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Emerging Pathogens of Global Significance; Priorities for Attention and Control

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Abstract

Emerging and re-emerging pathogens of zoonotic origin have become a major global concern. The World Health Organization (WHO) in line with its mandate to track emerging infectious diseases met in Geneva, Switzerland in December 2015 to prepare for potential major outbreaks in 2016. The aim of this review is to assess emerging diseases of global significance with the view of prioritizing them for global concerted efforts, attention and control. The major infectious diseases that are likely to be of concern in 2016 were ranked as most dangerous include Ebola Virus Disease, Marburg, severe acute respiratory syndrome, Middle East respiratory syndrome, Nipah, Lassa fever, Rift Valley fever, and Crimean Congo haemorrhagic fever. The second category ranked as serious includes chikungunya, severe fever with thrombocytopaenia syndrome and Zika. A third category comprising of HIV/AIDS, tuberculosis, malaria, avian influenza and dengue, were considered important because they have already received much attention and funding unlike the other two categories. Thus far in 2016, major outbreak of Zika virus occurred in South America and spreading northwards into the US and also eastwards to South East Asia, Lassa fever in Nigeria and yellow fever in Angola and Democratic Republic of Congo. The study concluded by suggesting priorities that healthcare policy could focus on in order to control emerging zoonotic infections.

Keywords: *Emerging Diseases; Healthcare Policy; Healthcare Priorities; Mosquitoes; Public Health Planning; RNA Viruses; Zoonotic Infections*

Introduction

Emerging and re-emerging pathogens have become a major cause for global concern in the 21st century affecting many sectors including tourism, major sporting events and global economy and has become a threat to humanity. Although, infectious diseases are not new, the increasing frequency and diversity of the infectious disease are a cause for concern. Major outbreaks of infectious diseases have been reported with high mortality rates globally. For instance, Martina and Osterhaus [1] cited the cause of smallpox in the 19th century, which infected over 50 million people annually with a case fatality rate of 30%. Smallpox was effectively eradicated in 1979. In human history, many infectious diseases causing high fatalities have been reported at different times in different parts of the earth such as influenza, anthrax, cholera, diarrhoea, hepatitis, Ebola, yellow fever, Japanese encephalitis. Notwithstanding the advances in medical sciences, infectious diseases still ranked among the highest causes of diseases burdens and death globally. For instance, respiratory infections cause about 3.9million death annually, malaria (1.3 – 3.0 million deaths), HIV/AIDS (2.5 million), diarrheal diseases (1.8 million), tuberculosis (1.7 million) and neglected tropical diseases (0.5 million) [2].

Recent studies/reviews have shown that there are over 1415 pathogens causing human diseases, out of which 177 are regarded as emerging or re-emerging with about 73% of zoonotic origin [3-5]. Most of these newly emerging and re-emerging diseases are caused by viruses particularly RNA viruses [5-8], such as HIV, influenza viruses, hepatitis viruses, Ebola virus, Marburg virus, SARS, and MERS.

It is quite surprising that many human diseases are linked to wildlife especially at a time when the world is fast urbanizing, as compared to previous centuries, when humanity was essentially primitive, rural and relatively closer to nature and wildlife. The increase in the reported cases of emerging diseases can be linked to several factors such as improved disease surveillance [9], agricultural intensification [10], global climate change [10-13] and the attendant increase in the host range of pathogens [4,5] and vectors [14-16], increased contacts between humans and natural reservoir of viruses [9,17,18] and development of biological weapons [19]. There is compelling evidence to suggest that many zoonotic viruses are mutating and evolving [1,8,20-22], and some have broad host range being able to infect humans, domestics animals and wildlife [10]. Jones., *et al*. [23] reported that emerging infectious diseases are mostly driven by socio-economic, ecological and environmental factors.

It has been variously reported that many of the emerging diseases caused by zoonotic viruses are linked or associated with bats [24-35]. Hence, spill over of zoonotic viruses to humans often result from contact with wildlife particularly bats [36-40]. Apart from bats, other reservoirs of zoonotic virus such as rodents and disease vectors such as mosquitoes are fast increasing their range. The diseases these organisms carry are the major ones to watch out for in future disease outbreaks. Engering., *et al*. [20] explained that the interplay of pathogen-host-environment is linked to disease emergence. Butchering and consumption of 'bushmeat' particularly bats have been linked to spill over of emerging viruses to humans [13,36-38,40,41]. After disease infects the first human (i.e., the index case), the pathogens are spread rapidly among human population through contacts, rapid air travel and nosocomially in hospital environment.

In December 2015, group of about two dozen experts comprising of virologists, microbiologists, immunologists, public health and clinicians, mathematical and computational modeling experts, product development and infectious disease experts met in Geneva to assessment emerging global disease. They assessed several emerging diseases and ranked the most dangerous emerging infectious diseases into two categories (most dangerous and serious), which are likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. The most dangerous diseases were Ebola Virus Disease (EVD), Marburg, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Nipah, Lassa fever, Rift Valley fever (RVF), and Crimean Congo haemorrhagic fever (CCHF). The second category ranked as serious includes chikungunya (CHIK), severe fever with thrombocytopaenia syndrome (SFTS) and Zika virus. A third category comprising of HIV/AIDS, tuberculosis, malaria, avian influenza and dengue, though considered important, were not ranked because they have already received much attention and funding.

Literature pertaining to the eight diseases ranked as most dangerous and three ranked as serious and other emerging diseases were reviewed. The viruses causing the eleven ranked diseases were described and the following acronyms were used hereafter: Ebolavirus (EBOV), Marburg (MARV), severe acute respiratory syndrome corona virus (SARS-CoV), Middle East respiratory syndrome corona virus (MERS-CoV), Nipah (NiV), Lassa fever, Rift Valley fever virus (RVFV), and Crimean Congo haemorrhagic fever virus (CCHFV), chikungunya virus (CHIKV), severe fever with thrombocytopaenia syndrome virus (SFTSV) and Zika virus (ZikV). The route (oral, nasal or dermal), mode (direct or indirect), cycle (sylvatic or urban) and direction (horizontal or vertical) of transmission were described. The vectors and reservoirs of the diseases were also described.

Emerging Pathogens of global significance

Table 1 present the list of emerging diseases as ranked by WHO in December 2015 as capable of causing future epidemics. The ranking was based on two criteria; ability to cause future outbreaks and the existence of countermeasures. Eight diseases were ranked most dangerous (Ebola virus disease, Marburg hemorrhagic fever, Crimean longe hemorrhagic fever, Lassa fever, Rift valley fever, SAR, MERS and Nipah), three serious (Chikunganya, SFTS and Zika), four others were considered less serious because they have received research attention, funding and existence of countermeasures (avian influenza, AIDS, tuberculosis, malaria and dengue fever), others not ranked specifically include Japanses encephalitis, yellow fever and melioidodis.

