondence to:
Osaretin Christabel Okonji
School of Pharmacy, University of the Western Cape Town, Cape Town 7530, South Africa.
Okonjichristabel@gmail.com

Stanley Chinedu Eneh
Levi Tuwleh
Inyangudo Gideon
Department of Community Health, Obafemi Awolowo University, Ile-Ife, Nigeria

Anyike Goodness Chiburoma
College of Medicine, University of Lagos, Lagos, Nigeria

Onukansi Francisca Ogochukwu
Department of Public Health, Federal University of Sciences and Technology, Owerri, Nigeria

Emeka Francis Okonji
School of Public Health, University of the Western Cape, Cape Town, South Africa

Fidele Nyimi Bushabu
Service of Oral and Maxilla-Facial Surgery, Department of Dental Medicine, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

National Center Laboratory of Oral Biomedicine Ministry of Research Innovation and Technology, Democratic Republic of the Congo, Kinshasa

Osaro Mgbere
Department of Health Systems and population Health Sciences, Tilman J. Fertitta Family College of Medicine, University of Houston, Houston, TX, USA

Introduction

Amid the coronavirus 2019 (COVID-19) pandemic, several African countries including Ghana and Equatorial Guinea have reported several zoonotic outbreaks. The COVID-19 pandemic has added more strain on the already fragile healthcare system, and consequently increasing the impact of both emerging and re-emerging diseases such as the current outbreak of Marburg virus disease (MVD) in Ghana and Equatorial Guinea.[1–4] On 28 June 2022, the health authorities in Ghana received reports of two fatal cases of MVD;[1] by 29 July 2022, four confirmed case of MVD were reported with three deaths (case fatality ratio of 75%).[5] On 13 February 2023, the Ministry of Health and Social Welfare (MOH) of Equatorial Guinea confirmed MVD in Kie Ntem province in the North Western part of the country.[4,6] As of 21 February 2023, nine cumulative cases were reported and all were fatal.[4,7] As of 1 March 2023, additional two suspected cases were reported in Equatorial Guinea and both cases were fatal, making it 11 cumulative cases in total, all fatal.[8] The high case fatality ratio (CFR) of 75% of the recent MVD outbreak in Ghana and 100% in Equatorial Guinea is a worrying concern.

The current outbreak of MVD in Ghana and Equatorial Guinea makes it the second and third time this viral disease is identified in West Africa, and the source of the outbreak in both countries is unknown. The Republic of Guinea experienced the first outbreak of MVD in West Africa, which had a 90% CFR.[9] Although there have been outbreaks and sporadic cases of MVD in other parts of Africa, such as Democratic Republic of Congo (DRC), Angola, Kenya, South Africa and Uganda,[9,10] the re-emergence of this viral disease in West Africa is a serious epidemic threat that warrants urgent attention.

Marburg virus disease is a lethal illness cause by Marburg virus (MARV) with a high CFR of about 24–88%.[10] The World Health Organization (WHO) has officially recognized MARV as an extremely important global pathogen and is currently classified as a risk group 4 pathogen.[11,12] Since its discovery in 1967, there have been 14 reported cases of MVD outbreaks, most of which have occurred in sub-Saharan Africa, particularly in the DRC, Kenya, Angola, Uganda, and South Africa.[9,10] A chronological summary of reported outbreaks of MVD from 1967 to 2023 is presented in Table 1. Based on the MVD outbreaks by countries and CFR, the largest outbreak ever reported was in Angola in 2005. The MVD outbreak in Angola recorded over 374 cases and over 329 deaths with a CFR of 88%.[9,10] In 2007 and 2012, Uganda experienced MVD outbreaks, in which the virus re-emerged in 2014 and 2017 with a CFR between 27% and 100%.[9,10,13]

Table 1. Chronology of outbreaks of Marburg virus disease.[a]

