Hantaviruses in East and Central Africa

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Abstract

Hantaviruses, family Bunyaviridae are emerging zoonotic RNA viruses with public health concern. This article explores Hantavirus distribution in East and Central Africa in relation to vegetation density as well as the risk factors associated with the transmission of the infections. In addition, the role of public knowledge and awareness in the prevention and control as well as diagnosis infrastructure preparedness to accommodate Hantavirus infections is highly needed. With a note on the diversity of reservoir hosts, such as rodent, shrew and bat species which rises an interest of Hantavirus research and other emerging viral research in East and Central Africa.

Key words: Hantaviruses, vegetation distribution, reservoir host, public health

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1. Introduction

Hantaviruses from a family Bunyaviridae, genus Hantavirus, currently are emerging viral pathogens with global public health concerns (Jiang *et al.*, 2017). These zoonotic RNA viruses are associated with multiple species of bats, moles, shrews and rodents(de Oliveira *et al.*, 2014; Kruger *et al.*, 2015). Hantaviruses are etiologic agents of hemorrhagic fever with renal syndrome

(HFRS) and Hantavirus cardiopulmonary syndrome (HCPS) with respective case fatality rate of up to 60% worldwide (Kruger *et al.*, 2015).

Investments in one health research from early 1980s, revealed the circulation of Hantavirus on both human and rodent populations across East and Central Africa with an infection rate of up to 7% (Witkowski *et al.*, 2014). Tremendous effort has been made as to identify other reservoir hosts that carries Hantavirus strains, where by different viral sero types has been identified from different reservoir host such as bats, shrews and rodents using advanced molecular techniques (Papa *et al.*, 2016). However, in Africa, only Sangassou virus has been isolated from febrile patient living on Sangassou village in Guinea (Boris Klempa *et al.*, 2012).

Since different reports shows Hantaviruses circulates in reservoir host such as bat, rodent and shrews as well as human population across East and Central Africa (Chau *et al.*, 2017; Heinemann *et al.*, 2016; Kang *et al.*, 2014; Těšíková *et al.*, 2017; Witkowski *et al.*, 2014), unfortunately, the level of clinical and public awareness on risk factors, sign and symptoms, treatment management and the distribution of pathogen itself, is not well known. In addition to that, also the strength of diagnostic infrastructure to provide accessible quality-assured diagnoses to patients with viral infection is uncertain. Therefore, this review accentuates the importance of clinical and public awareness (Hansen *et al.*, 2017; Tong *et al.*, 2017) in the management and control of Hantavirus pathogen as well as the need of diagnosis infrastructure preparedness as to ensure the accessibility of quality-assured diagnoses to febrile patients after arriving on the health care facility.

2. Hantavirus distribution in East and Central Africa

Fascinating diversity of rodent, shrew and bat species with higher relationship with vegetation density and climate change across East and Central Africa rise a concern on Hantavirus research and other emerging viral pathogens (Hansen *et al.*, 2017; Prist *et al.*, 2017; Rothenburger *et al.*, 2017). The relationship between Hantavirus and their specific host is of interest, however some of these viruses share different host due to spillover effects of the viral pathogens in small wild animal populations (de Oliveira *et al.*, 2014; Forbes *et al.*, 2018). Implemented one health research projects in East and Central Africa through collaborative partnership with developed countries enables the identification of different Hantavirus serotypes and other emerging viral pathogen. For example, the detection Makokou virus (MKV) on

Noacks round leaf bat (*Hipposideros ruber*) in Gabon (Witkowski *et al.*, 2016), Lom-pole virus (LMPV) on *Mops condylurus* in Democratic Republic of Congo (Krüger *et al.*, 2015) expanded the reservoir host for hantavirus worldwide.

Hantavirus of sister lineage as Sangassou virus were identified on *Hylomyscus endorobae* in Kenya, a different wood mouse specie from that of Guinea, however these species both belong on the same genus (Boris Klempa *et al.*, 2012; Těšíková *et al.*, 2017). Kilimanjaro virus and Uluguru virus were identified on mouse shrews, *Myosorex geata* and *Myosorex zinki* respectively in Tanzania (Kang *et al.*, 2014). The identified Hantavirus serotypes in different reservoir hosts such as bats, rodents and shrews indicates that virus has expanded the boundary of host range (Boris Klempa *et al.*, 2012).