Pathogen	Disease	WHO 2015 ranking/ priorities	Discovered	Place of discovery	Spread	Cases	Case fatality	Threat	Current treatment	Reference
Ebola virus (Filoviridae)	Ebola virus disease (EVD)	most dangerous	1976	Sudan, DRC	Africa, Europe, USA	28,500[z]	40 - 90 %	Global	No cure, but vaccines and drugs under trial	Ohimain [42,43]
Marburg (Filoviridae)	Marburg haemor-rhagic fever	most dangerous	1967	Germany, Uganda	11 countries	444 (total cases 1976-2014); 13 out-breaks	24 - 88%	Global	No cure,	Brauberger [44]
Nairovirus (*Bunyaviri-dae*)	Crimean Congo haemor-rhagic fever (CCHF)	most dangerous	1944	Crimea, Congo	30 countries		10 - 40%	Global	Treatment using riba-virin	WHO [45]
Lassa fever virus (*Arena-viridae*)	Lassa fever (haemor-rhagic fever)	most dangerous	1950s (1969*)	Nigeria	Africa	100,000 /yr	1%	Africa	Treatment using riba-virin	
RVFV Phlebovi-rus** (*Bun-yaviridae*)	Rift Val-ley fever (disease of mostly live-stock and humans)	most dangerous	1931	Kenya	30 countries	11 major out breaks (1992-2012)	50%	Africa	No drug or vaccine for human use, but vet vac-cine exists	Weiss and Martin [46] Vijayanand., et al. [47] Nanyingi., et al. [48]
SARS-CoV (Coronavirid-dae)	Severe acute respiratory syndrome (SARS); pneumonia	most dangerous	2002	China	30 countries	8400	10%	Global	No cure or vaccine	Shigeta and Yamase [49]
MERS-CoV (Coronavirid-dae)	Middle East respiratory syndrome (MERS)	most danger-ous	2012	Saudi Arabia	30 coun-tries	1368	36%	Global	No cure or vaccine	Jozefiak., et al. [50] Sch-weisfurth [51] Sharif-Yakan and Kanj [52] WHO [53]
Nipah virus (*Paramyxo-viridae*)	encepha-litis and respiratory illness	most danger-ous	1998	Malaysia, Singapore	Bangla-desh, India		39%	Asia	No cure or vaccine	

Chikungunya virus *Alphavirus* genus (*Togaviridae*)	high fever, joint pain, and rash	Serious	1953	Tanzania	Global	Over 1 million cases	0.1%	Global	No cure	Presti., *et al.* [54] Chia., *et al*. [55] Thiboutot., *et al.* [56] Staples., *et al.* [57]
SFTSV Phlebovirus (*Bunyaviridae*)	severe fever with thrombocytopaenia syndrome	Serious	2010	China	China		6-30%	Asia		Li [24]
Zika virus (Flaviviridae)	Zika fever	Serious	1947	Uganda	47 countries	On-going	1.2%	Global	No cure	
Avian influenza A virus subtypes H5N1 and H7N9 (Orthomyxoviridae)	avian influenza	Less serious***	H1N1 (1918), H5N1, (1997) H7N9 (2013)	USA (1918)	H1N1 reported in 70 countries		Up to 100%	Global	medical countermeasures exist	
HIV Lentivirus (retroviridae)	AIDS	Less serious	1980s		Global	Over 2 million cases annually	Up to 100%	Global	medical countermeasures exist	
Mycobacterium tuberculosis (Mycobacteriaceae)	Tuberculosis	Less serious	1882^	Germany	Global	Over 200 countries	23-50%	Global	medical counter measures exist	
Plasmodium *falciparum*, *P. Vivax*, *P. ovale*, and *P. malariae*	Malaria	Less serious	1880	Algeria	95 countries		1-7.3 %	Tropical world	medical countermeasures exist	
Dengue fever virus DENV Serotypes DEN1-4 (*Flaviviridae*)	Dengue fever	Less serious	1942	Japan	Over 100 countries	50-100 Million /yr	5%	Tropical world	no specific treatment but supportive care	Idress and Ashfag [58] Guzman., *et al.* [59] Diamond and Pierson [60]

Japanese Encephalitis virus (Flaviviridae)	Japanese Encephalitis	Not Ranked	1871	Japan	24 countries in Asia	68,000 /yr	30%	Asia	Vaccine available	
Yellow fever virus (Flaviviridae)	Yellow fever	Not Ranked	1900	Cuba	Tropical world	84 000 –170 000 /yr	7.5%	Global	no specific treatment but vaccines are available	Reiter [14] Kanunamoorthi [61] Boshra., *et al.* [62]
Burkholderia pseudomalei (Burkholderiaceae)	Melioidosis	Not Ranked	1882	Burma	79 countries	165,000/ yr	70%	Global	Drugs exist but no vaccine	Limmathurotsakul., *et al* [63] Dance [64]

Table 1: *Emerging pathogens of global significance.*

*First described in 1969 in the town of Lassa, in Borno State, Nigeria

** First reported in livestock in Kenya's Rift Valley in the early 1910s

*** less serious because it had received medical and research attention

**** *Aedes aegypti, Aedes africanus, Aedes apicoargenteus, Aedes furcifer, Aedes hensilli, Aedes luteocephalus* and *Aedes vitattus*

^The organism causing tuberculosis - Mycobacterium tuberculosis existed 15,000 to 20,000 years ago. It has been found in relics from ancient Egypt, India, and China. Genetics indicates that TB mycobacteria originated about 70,000 years ago in Africa.

[z]Over 28,500 cases with 11,318 death arising from the 2014 EVD outbreak in West Africa. 22 major outbreaks since discovery.

The diseases ranked most dangerous have many common features, which is the main focus of this review. All the emerging diseases under review causes complications (Table 2) particularly hemorrhages (Lassa, Marburg, SFTS, Ebola, CCHF, RVF,yellow fever and dengue), renal failures (MERS), respiratory disorders (SARS, MERS, Nipah), cardiac disorder (CCHF, MERS, Nipah), neurological disorders (Zika, RVF, Lassa fever, MERS, Nipah) and multi-organ failures (Marburg, Ebola, MERS), eye disorders (RVF, CHIKF). The Center for Food Security and Public Health [65] describes the CCHF as one of the most widely distributed viral hemorrhagic fevers. Complications arising from SFTSV include thrombocytopana, leukocytopena and lymphadenopathy [66]. In addition, Zika is linked to microcephaly and Guillan -Barre syndrome (GBS). Recent evidence suggests that Zika virus is linked to many neurological disorders now referred to as Zika virus syndrome (ZVS). Of all the eleven high priority diseases, only two (SARS and MERS) have been described to be self limiting i.e. can abate or subside on their own with or without intervention. Dengue fever is also self limiting usually in 2 – 3 weeks in non-complicated cases.