Countries	Number of outbreaks	Cases	Deaths	Case fatality rate	Year of outbreaks
Yugoslavia (Serbia)	1	2	0	0 %	1967
Germany	1	29	7	24%	1967
South Africa	1	3	1	33%	1975
Kenya	1	1	1	100%	1980
	1	2	1	50%	1987
Democratic Republic of Congo	1	154	128	83%	1998–2000
Angola	1	374	329	88%	2005
Netherland (ex-Uganda)	1	1	1	100%	2008
United States of America (ex-Uganda)	1	1	0	0%	2008
Uganda	1	4	2	50%	2007
	1	15	4	27%	2015
	1	1	1	100%	2014
	1	3	3	100%	2017
Guinea	1	1	1	100%	2021
Ghana	1	4	3	75%	2022
Equatorial Guinea	1	11	11	100%	2023

[a]Adapted from WHO Fact sheet for Marburg virus disease.[4,5,8,10,14]

Marburg virus is of the same family as the Ebola virus – Filoviridae family (filovirus).[10,15] MARV is a single stranded, enveloped, negative-sense RNA virus with a length of between 800 and 14000 nm.[11,16,17] MARV comprises of seven structural proteins. Although MARV is nearly identical to the Ebola virus in its structure, it can induce different antibodies in infected individuals.[16] Although generally less well known than its cousin the Ebola virus, MARV was the first filovirus discovered after epidemics in Germany and Yugoslavia (now Serbia) in 1967.[11] The reason for the re-emergence of MARV during the COVID-19 pandemic is as a result of zoonotic spill over.[18]

Marburg virus disease is generally transmitted from animals to humans, but it can be transmitted via direct contact (through cuts in the skin or ruptured mucous membranes) with the blood, secretions, organs, or other bodily fluids of an infected person, as well as close contact with contaminated surfaces and materials like bedding and clothing.[9,10] The Egyptian fruit bat, *Rousettus aegyptiacus* of the Pteropodidae family, is known as the natural host of MARV. Long-term contact with mines or caves where *Rousettus* bat colonies are present causes human infection with MVD.

Marburg virus has high levels of virulence and can cause hemorrhagic fever, severe headaches, and malaise.[9,10] Other common symptoms include muscle aches, pains, severe watery diarrhoea, abdominal pain and cramping, nausea and vomiting. Fatal cases experience confusion, irritability, aggression and bleeding from multiple areas including nose, gums and vagina.[10] In patients with severe cases, death occurs between

eight and nine days after symptom onset, usually as a result of severe blood loss and shock.[10] The average CFR for MVD is 54%.[19] The incubation period of MVD ranges from 2 to 21 days.[10]

There are several limitations to the diagnosis and treatment of MVD. It can be challenging to differentiate the viral disease in its early stages from other infectious diseases such as malaria, shigellosis, meningitis, typhoid fever and other viral haemorrhagic fevers.[10] The diagnosis of MARV infection is challenging; the viral infection is confirmed using the following diagnostic methods: an antibody-capture enzyme-linked immunosorbent assay (ELISA), an antigen-capture detection test, a serum neutralization test, a reverse transcriptase-polymerase chain reaction (RT-PCR) assay, electron microscopy and virus isolation using cell culture.[10] In addition, to date there is currently no MARV vaccines and therapeutics approved by regulatory agencies, and the sporadic nature of outbreaks, among other factors, makes it difficult to test new countermeasures during outbreaks in terms of ethics and logistics. Due to the absence of vaccine or approved therapeutics, its high lethality and infectivity, and the potential for aerosol transmission, laboratory investigation of MARV is carried out in high-containment Biosafety Level 4 (BSL-4) laboratories.

The management of MVD is mainly through supportive treatment such as intravenous fluids and electrolyte replacement, as well as treatment of specific symptoms, which may significantly improve survival rate.[9,10] Several MARV vaccines are undergoing different phases of clinical studies.[13,16,20] To promote the rapid development of MARV vaccines, the WHO R&D Blueprint have gathered a group of experts to promote the preclinical and clinical development of MARV vaccine candidates.[20] The re-emergence of this fatal disease, the lack of effective therapy and the lethality of this viral disease calls for rapid and quick production of effective vaccines and antiviral drugs.