Furthermore, investigations on asymptomatic and febrile patients revealed the circulation of the virus on human population with a sero prevalence ranging from 0.2% to 7% across East and Central Africa and this rise a public health concern of Hantavirus pathogen (Heinemann *et al.*, 2016; Hofinger *et al.*, 2006; Witkowski *et al.*, 2014; Witkowski *et al.*, 2015).

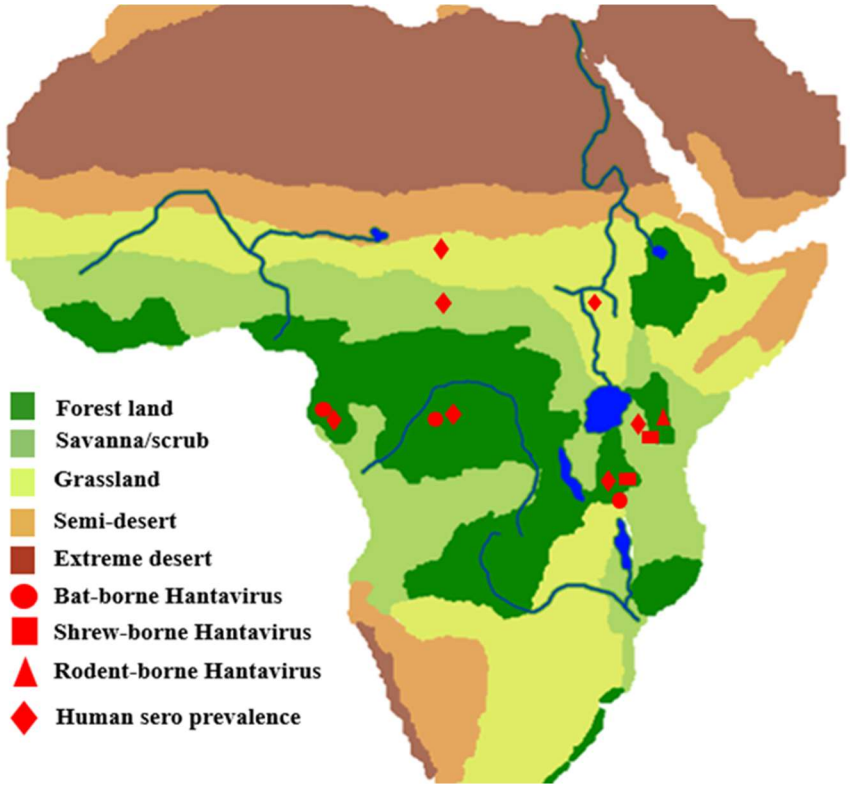

Figure.1. A map of Africa showing Hantavirus distribution in relation to vegetation distribution across East and Central Africa.

3. Hantavirus reservoir hosts

3.1.Rodents

In Africa there are nearly above 400 rodent species, with an ability to survive in dense vegetation and barren environments. Some of these species have the tendency to associate with human dwellings while some of the species they are naturally from the wild environment but they tend to invade the human dwelling due to climate change or catastrophic reasons (D'Onofrio *et al.*, 2017; NAKAMURA *et al.*, 2017; Stanley *et al.*, 2011).

The family Murinae (rats and mice) and Cricetidae are of most important as far as Hantavirus is concerned since they contain rodent species, which found commonly in East and Central Africa. In West Africa as well as in East Africa, species such as *Hylomyscus simus* and *Hylomyscus endorobae* has been associated with Sangassou Hantavirus strain (Boris Klempa *et al.*, 2007; Těšíková *et al.*, 2017). Different reports show the specificity of Hantaviruses to their host but due to syntopic and sympatric reasons, viral spillover events can cause interspecies and intraspecies transmission (de Oliveira *et al.*, 2014; Guterres de Lemos, 2018; Klingström *et al.*, 2002). Therefore, since we share the same ecology, the reports of emerging and re-emerging viral pathogens such as Hantavirus, Nipah virus, and Arena viruses in rodents, rises a public health concern.