Pathogen	Disease	Complications	Outbreak type	Outbreak spread	Self limiting?	Specific Therapy	Licensed Vaccines	Reference
Ebola virus	Ebola virus disease (EVD)	Multi-organ failures	Sporadic	Epidemic	No	None	None	Ohimain [42,43]
Marburg	haemorrhagic fever		Sporadic	Epidemic	No	None	None	Richter and Cumming [71]
Nairovirus (family *Bunyaviridae*)	Crimean Congo haemorrhagic fever (CCHF)	Cardio-vascular diseases	Season al	Endemic	No	None	None	

Lassa fever virus (family *Arenaviridae*)	Lassa fever (haemorrhagic fever)	Uraemia, neurologic disorder	Periodic (frequent)	Endemic	No	None but ribavirin is used	None	AbdulRaheem [72] Monath [73] Adewuyi., *et al.* [74]
RVFV Phlebovirus** (*Bunyaviridae*)	Rift Valley fever (disease of mostly livestock and humans)	Eye disorders, haemorrhage, encephalitis, neurological disorder	Periodic/ seasonal	Endemic	No	None	None	Rolin., *et al.* [75] Wang., *et al.* [76] Nanyingi., *et al.* [48] Pepin., *et al.* [77]
SARS-CoV	Severe acute respiratory syndrome (SARS)	Pneumonia, LRTI, fevers, diarrhoea, lymphopenia	Sporadic	Pandemic	Yes	None	None	Tseng., *et al.* [78] Kumar., *et al.* [79] Holmes [80] Wang., *et al.* [76]
MERS-Co	Middle East respiratory syndrome (MERS)	Renal failure, URTI, high fever, neurological disorder, cardiac disorder	-	Pandemic	Yes	None	None	Momattin., *et al.* [81] Durai., *et al.* [82] Brand., *et al.* [83]
Nipah virus (*Paramyxoviridae*, genus Henipavirus)	encephalitis and respiratory illness	Systemic vasculities, respiratory disorders, neurological disorders	Almost yearly	Epidemic	No	None	None	Wits and Munster [84] Sampann., *et al.* [85] Escraffre., *et al.* [86] Wahed., *et al.* [87] Halpin and Rota [88]
Chikungunya virus *Alphavirus* genus (*Togaviridae*)	high fever, joint pain, and rash	Eye disorders	Periodic	Pandemic	Yes	None	None	Weaver and Leayit [89] Mahendradas., *et al.* [90] Laheriya and pradham [91]
SFTSV Phlebovirus (*Bunyaviridae*)	severe fever with thrombocytopaenia syndrome	Myalgia, haemorrhage, leucocytopaenia	-	Endemic	No	None	None	Zhang., *et al.* [93]
Zika virus (Flaviviridae)	Zika fever	Microcephaly, GBS, neurological disorders	Sporadic	Pandemic	No	None	None	Mlakar., *et al.* [70] Aubry., *et al.* [94] Kindhauser., *et al.* [68]

Table 2: *Description of emerging disease of global significance.*

Among the eleven high priority diseases, some have been discovered almost 100 years ago e.g. influenza virus (1918), over 50 years (CCHF, Lassa fever, RVF, CHIN and Zika) compared to malaria (1880), tuberculosis (1882), dengue (1942), Japanese encephalitis (1871), yellow fever (1900) and melioidosis (1882). In terms of health policy, attention ought to be focused on diseases that have historically plagued humanity and have not been successfully eradicated. For instance, there have been much global attention and funding for malaria, melioidosis and tuberculosis, but unfortunately they have not been eradicated and no licensed vaccine for their control. Also, Zika virus that was first discovered in Uganda in 1947 is now ravaging the entire South America continent and cases of autothocnus transmission of Ziva virus by mosquitoes was reported in the US state of Florida in July 2016 and also in PuertoRico and Texas. Zika virus have recently emerged in southeast Asia specifically in Singapore, Malaysia and Thailand. In a recent study, Mesisna., *et al*. [67] show that the entire tropical world has suitable environment for zika virus, with about 2.17 billion people at risk. Complications such as Microcephaly and GBS were not detected in previous outbreaks of Zika virus, hence it therefore appears that in the current 2015 – 2016 outbreak in the Americas and Asia that Zika virus have changed in character while expanding their geographical range [68-70]. Yellow fever, which is endemic to Africa, was first discovered in 1942 in Cuba. 2016 witness outbreaks of yellow fever in Angola and Congo Democratic Republic. Mandatory yellow fever vaccination is a requirement for entry into South Africa.

The majority of the emerging pathogens were either discovered in Africa (Ebola, Marburg, CCHF, Lassa fever, RVF, CHINF, Zika, malaria, AIDS) or endemic in the tropical world (Nipah, dengue fever, yellow fever, and melioidosis). Many of these emerging diseases originated from poor countries, with little capacity for disease detection, surveillance and control. Many of the diseases, because they were not detected early or controlled from the source or endemic areas, have spread globally e.g AIDS, tuberculosis, yellow fever and melioidosis. For instance, if global efforts had contained zika virus when it was first discovered in Uganda in 1947, the current epidemics and complications being witnessed in South America and Asia perhaps could have been averted.

Among the eleven high priority diseases, Lassa fever has been reported in almost all West African countries, Zika in 47 countries.Others have spread to over 30 countries (CCHF, RVF, SARS, MERS), avian influenza in 70 countries compared to malaria in 95 countries, melioidosis in 79 countries, dengue in over 100 countries, yellow fever in the tropical world and HIV/AIDS and tuberculosis that are global. Nipah virus was discovered in Malaysia and Singapore in 1998 has now spread to India and Bangladesh, and could spread further if not checked. SFTSV was recently discovered in China in 2010 and could spread further if not controlled. Health policy should therefore focus on source control of emerging pathogens to avert major global epidemics.

In terms of burden of diseases, Lassa fever ranked among the highest in the eleven high priority emerging pathogens. There are about 100,000 – 300,000 cases of Lassa fever infections with 5000 deaths annually [72,74]. There is a current outbreak of Lassa fever that started in 2015 in Nigeria. From August 2015 – February 2016, Lassa fever cases were 175 with 101 deaths in Nigeria. The virus has spread to 19 states out of the 36 states of the country with a population of 170 million people. Among the emerging diseases, dengue fever has the largest number of cases. Each year, dengue infects 50 – 300 million persons causing 500,000 hospitalizations and 20,000 deaths with 2.5 billion people at risk globally [58,59]. Being, the worst affected country in the Americas, from May to December 2015, an estimated 440,000 – 1.3 million cases of autochthonous ZIKV infections was reported in Brazil [70].