Description of MVD outbreak in Ghana

The first MVD case in Ghana was discovered in a 26-year-old farmer who resides in the Ashanti region and had previously had a history of travel to the Western region in Ghana.[1] He went for a medical check-up on 26 June 2022, and on 27 June 2022, he was confirmed dead. The corpse was transported and interred in the district of Sawla-Tuna-Kalba (Savannah region), which serves as a border between Burkina Faso and Côte d'Ivoire. Before his laboratory results were known, he had already been buried.[1] The second incident involved a man, 51 years old, who was also a farmer in the Ashanti Region. He was hospitalized in the same hospital as the index case on 28 June 2022 but died that same day.[1] The first two reported fatal cases had symptoms such as fever, nausea, diarrhoea, mouth and nose bleeding and other related Ebola-like symptoms. Both victims were unrelated and had no history of contact with dead animals, ill persons or animals, but they both live in a forest environment community. The third case was a 22-year-old female, wife to the index case, who presented with symptoms on 29 June 2022 and was reported missing on 24 July 2022.[5] The fourth case was a 1-year-old child, who was son of the index and third case. The child presented with symptoms including diarrhoea on 13 July 2022 and died 19 July 2022, making a total of three deaths of MVD in Ghana.[5] More than 100 close contacts of all cases have been identified and monitored closely. The notification of four confirmed cases of MVD in Ghana with a CFR of 75% (3 of 4) raises serious concern and represents a serious public health threat. There are currently no confirmed cases pending in Ghana, but monitoring and other public health measures are ongoing to contain any threat to health security.[21]

Description of MVD outbreak in Equatorial Guinea

On 13 February 2023, the Ministry of Health and Social Protection (MoH) of Equatorial Guinea reported a confirmed MVD outbreak in the North Western province of Kie Ntem in the West Africa country.[6] One confirmed case, 11 deaths and 16 suspected cases were reported in two communities across the province.[6,8] This is the first MVD outbreak ever reported in Equatorial Guinea. The source of this outbreak is still uncertain, and genome sequence results are still pending. The outbreak was identified by a District Health Officer on 7 February 2023. The only confirmed case presented with fever, non-bloody vomiting, bloody diarrhoea, and convulsions and died on 10 February 2023, and this case had epidemiological links to four deceased cases from one of the villages in Nsoc-Nsomo district.[4] The other

suspected cases presented with symptoms such as fever, fatigue, bloodstained vomit and diarrhoea.[4,6] Two cases also presented with skin lesions and bleeding from the ear. As of 21 February 2023, there were nine cumulative cases, including one confirmed case, four probable cases and four suspected cases. The nine cases were fatal, one died in a healthcare facility and the other eight died in the community. As of 1 March 2023, two new suspected cases were reported and both cases were fatal, bringing the total cumulative cases of MVD to 11 cases and all were fatal.[8] Thirty-four contacts are identified and been monitored closely.

Challenges and effort

A major challenge is the inability to identify the source of this outbreak in both Ghana and Equatorial Guinea. Although investigations are still being carried out, including expanded surveillance using the Integrated Disease Surveillance and Response (IDSR) system and contact tracing. But due to a poor surveillance system, both countries surveillance team are yet to identify the source of this outbreak, which could lead to a huge risk of disease spread to other parts of the community and neighbouring nations. It was also reported that the first two cases of MVD were not safely buried in Ghana.[1] Eight of MVD cases died in the community in Equatorial guinea, and their burial conditions are unknown;[4] this could increase the risk of transborder transmission to other neighbouring countries close to Ghana like Burkina Faso and Côte d'Ivoire and countries close to Equatorial Guineas like Cameroon and Gabon.