3.2.Shrews

Diversity of shrews in East and Central Africa is of most importance in human health, due to ongoing interaction between wild life environment and human population in the concept of emerging and re-emerging viral diseases. Existence of vast of species, from the order Soricidae (shrews) within Savanna and forestland vegetation (Fig.1 above) highlight the need to exploit more in terms of disease transmission and Hantavirus diversity (de Oliveira *et al.*, 2014; Forbes *et al.*, 2018). Some of these species already identified while other are not yet identified. Crocidura species and Myosorex species already explained to carry Hantavirus in Africa (Kang *et al.*, 2011; Kang *et al.*, 2014; Boris Klempa *et al.*, 2007). For example, identification of Kilimanjaro virus (KMJV Strain FMNH174124) and Uluguru virus (ULUV strain FMNH 158302) on *Myosorex*

geata and *Myosorex zinki* expanded the understanding of Hantavirus reservoir host in East and Central Africa (Kang *et al.*, 2014).

3.3. Bats

Chiropterans (bats) plays an important role in the ecology and biodiversity, however can act as the potential reservoir hosts for many viral pathogens such as Bunya viruses, Filoviruses, Corona viruses, Paramyxo viruses, and Lyssa viruses (Bird Mazet, 2017; Dulo Pal, 2017; Van Cakenberghe *et al.*, 2017). The features such as global distribution, abundance, flight capacity, colonies with dense population and social behaviors favor the maintenance, evolution and spread of viral pathogens (Calisher *et al.*, 2006; de Oliveira *et al.*, 2014). Other characteristics includes long life span in comparison with their body size and hibernation capacity. These features facilitate viral persistence, transmissibility, reduced viral replications and immune functions (Calisher *et al.*, 2006; de Oliveira *et al.*, 2014).

Current reports shows, the potential of chiropterans to act as the reservoir host for Hantavirus across East and Central Africa. For example, the identification of Makokou virus (MKV) on Noack's round leaf bats (*Hipposideros rubber*) on Gabon (Witkowski *et al.*, 2016) and Lom-pole virus (LMPV) on *Mops condylurus* in Democratic Republic of Congo, expanded the diversity of bat species acting as reservoir host for Hantavirus in Africa and worldwide in general (Krüger *et al.*, 2015).

Bat species distribution across East and Central Africa in relation to vegetation distribution is of most interest as far as emerging diseases is concerned. However, other factors which contributes to the distributions of these chiropteran species includes geology (roosting area of some species is associated with geological features such as caves, mines, and rock crevices), land use/land cover (some species tend to use human structures such as houses and domesticated crops as the roosting sites), biome (Figure.1), temperature variability and precipitation parameters (D'Onofrio *et al.*, 2017; Jaberg Guisan, 2001).

4. Risk factors for Hantavirus transmission to human

Hantavirus infections affects individuals of low income living in rural and peri-urban areas due to low hygienic standards, since the disease tend to be associated with

living conditions, agriculture activities, habitat sharing between human population and bats or rodents and thereby expose the human onto the risk of being infected with Hantavirus (de Oliveira *et al.*, 2014; Watson *et al.*, 2014).

Worldwide, Hantavirus outbreaks have been associated with rodent population increase influenced by external factors such as interspecific competition, climate change and anthropic activities. Global warming (increase in temperature) and heavy rainfall may results into the increase on food supply since trees shed many seeds into the soil, as well as increase in grain products from farm areas. The increase on food supply for rodents may have an impact on rodent population increase and hence increases the risks for human infections due to habitat sharing (B Klempa, 2009).

In relation to the population increase of bat species due vegetation distribution as indicated on figure 1 on East and Central Africa, with other influencing factors such as the tendency of other bat species e.g. *Mops condylurus* and others, to use human structures or houses as roosting sites. It increases the risk of human population be infected with the virus if a particular bat specie carries Hantavirus. Not only that the collection of bat organic manure for agricultural purpose without wearing gloves and mask, exposes the human into higher risk of Hantavirus infections but also sweeping the houses habited by bats or sweeping under the trees which are roosting sites for bats without wearing protective equipment increases the risk.