Among all the emerging diseases under consideration, the disease that received the greatest attention and funding is HIV/AIDS. The UN have an agency called UNAIDS that coordinate activities related to HIV/AIDS globally. Despite all the global converted efforts, there are over 2 million new cases of AIDS each year and as of 2015, there were about 36.9 million people living with AIDS globally of which 15.8 million accessing antiretroviral drugs as of June 2015. In 2014, 1.2 million people died from AIDS related diseases compared to 2 million people in 2015 [95]. The global mortality due to melioidosis (89,000/year) is comparable to measles (96,500/year), but by far higher than dengue (9,100 – 12500/year), which are among diseases considered as high priority by many international health organizations [63].

Among the eleven high priority emerging diseases, some have very high case fatalities 50 - 100% (Ebola, Marburg, RVF), high i.e. 10 – 49% (SARS, CCHF, MERS, SFTS), low i.e. < 10% (Zika, Lassa fever) and very low i.e. < 1% (CHIKF) compared to AIDS (almost 100%), melioidosis

(70%), Japanese encephalitics (30%) and yellow fever (7.5%). Despite SARS and MERS are both caused by coronavirus, MERS fatality rate is about 4X SARS [82]. It should be noted that the three major epidemics reported in 2016 are caused by pathogens ranked among the lowest case fatalities i.e. Zika, yellow fever and Lassa fever in the Americas, Angola/DRC and Nigeria respectively. Hence, despite their low case fatalities, they still pose considerable global threat. It should also be noted that Lassa fever historically had very high case fatalities 50 – 65% [72,73], but due to management, it has reduced to 1%. However, the virulence of the pathogens appears to have increased in the 2015/2016 outbreak in Nigeria, where 101 persons died out of 175 cases resulting in 57.7% fatality.

The causative pathogens of all the eleven high priority emerging pathogens are all caused by viruses with RNA genomes and of zoonotic origin (Table 3). Few authors have also observed this trend [7,8] and have explained that RNA viruses generally have higher mutation rates than DNA virus partly because viral RNA polymerase lack the proofreading ability of DNA polymerase, hence they have higher error rates during replication. Apart from the eleven high priority emerging viruses, other high impact diseases are caused by RNA viruses including dengue, Japanese encephalitis, hepatitis, HIV/AIDS.

Pathogen	Disease	Genome	Safety category*	Potential for terrorism?	Sub-types/ species/ strains	Mutation rates	Disease vectors	Primary Reservoir	Intermediate host
Ebola virus	Ebola virus disease (EVD)	SS RNA (-)	A	Yes	5	High	None	Bats (several)	great apes and duikers
Marburg	Marburg haemorrhagic fever	SS RNA (-)	A	Yes	2	High	None	African fruit bat (Rousettus aegyptiacus).	African green monkeys (*Cercopithecus aethiops*)
Nairovirus (family *Bunyaviridae*)	Crimean Congo haemorrhagic fever (CCHF)	RNA	C	Yes	-	High	Ticks *Hyalomma* sp**	Ticks	Cattle, goats, sheep, horses
Lassa fever virus (*Arenaviridae*)	Lassa fever (haemorrhagic fever)	SS RNA (-)	A	Yes	-	High	-	Multi-mammate rat *Mastomys natalensis*	-
RVFV Phlebovirus** (*Bunyaviridae*)	Rift Valley fever (disease of mostly livestock and humans)	RNA	A	Yes	-	High	Mosquito vectors	Bats	-
SARS-Co	Severe acute respiratory syndrome (SARS); pneumonia	SS RNA (+)	C	Yes	-	High	-	Bats	-
MERS-Co	Middle East respiratory syndrome (MERS)	SS RNA (+)	C	Yes		High	-	Bat	Camels

Nipah virus (*Paramyxoviridae*)	encephalitis and respiratory illness	SS RNA (-)	C	Yes	Many strains	High	-	Bats flying foxes (*Pteropus* sp)	Pigs, dogs, cats, sheep, horses
Chikungunya virus *Alphavirus* genus (*Togaviridae*)	high fever, joint pain, and rash	SS RNA (+)	C	yes		Very high	Mosquitoes (*Aedes aegypti* and *Ae. albopictus*)	Monkeys, birds, cattle, and rodents	
SFTSV Phlebovirus (*Bunyaviridae*)	severe fever with thrombocytopaenia syndrome	RNA	C	Yes	-	High	Tick *Haemaphysalis longicornis*, Rhipicephalus microplus	-	-
Zika virus (Flaviviridae)	Zika fever	SS RNA (+)	-	-	-	High	Aedes mosquitoes (several species)	Monkey	-

Table 3: *Description of microbes implicated in emerging diseases of global significance*

** NIAID/CDC categories*

*** Other ixodid ticks include Rhipicephalus, Boophilus, Beranacantor. Source [65].*

Due to the higher mutation rates, it appears that the RNA viruses are evolving higher than DNA viruses. Also, among the high priority emerging pathogens, Ebola viruses have five species, Marburg virus 2 species, while Nipah virus has many strains. Dengue fever has 4 serotypes (DenV 1-4). There appears to be multiple strains of Nipah virus in circulation [96]. The presence of different species strains and serotype posses a challenge especially in the development of vaccine.

Most of the high priority emerging pathogens belong to category A (Ebola, Marburg, Lassa fever, RVFV) or C (CCHF, SARS-CoV, MERS-CoV, Nipah, CHIK, SFTSV) biodefense according to the NIAID classification. Zika virus has not been classified by NIAID. Hence, virtually all the high priority organisms could be used in bioterrorism if not effectively controlled.

The eleven high priority emerging pathogens belongs to few families; 2 filoviridae (Ebola and Marburg), 3 *Bunyaviridae* (RVFV, Nairavirus and SFTSV). 1 *Arenaviridae* (Lassa), 2 *Coronaviridae* (SARS and MERS), 1 *Paramyxoviridae* (Nipah), 1 *Togaviridae* (Chihungunya) and 1 *Flaviviridae* (Zika virus) (Table 4) compared to other high impact merging pathogens including HIV (*Retroviridae*), avian influenza (ortho-myxoviridae), while dengue virus, yellow fever virus and Japanese encephalitis virus belonged to the *Flaviviridae* family. Therefore, healthcare policy should focus on these families in order to reduce the risk of emerging infections particularly members of the family *Flaviviridae, Bunyaviridae, Filoviridae* and *Coronaviridae*.