Several efforts are being made by WHO, Africa Centres for Disease Control and Prevention, Ghanaian Ministry of Health and the Ministry of Health and Social Welfare of Equatorial Guinea to help establish active surveillance systems, contact identification and working with communities to increase awareness of the viral disease.[1,4,6] The Ashanti region healthcare directorate commenced the implementation of coordination mechanisms and response activities across affected health districts in Ghana.[21] In addition, at the community level, recruitment and orientation of surveillance volunteers for community-based surveillance have been implemented. Furthermore, the WHO has supplied adequate reagents for sample testing in Ghana.[1] Equatorial Guinea is facing an outbreak of MVD for the first time, and the country has inadequate capacity to manage the outbreak. The WHO is supporting the transportation of samples to laboratories in Senegal and Gabon, as plans are underway to set up laboratory facilities in Equatorial Guinea.[4] The WHO is also exploring the feasibility of testing Marburg vaccines that are in various stages of development in Equatorial Guinea, but a successful trial seems impossible due to several logistics.[7]

The quick response of the Ghana Health Service and the Ministry of Health with support from WHO has resulted in the declaration of the end of the MVD outbreak on 16 September 2022 in Ghana.[22] To prevent future outbreaks, the WHO and the United Kingdom (UK) Foreign, Commonwealth and Development Office (UK-FCDO) are supporting the Government of Ghana to conduct a socio-ecological study of MVD in Ghana so as to understand the risks in the country for mitigation intervention to prevent recurrence.[22] It is of great concern that Ghana is experiencing multiple outbreaks, including mpox, yellow fever and COVID-19 at the same time; multiple outbreaks occurring simultaneously exert pressure on the already weak healthcare systems.[5,23,24] Multiple outbreaks of infectious diseases remain a significant threat to public health, especially in the African region; however, little attention has been paid to enhancing health surveillance systems.[5,23,25,26]

Recommendations and future direction

The occurrence of other infectious diseases is quite predictable given that the COVID-19 pandemic has disrupted health systems in most low- and middle-income countries (LMICs), like Ghana and Equatorial Guinea. The outbreak of the MVD in the West African region, with Ghana having its first cases in 2022, and Equatorial Guinea in 2023 calls for increased surveillance and monitoring of zoonotic diseases, particularly in African countries. Marburg virus disease could pose a major epidemic threat as surveillance of the disease remains a challenge, and there are no approved vaccines or specific antiviral drugs or treatments. There is urgent need to strengthen disease surveillance, in Ghana, Equatorial Guinea and other Africa countries, as well as identifying the areas where spill over from bats may occur. It

is also necessary to strengthen the relevant regulations and guidelines on the cooking of animal products (meat) and fruit prior to consumption. Massive awareness about MARV aetiology and outbreak, symptoms, mode of transmission and infection prevention control is necessary in African communities; this would support the implementation of preventive measures to prevent further spread of this fatal disease. The regulation of borders and proper burials of deaths resulting from fatal cases of MVD is necessary in reducing the spread of the virus.

Most of the newly emerged and re-emerged zoonotic diseases are mostly reported across Africa. A WHO analysis found that the number of zoonotic epidemics in the African region increased by 63% between 2012 and 2022, compared with 2001 and 2011.[23,27] According to the analysis, between 2001 and 2022, 1843 substantiated public health events were reported in the African region, 30% of which were zoonotic outbreaks. While these figures have increased over the past two decades, there was a particular peak in 2019 and 2020 when zoonotic pathogens accounted for about 50% of public health events. Ebola virus disease and other viral haemorrhagic fevers are responsible for nearly 70% of these outbreaks, with mpox, dengue, anthrax, plague and a host of other diseases comprising the remaining 30%. These are expected to rise along with human-to-animal host contact due to increased environmental mortification that reduces wildlife's activities globally.

We propose that the one-health approach[28] should be implemented to stop the spread of zoonotic infectious diseases, as infectious diseases continue to emerge and re-emerge in the African continent. The one-health approach is a unique approach to health that requires multiple sectors, disciplines and communities to work together. This includes a broad range of experts, including those involved in human, animal health and environment research. Furthermore, collaboration under the one-health concept would improve Africa's surveillance and emergency response teams against emerging and re-emerging zoonotic infectious diseases. In addition, a comprehensive research is necessary to identify the environmental, socio-economic and cultural factors that stimulate the emergence and transmission of zoonotic diseases, and a better understanding of the factors that affect the impact and spread of these outbreaks.