The diversity of cultural behaviors of some communities across East and Central Africa on consuming bush meat as source of protein from wild animals such as bats and rodents expose them onto the risk of not only Hantaviruses but also other emerging viral diseases such as Corona viruses, Arena viruses, filo viruses and Paramyxo viruses (Han *et al.*, 2015; Weiss *et al.*, 2012). Furthermore, individuals who have the tendency of visiting geological features such as caves with higher population of infected bats, have higher risk of acquiring infection (Kuzmin *et al.*, 2010).

Other risk factor include, living in the house with low ventilation also have the rodent breading sites, increases the risk of infections since during cleaning the breading areas; there is higher possibility of inhaling aerosols of excreta from infected animals and hence being infected.

5. Management, prevention and control of Hantavirus infections

5.1.Management of Hantavirus infection

Hantaviruses are zoonotic pathogens causing two threats to human life, Hemorrhagic fever with renal syndrome (HFRS) and Hantavirus cardiopulmonary syndrome (HCPS). Only Hantaan virus (HNTV), Seol virus (SEOV), Puumala virus (PUUV) and Dobrava – Belgrade virus (DOBV) have been reported to cause HFRS (Mattar *et al.*, 2015) while other Hantavirus serotypes responsible HCPS. When the febrile patients arrives at the hospital first has to get diagnosis (both clinical and laboratory) and then managed properly regarding to the phase of the disease he/she presents.

5.1.1. Diagnosis of Hantavirus infections

The clinical diagnosis of the Hantavirus infections depends on the type of the disease as well as Hantavirus serotypes causing the disease. Symptomatic stages of a patient with HFRS includes febrile stage, hypotensive stage, oliguric stage, polyuric stage and convalescence stage. On the febrile stage a patient experience fever, flu like, backache and visual disorder sometimes. This stage takes 3-7 days after the incubation period of the virus in the body. After the febrile stage, a patient enters the hypotensive stage, where the level of blood platelets drops and the symptoms may lead to tachycardia and hypoxemia. This stage usually last for three to seven days. In Oliguric stage, a patient may experience renal failure and proteinuria within three to seven days. Thereafter follows a polyuria stage where a patient experience an abnormal production of urine, which results into frequent urination, a patient, may pass three to six liters per day. The last stage is convalescence stage where a patient start to recover and the symptoms start to improve. Patient with HCPS may pass through febrile stage, prodromal stage, cardiogenic stage and convalescence stage during disease progression. Febrile stage may take 3-6 days after the incubation stage, if not managed properly patient may enter prodromal stage, where he/she may experience fever, headache, myalgia, vomiting, diarrhea and abdominal pain and this may last 3-5 days. On the cardiogenic stage, a patient experiences dyspnea, non-productive cough and circulatory collapse, 75% of the patients with cardiopulmonary edema may require mechanical support on ventilation. However, this stage takes 24-

48 hours. and finally rapidly improvement from the symptoms(a convalescence stage) (Avšič-Županc *et al.*, 2015; Vapalahti *et al.*, 2003). Clinical misdiagnosis and improper management may results to death.

Laboratory diagnosis is very crucial for the detection and confirmation of the Hantavirus infections. Assays available for the detection of the Hantavirus pathogens are Immunosorbent assays (IgG and IgM ELISA), immunoblotting assays (in house western blot and Microgen blot assays), immunofluorescence assay (IFA), reduction neutralization assay (FRNT) and molecular detection assays (PCRs). Each method is very sensitive depending on the stage of the disease. The method such as molecular detection assay is very sensitive from day 2 to day 10 of infection since the viral load titer is higher in the body however, the sensitivity decreases as the disease progress. The sensitivity IgM ELISA assay extends up to day 13 to 15, after that since the expression of Immunoglobulin M (marker for acute infection) starts to decrease in the body then also the sensitivity of the assay also decreases. However, confirmatory assays such IFA and FRNT are very crucial for the laboratory confirmation of Hantavirus infection after the detection by ELISA assays (Mattar *et al.*, 2015; Witkowski *et al.*, 2014).

5.1.2. Treatment management of Hantavirus infection

Currently, there is no specific treatment of Hantavirus infections however, patients with suspected and confirmed Hantavirus infections receive supportive treatments such as broad-spectrum antibiotics and if the patient is on early stages of the diseases, may get administration of antipyretics and analgesics (CDC).