Pathogen	Disease	Route	Mode	Cycle	Nosocomial transmission?	Direction
Ebola virus (Filoviridae)	Ebola virus disease (EVD)	Oral	Direct	Sylvantic, urban	Yes	Vertical, horizontal
Marburg (Filoviridae)	Marburg haemorrhagic fever	Oral	Direct	Sylvantic, urban	Yes	Vertical, horizontal
Nairovirus (*Bunyaviridae*)	Crimean Congo haemorrhagic fever (CCHF)	Oral, dermal	Direct, indirect	Sylvantic, urban	Yes	Vertical, horizontal
Lassa fever virus (*Arenaviridae*)	Lassa fever	Oral, nasal	Direct, indirect (droplet)	Sylvantic, urban	Yes	Vertical, horizontal
RVFV Phlebovirus (*Bunyaviridae*)	Rift Valley fever	Oral, nasal	Direct, indirect (droplet, airborne)	Sylvantic, urban	Yes	Vertical, horizontal
SARS-CoV (Coronaviridae)	Severe acute respiratory syndrome (SARS)	Nasal	Direct, indirect (droplet)	Sylvantic, urban	Yes	Horizontal
MERS-CoV (Coronaviridae)	Middle East respiratory syndrome (MERS)	Nasal	Direct, indirect (droplet)	Sylvantic, urban	Yes	Horizontal
Nipah virus (*Paramyxoviridae*)	encephalitis and respiratory illness	Oral, nasal	Direct, indirect (airborne)	Sylvantic, urban	Yes	Vertical, horizontal
Chikungunya virus (Togaviridae)	high fever, joint pain, and rash	Dermal	Direct	Sylvantic, urban	Yes	horizontal
SFTSV Phlebovirus (*Bunyaviridae*)	severe fever with thrombo cytopaenia syndrome	Dermal	Direct	Sylvantic, urban	Yes	horizontal
Zika virus (Flaviviridae)	Zika fever	Dermal	Direct, indirect	Sylvantic, urban	Yes	Vertical, horizontal

Table 4: *Transmission of microbes causing emerging diseases of global significance.*

Among the eleven high priority emerging pathogens of global significance, three (RVFV, CHINV, and Zika virus) are transmitted by mosquitoes, while 2 (SFTSV and Nairavirus) are transmitted by ticks. It should be noted that mosquitoes also transmit other high impact emerging pathogens causing major disease threatening humanity including malaria, Japanese encephalitis, dengue fever, yellow fever, and West Nile fever (Table 5). Mosquitoes have become a major challenge to humanity. Despite the discovery and use of many pesticides (some of which are dangerous to human health and the environment in general), mosquitoes have not been controlled worldwide. Mosquitoes appear to be effective in transmitting not only plasmodium, but members of *flaviviridae* family (Zika, Japanse encephalitis, West Nile, yellow fever and dengue viruses). Over 30 species of mosquitoes from different genera including *Aedes, Culex* and *Anopheles* are involved in the transmission of RVFV [48,75,77].

Mosquitoes also transmit other encephalitis virus including western equine encephalitis, Eastern equine encephalitis, California encephalitis, Lacrosse encephalitis, St Louis encephalitis and Venezuela equine encephalitis. Japanese encephalitis, though relatively rare, causes viral encephalitis in over 24 countries in South East Asia with an estimated 68,000 annual cases and a case fatality rate of 30 – 50%. There are no cure or vaccine for the disease, thus putting over 3 billion people at risk.100 Yellow fever virus transmitted by mosquitoes causes an estimated 84000 – 170,000 infections per year, 90% of which occur in Africa with case fatality up to 50%. Several outbreaks have occurred in Africa and South America, putting a combined population of about 900 million people at risk. There are currently no known cures, but vaccine has been the most effective preventive measure [61,98]. Evidence suggests that yellow fever and dengue had appeared in western countries including USA, UK, and other European nations, but were controlled [14]. Although, yellow fever appears

to be declining globally, the recent resurgence in many countries including Angola and DRC (2015 – 2016), Sudan (2012), and Uganda (2010) is a cause for concern. On 10 May 2016, WHO declared the outbreak of yellow fever a global emergency after the virus killed 277 people from December 2015 – May 2016. The virus has spread to neighboring countries particularly Kenya and China.

Mosquito species	Disease	Causative pathogen	References
Aedes	Rift valley fever	Rift valley fever virus	Rolin., *et al*. [75]
Aedes	Chinkungiya fever	Chinkungiya fever	Lahariya and Pradhan [91]
Aedes	West Nile	West Nile virus	WHO [97]
Aedes aegypti	Dengue fever	Dengue fever virus	Idress and Ashfag [58] Diamond and Pierson [60]
Aedes aegypti	Zika fever	Zika fever virus	Kindhouser., *et al*. [68] Aubry., *et al*. [94]
Aedes aegypti	Yellow fever	Yellow fever virus	WHO [98] Reiter [14]
Aedes albopictus	Dengue fever	Dengue fever virus	Idress and Ashfag [58] Diamond and Pierson [60] Reiter [14]
Aedes albopictus	Zika fever	Zika fever virus	Kindhouser., *et al*. [68] Aubry., *et al*. [94]
Aedes albopictus	Yellow fever	Yellow fever virus	Reiter [14]
Anopheles	Rift valley fever	Rift valley fever virus	Rolin., *et al*. [75]
Anopheles	Chinkungiya fever	Chinkungiya fever	Lahariya and Pradhan [91]
Anopheles	West Nile	West Nile virus	WHO [97]
Anopheles	Malaria	*Plasmodium falciparum*	WHO [99]
Anopheles	Malaria	Plasmodium vivax	WHO [99]
Culex	West Nile	West Nile virus	WHO [97]
Culex	Rift valley fever	Rift valley fever virus	Rolin., *et al*. [75]
Culex	Chinkungiya fever	Chinkungiya fever virus	Lahariya and Pradhan [91]
Culex tritaeniorhynchus	Japanese encephalitis	Japanese encephalitis virus virus	WHO [100]
Cx. Pipiens	West Nile	West Nile virus	WHO [97]
Haemogogus	Yellow fever	Yellow fever virus	WHO [98]

Table 5: *Some mosquito vector-borne diseases.*

There are about 3,500 species of mosquitoes worldwide, with a few hundreds sucking about 300 ml of blood daily [15]. Bates [101] reports that it is only about 60% of mosquitoes suck blood from humans. Mosquitoes suck blood from other animals including non-human primates, domestic animals and several wild animals including snakes, hence their ease to serve as vector of many zoonotic infections.

The CDC listed 65 species of mosquitoes that were detected in the United States from 1999 – 2013 transmitting the West Nile virus. Of these 65 species, 49 belong to three genera namely *Aedes, Anopheles* and *Culex*. These three genera are mostly implicated in the transmission of high impact emerging pathogens (Table 5). Hence, the scientific community is debating on the total eradication of mosquitoes. Though, some argue that eradication of mosquitoes could affect general ecology such as the food chain. Mosquitoes performed ecological functions such as pollination and their larva are food for fish species. Scientists are of the opinion that these ecological roles could be filled by other insect species. It should however be noted that mosquitoes have existed on earth for over 100million years and are found in every continent and habitats [15]. The three most notorious mosquitoes, which appears to be localized in the tropical world and being responsible for the transmission of many high impact emerging pathogens appears to be migrating northward and perhaps as far as the Scandinavia. *Aedes aegypti* and *A. albopictus* have expanded their range into Europe. Kraemer., *et al*. [102] mapped the global distribution of these two species of Aedes mosquitoes, and found that these mosquitoes are found in all continents including North America and Europe. Outbreaks and autochthonous transmission of yellow fever have been reported in many western nations [14]. It is uncertain if the Artatic Aedes mosquitoes (*A. impiger* and *A. nigripes*) under tundra climatic conditions could acquire and also transmit high impact emerging viral species. Karunamoorthi [61] reported that climate change, which creates warmer temperature, could fasten/accelerate

mosquito metamorphosis and expand the range/distribution of *A. aegypti* and other mosquitoes, while reducing/shorten the extrinsic incubation period of emerging pathogens. Environmental factors such as rainfall and flooding, which enhances mosquito breeding also facilitates the spread of mosquito-borne diseases.