The outbreak of neglected zoonotic diseases like MVD will continue to re-emerge because the world is currently focused on the COVID-19 pandemic and the mpox outbreak that has been declared a public health emergency of international concern by the WHO. Thus, some zoonotic illnesses have received little awareness or recognition as the world has focused primarily on infectious diseases that threaten global health and global economy. This emphasizes the importance of paying more attention to endemic zoonotic illnesses.

The recent outbreaks of MVD in Guinea, Ghana and Equatorial Guinea during the COVID-19 era necessitate detailed and comprehensive research studies to understand the viral disease. Although several outbreaks have been reported globally, with only few reported cases, there has been insufficient clinical research conducted. While the magnitude of the COVID-19 pandemic surpasses most infectious diseases in Africa, the WHO should strengthen coordination with respect to MVD in endemic countries and provide continued funding support to minimize the reoccurrence of this deadly disease. There are concerns that globalization may lead to viral transmission across countries and continents, like what happened in the case of COVID-19 pandemic. In addition, it is also important to develop effective vaccines and therapeutics in a timely manner to combat this deadly disease.

Conclusion

With the recent outbreak of MVD in Ghana and Equatorial Guinea during the COVID-19 era, with a very high CFR of 75%, and 100%, respectively, and the absence of authorized medical countermeasures, there is need for urgent action to accelerate the development, evaluation and approval of MVD vaccines and therapeutics. It is important that effective vaccines and antiviral drugs are developed swiftly, before this viral disease becomes a pandemic threat due to its extremely high mortality rate. Increased surveillance and diagnosis are necessary for the early detection of future outbreaks as well as a rapid rollout of vaccines and therapeutics.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Stanley Chinedu Eneh: Conceptualization; Investigation; Project administration; Writing – original draft; Writing – review & editing.

Osaretin Christabel Okonji: Conceptualization; Investigation; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Anyike Goodness Chiburoma: Writing – original draft; Writing – review & editing.

Onukansi Francisca Ogochukwu: Writing – original draft; Writing – review & editing.

Levi Tuwleh: Project administration; Writing – original draft; Writing – review & editing.

Inyangudo Gideon: Writing – original draft; Writing – review & editing.

Emeka Francis Okonji: Investigation; Project administration; Writing – original draft; Writing – review & editing.

Fidele Nyimi Bushabu: Writing – original draft; Writing – review & editing.

Osaro Mgbere: Writing – original draft; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
Not applicable.

ORCID iDs
Osaretin Christabel Okonji https://orcid.org/0000-0002-1511-2094

Levi Tuwleh https://orcid.org/0000-0001-5343-9840

References

1. WHO. Marburg virus disease – Ghana, https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON402 (accessed 14 September 2022).
2. CDC. Marburg in Ghana – watch – level 1, practice usual precautions – travel health notices travelers' health, https://wwwnc.cdc.gov/travel/notices/watch/marburg-ghana (accessed 14 September 2022).
3. Wellington J, Nur A, Nicholas A, *et al*. Marburg virus outbreak in Ghana: an impending crisis. *Ann Med Surg* 2012; 81: 104377.
4. WHO. Marburg virus disease – Equatorial Guinea, https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON444 (accessed 26 February 2023).
5. WHO. Weekly bulletin outbreaks and other emergencies, https://apps.who.int/iris/bitstream/handle/10665/361243/OEW31-2531072022.pdf (accessed 14 September 2022).
6. Africa CDC. Press release on Marburg virus disease in Equatorial Guinea, https://africacdc.org/news-item/press-release-on-marburg-virus-disease-in-equatorial-guinea/ (accessed 26 February 2023).
7. Callaway E. Marburg virus outbreak: researchers race to test vaccines. *Nature* 2023; 614: 603–603.
8. CIDRAP. Equatorial Guinea reports 2 more suspected Marburg virus deaths CIDRAP, https://www.cidrap.umn.edu/marburg/equatorial-guinea-reports-2-more-suspected-marburg-virus-deaths (accessed 1 March 2023).
9. Okonji OC, Okonji EF, Mohanan P, *et al*. Marburg virus disease outbreak amidst COVID-19 in the Republic of Guinea: a point of contention for the fragile health system? *Clin Epidemiol Glob Health* 2022; 13: 100920.
10. WHO. Marburg virus disease, https://www.who.int/news-room/fact-sheets/detail/marburg-virus-disease (accessed 14 September 2022).