However, when a patient presents with fulminant illness due to HCPS, may have the poor prognosis despite of intensive care management. The intensive-care management of the patient should include careful assessment, monitoring, adjustment of volume status and cardiac function including inotropic and vasopressor if needed. Administration of fluids should be in careful attention due to the capillary leakage, and when a patient is hypoxic, oxygenation highly recommended (Anderson *et al.*, 2017; Avšič-Županc *et al.*, 2015).

Ribavirin drug is now a suggestive drug on management of patient with HFRs and already shown to decrease case fatality rate on patients with HFRS and not HCPS. However, from a current report, a drug has insufficient efficacy and safety (Malinin Platonov, 2017).

5.2. Prevention and control of Hantavirus infections

The insurance of human health is of public health importance as far as Hantavirus is existing in East and Central Africa, therefore implemented preventive and control measures of the Hantavirus infections must ensure the safety of population. The strategies divided into preventive strategies and communicative strategies, both strategies warrant the elimination and minimize the Hantavirus infections to the human population.

Most of reported Hantaviruses that cause diseases in human are rodent-borne Hantaviruses. Therefore, when removing the rodent breading sites in the house or clean the breading sites, an individual may wear the disposable FP3 mask and before the start of cleaning, or may pour disinfectants solutions (1-5% Sodium hypochlorite, 1-5% of the Clidox reagent, 1-5% Dettol and 1-5% Virkon reagent) as to kill the virus. Also minimizing or eliminating the contact between rodents and human by preventing the rodents from entering the houses or using rodents traps to remove them.

In those areas, where bats share the habitat with human population, the following precautions should be in considerations; when cleaning (sweeping) places e.g. close to the tree where bats are roosting wear disposable FP3 mask as to prevent yourself from inhaling contaminated aerosols. Other society within East and Central Africa they tend to use organic manure from bats as organic fertilizer, during the collection of bat manure (places with huge bat colonies), personnel should take precautions of wearing gloves and disposable FP3 mask and also avoid a bite from bats or never touch a bat with bare hands.

Another strategy is to rise a public awareness and clinical awareness for Hantavirus infections. Knowledge and awareness on infectious disease are very important tools in the prevention and control of diseases. Therefore, the knowledge dissemination for Hantavirus infections concerning the pathogen itself, risk factors for the transmission of the diseases, symptoms and treatment management, has to be in both clinical and non-

clinical societies, and this will help on preventing and managing Hantavirus infections to the society.

6. Recommendations and way forward

Across East and Central Africa, there is a need to update the diagnostic infrastructure and treatment policies as to accommodate the Hantavirus infections. Since laboratory diagnosis of HCPS/HFRS need a biosafety level two (BSL-2) with precaution practice of biosafety level three (BSL-3) (Knudsen *et al.*, 1994). Health care facilities in urban and rural setting should have the laboratory capacity in terms of infrastructure, equipment and reagents as well as skilled staff to enable the laboratory diagnoses to continue when suspected cases arrive in the hospital.

Development of rapid diagnostic kits, which combine all African Hantaviruses, is more crucial as to facilitate the detection of viral infections in febrile patients within the rural and urban health centers across the East and Central Africa in general. However, the current available POC Hantec RDT kit (Koishi *et al.*, 2016) developed and validated using Hantaviruses serotypes from Brazil and South America, has to be validated for the detection of African Hantaviruses as to ensure sensitivity and specificity before implementing on health care setting. Continuous monitoring of point of care test kits is more important as ensure the validity of the results.

Strengthening the public and clinical awareness on Hantavirus infections especially in terms of pathogen itself, risk factors, sign and symptoms, management treatments, prevention and control of the disease is of most important as to ensure a public health. Since Hantavirus pathogens circulates in East and Central Africa, community knowledge and awareness on the infections is more important as preventive strategy of the disease onto the population at risk.

Implement and strengthening of one health projects within East and Central Africa provides a chance for the identification of more reservoir hosts for Hantavirus and other non-identified viral serotypes as well as the infected areas but also further geographical distribution of the virus as far as public health is concerned.

7. Competing interest

Authors declare that they do not have competing interest.

8. Author's contribution

LS, NEN and GS conceived the idea and designed the manuscript draft. LS, GS, NEN, TMT, and CDM contribute on the comments and LS, NEN and GS approved the final version. All authors contributed to the comments and approved the manuscript.

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