Although, the WHO has presented data showing a global decline (37% reduction) in malaria cases in the past 15 years (2002 – 2015), over 3.2 billion people are still at risk [99]. Fang [15] reported that mosquitoes infect 247 million people worldwide killing about one million yearly.

Because mosquitoes are vectors to many high impact emerging infections such as malaria, yellow fever, RVF, dengue fever, chikungunya, west Nile, and Japanese encephalitis, there are urgent call for their control and eradication. Various methods have been developed and new once emerging (Table 6) for the control of mosquitoes. The methods could be broadly classified into chemical, physical and biological, which could be further subdivided into genetically modified mosquitoes (GMM) and non-GMM techniques. Two approaches that have been traditionally used for the control of mosquitoes are the physical decontamination of the environment and water containers and application of pesticides (adulticides, larvicides, and repellants). Others are relatively new, except the use of some botanicals by indigenous people. The elimination of potential mosquito breeding sites and the application of larvicides have been quite successful in the control of mosquitoes [61]. For instance, the application of adulticide DDT led to the control of vector *A. gambiae* in the US in 1940. Also the use of the larvicide Paris Green enabled Brazil to control the malaria vector [15].

Method	Technology	Stage of development	Application	References
Molecular	RNA interference (gene silencing/ suicide)	Experimental	Female A. Aegypti control	Gu and Knipple [103] Fang [15]
Molecular	Virus vectored RNA interference	Experimental	Densovirus vector control *A. Albopictus, A. aegypti* larvae	Gu., *et al*. [104] Cook., *et al*. [105]
Molecular	Sterile insect technique (biological)	Pilot field application	Used for the control of dengue fever virus tested in some countries (Brazil, Cayman Islands, Malaysia, Panama), and currently being tested for Zika virus in Brazil	Alphey., *et al*. [106]
Molecular	Cytoplasmic incompatibility	Pilot field application	Field applications in Brazil, Vietnam, Australia and Indonesia for the control of dengue carrying Aedes aegypti	Lee., *et al.* [107]
Molecular	Cytoplasmic incompatibility (Microbiological)	Experimental	Transfer of *Wolbachia* into Aedes aegypti	Cook., *et al.* [105]
Biological	Cytoplasmic incompatibility (Microbiological)	Natural process	*Wolbachia*-mediated cytoplasmic incompatibility for the control of *Ae. Albopictus*	Cook., *et al*. [105] WHO [97]
Biological	Botanicals	Experimental	*Hyptis suavolens* repels adult and kill mosquito larva	Ohimain., *et al*. [108]
Biological	Botanicals	Experimental	Cedar oil	Fang [15]
Biological	Microbiological	Pilot field application	Enthomopathogenic fungi *Metarhizium anisopliae* control of malaria parasite *Anopheles gambiae* tested in Tanzania	Cook., *et al*. [105]
Physical	Sterile insect technique (irradiation)	Pilot field application	Used to eradicate screw worms (a pest of cattle) in the US in 1980s and control of tsetse fly in Tanzania	Fang [15]
Physical	Mosquito traps	Pilot field application	Mosquito *A.taeniorhynchus* was eradicated from Florida US	Fang [15]

Physical	Decontamination of containers and sanitation	Current practice	Have been used globally.	Karunamoorthi [61]
Chemical	Mosquito repellent	Current practice	Used globally	Karunamoorthi [61]
Chemical	Pesticides application including DDT, organophosphates, pyrethroids	Current practice	DDT used for the eradication of *A. aegypti* in 22 countries in South America; used globally	Reiter [14] Karunamoorthi [61]

Table 6: *Traditional and novel techniques for the control of mosquitoes.*

Application of pesticides led to the eradication of *A. aegypti* from 22 countries in the Americas post second world war [14]. Despite the initial successes, there have been some challenges in the use of these traditional techniques. For instance, it is practically impossible to eliminate all standing water or mosquito breeding sites especially in coastal areas with heavy and frequent rainfalls. The proper management of disposed household containers such as bowls/buckets, jars, pots, plates, cups, bottles, vases and pans is a challenge especially in many developing countries with history of poor waste management. Similarly, it is also a challenge to manage industrial wastes in developing countries such as used tyres, wreckages (vehicles, trains, ship) and other structures that retain water serving as breeding sites for mosquitoes. Moreover, dichloro diphenyl trichloroethane (DDT) and similar pesticides that were effectively used to control mosquitoes post second world war, have either been restricted or outrightly banned in most countries due to environmental considerations,. Hence, pyrethroids are now commonly used. Recently, mosquito resistance to pyrethroids has emerged in many countries [99]. Furthermore, pesticides are less selective; they eliminate both beneficial and detrimental insects. Pesticides have been implicated in the contamination of surface and groundwater sources through run off. Hence, the scientific community is searching for alternative chemicals sourced from botanicals that could be effective against mosquitoes but with less environmental consequences. Cedar oil [15] and *Hyptics suavolonse* [108] are promising candidates.

Recent advances in molecular biology have opened a vista of opportunities for the development of biological methods for the control of mosquitoes. Several genetically modified mosquitoes (GMM) and non-GMM have been developed to counter wild species (Table 6). Two of the most advanced GMM that have entered pilot phase having been field tested in many countries are based on sterile insect techniques (SIT) and the use of GMM containing *Wolbachia* sp. The sterile insect techniques involve the release of GMM male *Aedes aegypti* that will seek and mate with wild females producing offspring that will die before maturity. Oxitec, a USA/British company have produced GMM *Aedes aegypti* that have been tested in many countries including Brazil, Cayman Island, Malaysia and Panama for the control of dengue fever and currently been tested for the control of zika in Brazil. Over 90% success rates have been recorded by this approach for the control of *Aedes aegypti.* The oxitec approach involved the insertion of two genes, a colour maker for monitoring and a self limiting gene that will make the GMM not to be persistent in the environment. Unlike the chemical method, this approach is species specific, resulting in the elimination of Aedes aegypti alone and not all mosquitoes. Note that *Aedes aegypti* is involved in the transmission of yellow fever, dengue fever, Japanese encephalitis, and Zika. Incidentally, the use of interfering RNA for the control of insects by the topical application of dsRNA was first demonstrated in *Aedes aegypti* Linnaeus [103]. These and similar approaches can be developed for the two other problematic mosquitoes *Anopheles* and *Culex.*