11. Shifflett K and Marzi A. Marburg virus pathogenesis – differences and similarities in humans and animal models. *Virol J* 2019; 16: 165.
12. Sah R, Mohanty A, Reda A, *et al*. Marburg virus re-emerged in 2022: recently detected in Ghana, another zoonotic pathogen coming up amid rising cases of Monkeypox and ongoing COVID-19 pandemic – global health concerns and counteracting measures. *Vet Q* 2022; 42: 167–171.
13. Nyakarahuka L, Shoemaker TR, Balinandi S, *et al*. Marburg virus disease outbreak in Kween District Uganda, 2017: epidemiological and laboratory findings. *Plos Negl Trop Dis* 2019; 13: e0007257.
14. Marburg virus disease – Guinea, https://www.who.int/emergencies/disease-outbreak-news/item/marburg-virus-disease—guinea (accessed 7 November 2022).
15. Reuben RC and Abunike SA. Marburg virus disease: the paradox of Nigeria's preparedness and priority effects in co-epidemics. *Bull Natl Res Cent* 2023; 47: 10.
16. Zhao F, He Y and Lu H. Marburg virus disease: a deadly rare virus is coming. *Biosci Trends* 2022; 16: 312–316.
17. Changula K, Kajihara M, Mweene AS, *et al*. Ebola and Marburg virus diseases in Africa: increased risk of outbreaks in previously unaffected areas. *Microbiol Immunol* 2014; 58: 483–491.
18. Letko M, Seifert SN, Olival KJ, *et al*. Bat-borne virus diversity, spillover and emergence. *Nat Rev Microbiol* 2020; 18: 461–471.
19. Nyakarahuka L, Kankya C, Krontveit R, *et al*. How severe and prevalent are Ebola and Marburg viruses? A systematic review and meta-analysis of the case fatality rates and seroprevalence. *BMC Infect Dis* 2016; 16: 708.
20. Cross RW, Longini IM, Becker S, *et al*. An introduction to the Marburg virus vaccine consortium, MARVAC. *Plos Pathog* 2022; 18: e1010805.
21. Denkyira SA, Adesola RO, Idris I, *et al*. Marburg virus in Ghana: a public health threat to Ghanaians and to Africans. *Public Health Chall* 2022; 1: e32.
22. Ghana ReliefWeb. Beating Marburg virus outbreak: Ghana's journey to victory, https://reliefweb.int/report/ghana/beating-marburg-virus-outbreak-ghanas-journey-victory (accessed 11 February 2023).
23. Okonji OC and Okonji EF. Monkeypox during COVID-19 era in Africa: current challenges and recommendations. *Ann Med Surg* 2012; 81: 104381.
24. Nchasi G, Okonji OC, Jena R, *et al*. Challenges faced by African healthcare workers during the third wave of the pandemic. *Health Sci Rep* 2022; 5: e893.
25. Okonji EF, Okonji OC, Mukumbang FC, *et al*. Understanding varying COVID-19 mortality rates reported in Africa compared to Europe, Americas and Asia. *Trop Med Int Health* 2021; 26: 716–719.
26. Rackimuthu S, Hunain R, Uday U, *et al*. COVID-19, measles, and yellow fever: the need to reinforce vaccination in the Democratic Republic of Congo. *Clin Epidemiol Glob Health* 2022; 13: 100956.
27. WHO Regional Office for Africa. In Africa, 63% jump in diseases spread from animals to people seen in last decade, https://www.afro.who.int/news/africa-63-jump-diseases-spread-animals-people-seen-last-decade (accessed 30 January 2023).
28. Mackenzie JS and Jeggo M. The one health approach – why is it so important? *Trop Med Infect Dis* 2019; 4: 88.