Another approach that have also been field tested involves producing GMM containing *Wolbachia* sp, which has antiviral properties [104,107,109,110]. This approach has been used for the control of dengue viruses. *Wolbachia* prevent viral replication within *Aedes aegypti* and also prevents its transmission. Successful field tests were carried out in Brazil, Australia, Vietnam and Indonesia. Over 80% success rates have been recorded by this method. The enthomopathogenic fungi *Metarhizium anisopliae* have been demonstrated to control the malaria parasites *Anopheles gambiae* [105]. Most of the biological control methods are species specific, which could potentially result in the elimination of key mosquito species particularly *Aedes aegypti, Anopheles gambiae* and *Culex* sp from mostly urban or human environment. However, the total elimination of these species in the forest (sylvatic cycle) by these methods may be challenging.

Notwithstanding, the WHO has started issuing certifications to countries that have successfully eliminated malaria, which have recorded zero local cases of malaria for at least three consecutive years. Countries that have achieved this feat and have been certified include UAE (2007), Morocco (2010), Turkmenistan (2010), Amenia (2011), Maldaves (2015), while three other countries (Argentina, Sri Lanka, and Krygyzstan) have commenced the certification process [99].

Beside mosquitoes, another vector that is implicated in the transmission of two high priority pathogens (CCHF and SFTSV) is ticks. Incidentally, both viruses belong to the *Bunyaviridae* family. Apart from Hantavirus, members of the *Bunyaviridae* family are usually maintained in arthropod vector by transovarial transmission, with their vertebrate host serving as amplifying agents [93]. While SFTSV outbreaks have occurred sporadically mostly in central China in Henan, Hubel and Shandong provinces [93] i.e. fairly localized, CCHF is endemic in Africa, Asia, Eastern Europe and the middle East [111]. Although, the *Hyalomma* spp has been widely reported as the principal vectors of the CCHF, the Center for Food Security and Public Health [65] have listed at least 31 species of ticks responsible for the transmission of CCHFV including members of the ixodidae family such as *Ixodas, Rhipicephalus, Boophilus* and *Dermacentor*. Transoviral, transstadial and veneral transmission occur in *Hyalomma* ticks. The ticks also feed on numerous wildlife and domestic animals such as goats, sheeps, dogs, donkeys, hares, chickens, pigs and cattles, which probably serve as amplifying hosts. CCHFV has also been detected in wildlife such as giraffe, buffalo, rhinocerosae and the Mastomys mice responsible for the transmission of Lassa fever virus. The center for food security and public health [65] also warned that due to the changing climate, the ticks are probably expanding their ranges. Appannanavar and Mishra [111] noted that the wide distribution of CCHF appears to correlate with the distribution of *Hyalomma* ticks. Li [24] also reported that the endemic area (central China) of SFTSV is expanding. It is therefore important for the world to act now before SFTSV becomes a global phenomenon.

All the eleven high priority emerging pathogens are of zoonotic origin (Table 3 and 4) with distinct enzootic (sylvantic) and epizootic (urban/human) cycles. Most of the viruses are maintained in nature by circulating among primary reservoirs (bats and rats), amplified by domestic animals (cattle, goats, horses, dogs, sheeps, hares, chicken) and wildlife (duikers, great apes i.e. Chimpanzees and gorilla). In the case of CCHF, ticks serve as both vectors and primary reservoir of the virus, while domestic animals (sheep, dogs, hares, horses, pigs, goats) and wildlife (mice, giraffe, buffalo) serve as intermediate secondary or amplifying hosts. Bats and rats are unusually notorious in harbouring many emerging pathogens [9,27]. However, among the 11 high priority emerging diseases only Lassa fever is primarily hosted by the multi-mommate rat *Mastomysnatalensis*, which appeared to be a secondary host for CCHFV. The pathogens are typically maintained in the enzootic cycle via transovarian and transstandal transmission. When spill over occurs to the first human case (usually referred to as index case) either directly via vectors (CCHF, Zika, RVF, CHIKF, SFTSV) or through direct contact with wildlife via slaughtering (Ebola, Marburg, RVF, SFTSV), drinking of poorly pasteurized milk (Nipah, CCHF, RVF), drinking of palm sap contaminated by bats (Nipah). In the urban cycle, human-to-human transmission occur directly through contacts with infected persons' body fluids like blood, stool, urine, sweat, vomits (horizontal transmission).

Virtually all the 11 high priority infections are transmitted nosocomially in hospital environment through contacts with the patients, their secretions or other formites. Fisher-Hock [112] reviewed literature pertaining to the nosocomial transmission of viral hemorrhagic fevers. Vertical transmission occurs when the diseases are transmitted from mother to child e.g. Zika, Ebola, Marburg, Lassa, RVF, Nipah, CHIK. Some of the infections could be transmitted by droplets or aerosols through the nasal/respiratory routes (SARS, MERS, CCHF, Lassa fever, Nipah), orally through food and water (Nipah, Lassa fever, Ebola, Marburg), while others dermally through body contact with an infected person excretions or other formites (SFTSV, Zika, CCHF, Ebola). RVFV is transmitted using a combination of modes including vector transmission, direct transmission, through contact and vertical transmission from mother to offsprings [16].

Bats probably serve as a primary reservoir/ host to six (Ebola, Marburg, RVF, SARS, MERS and Nipah) of the eleven high priority emerging pathogens (Table 3 and 7). Beside these, bats have also been implicated in the transmission of many other high impact emerging viruses. Some specific bat species implicated in the transmission of some emerging zoonotic diseases are listed in Table 7.

Bat species	Disease	Causative pathogen	References
Taphozous perfortus	MERS	MERS-CoV	McIntosh., *et al*. [113] Muller., *et al*. [114] Kayali and Peiris [115]
Tylopnecteris	MERS	HKU4	Zaki., *et al*. [116]
Pipistrellus	MERS	HKU5	Zaki., *et al*. [116]
Rhinolophus (horseshoe)	SARS	SARS-CoV	Wang., *et al*. [76]
Pteropus vampyrus	Encephalitis	Nipah virus	Wang., *et al*. [76] Sendow., *et al*. [117]
P. hypomelanus	Encephalitis	Nipah virus	Wit and Munster [84]
P. giganteus	Encephalitis	Nipah virus	Wit and Munster [84] Yadav., *et al*. [118]
P. lylei	Encephalitis	Nipah virus	Wit and Munster [84]
Rousettus leschen	Encephalitis	Nipah virus	Halpin and Rota [88]
Cynoptera sphinx	Encephalitis	Nipah virus	Halpin and Rota [88] Yadav., *et al*. [118]
Eidolum helvum	Encephalitis	Nipah virus	Pernet., *et al*. [39] Baker., *et al*. [119]
Hypsignathus monstrosus	EVD	Ebolavirus	Leroy., *et al*. [120] Hayman., *et al*. [121] Pourrut., *et al*. [122]
Epomops franqueti	EVD	Ebolavirus	Leroy., *et al*. [120] Hayman., *et al*. [121] Pourrut., *et al*. [122]
Myonycteris torquata	EVD	Ebolavirus	Leroy., *et al*. [120] Hayman., *et al*. [121] Pourrut., *et al*. [122]
Mops condylurus	EVD	Ebolavirus	Saez., *et al*. [123]
Eidolum helvum	EVD	Ebolavirus	Hayman., *et al*. [124]
Rousettus aegyptiacus	EVD	Ebolavirus	Towner., *et al*. [125]
Epomophorus gambianus	EVD	Ebolavirus	Hayman., *et al*. [121]
Rousettus leschenaultii	EVD	Ebolavirus	Olival., *et al*. [126]
Rousettus aegyptiacus	Marburg	Marburgvirus	Towner., *et al*. [125] Brauberger., *et al*. [44] Pourrut., *et al*. [122] Swanepoel [127]
Rhinolophus eloquens	Marburg	Marburgvirus	Swanepoel [127]
Miniopterus inflatus	Marburg	Marburgvirus	Swanepoel [127]
Hypsignathus monstrosus	Marburg	Marburgvirus	Pourrut., *et al*. [122]
Micropteropus pusillus	RVF	RVFV	Boiro., *et al*. [128]
Hipposideros abae	RVF	RVFV	Boiro., *et al*. [128]

Table 7: *Pathogenic microbes carried by some bats.*

Bats are natural reservoirs of emerging and reemerging zoonotic viruses including *Rhabdovirues, Coronaviruses, Paramyxoviruses, Lyssaviruses, Reoviruses, Flaviviruses, Adenoviruses* [27,30,32-34,118,129-131]. There are over 1200 bat species globally, but only a small fraction < 15% have been studied for harboring high impact zoonotic viruses [132]. Moratolli and Calisher [28] reported that over 200 viruses, some of them deadly zoonotic viruses have either been isolated or detected in bats. Most human and domestic pathogens of at least 4 viral families originated from bats; *Coronaviridae, Filoviridae, Paramyxoviridae* and *Lyssaviridae* [133]. Few bat species such as *Rousettus aegypticcus* (Ebola, Marburg) and *Eidolon helvum* (Ebola, Marburg, Nipah) and *Rhinocopus* (SARS, Marburg) have been implicated insome of the high priority emerging pathogens (Table 7). African straw coloured fruit bat *Eidolen helvum* is a reservoir to multiple viruses apart from Ebola and Marburg viruses such as several species of Paramyxoviruses [119] and Lyssaviruses particularly Lagos bat virus [124]. Some characteristics that made bats to be able to spread zoonotic infections even over large distances include their ability to travel long distances i.e. over 2500km, often roost in large colonies of over one million, migrate seasonally in response to fruit availability, ability to hibernate, possess long life span in comparison to other mammals of comparative size, some are found in urban locations, and some are consumed as bushmeat particularly in Africa [131,132,134]. The consumption of bat as bush meat is increasing the risk of zoonotic disease in Africa [36-38,40]. Hence, attention should be focused on these bat species (*Eidolonhelvum, Rousttus aegypticcus* and

Rhinolopus) that are associated with multiple high impact viruses. These species should now be monitored routinely to prevent and/ or provide early signal of impending outbreaks.

Treatment has been a major challenge in the management of these high priority emerging pathogens. There are virtually no licensed drugs and vaccines for all the eleven priority infectious diseases. Management of infections is mostly limited to supportive care, barrier nursing and treatment of complications or symptom such as pains, headaches, high blood pressure and rehydration in diarrhoeal cases. However, some experimental drugs and vaccine has been developed for some of these diseases. For instance, due to massive scale of the 2014-2015 West Africa Ebola disease outbreak, concerted global efforts resulted in the development of drugs and vaccine that are at various phases of trial and promising results have been recorded. Ohimain [42] reviewed some of the promising first generation anti-ebola virus experimental drugs, some of which were tried during the 2014-2015 EVD outbreak including ZMapp, TKM-Ebola, Favipiravir, AVI6002, BCX 4430 and Brincido forvir. Favipriavir (T-705) have also been demonstrated to be effective in the treatment of RVF [135]. Similarly, Ohimain [43] listed some vaccines that have been tested against Ebola which have successfully passed through phase I clinical trials, which demonstrated their immunogenicity and safety. Some have entered phase 3 clinical trials with equally promising results. Most of the leading Ebola vaccines were produced not with conventional techniques of inactivation, but with novel techniques involving the use of vectors. Some of the promising candidate vaccines are Vesicular Stomatitis Virus (VSV), Rabies Virus (RABV), Adenovirus (Ad), Modified Vaccinia Ankara (MVA), Cytomegalovirus (CMV), human parainfluenza virus type 3 (HPIV3), Venezuelan Equine Encephalitis Virus (VEEV), virus like particle (VLP), DNA and subunit vaccines.

Due to the general absence of specific drugs for these emerging pathogens, the broad spectrum anti-viral drug, ribavirin has been used in many instances, although with limited level of successes. For instance, Ribavirin has been successful for Lassa fever, partially successful for CCHF and unsuccessful with Ebola. Also, licensed vaccinesexist for prophylactic treatment of RVF in livestock but none for humans. Lack of specific drugs and/ or prophylactic vaccines are still been experienced in some of other emerging diseases not ranked in December 2015 by WHO because of the existing attention on these diseases. For instance, there are available licensed drugs for the treatment of malaria but no licensed vaccine. Artemisin-based combination therapy (ACT) that was considered the best for the treatment of *Plasmodium falciparium* malaria, but just like chloroquine, parasitic resistance to artimisins have been reported in five countries; Caubodia, Laos, Myanmar, Thailand and Vietnam. However, despite the lack of malaria vaccine, one promising candidate called RTS S/ASO1 has reached advanced stage of development [99]. There are no specific treatment for yellow fever or dengue, 14 but vaccines [136] are currently been used for the control of the 2015/2016 yellow fever outbreak in Angola. Due to the presence of four different serotypes of dengue fever virus, it has become very challenging developing vaccines that are effective against all the four serotypes in one shot. Notwithstanding, Guzman., *et al*. [59] listed at least nine promising dengue vaccine candidates that are various stages of development.

Aubry., *et al.* [94] recently demonstrated that amotosalen combined with UVA light inactivates ZIKV in fresh-frozen plasma. The WHO and USA are calling for more research in the development of drugs and vaccines for ZIKV. Some authors have similarly listed promising vaccines against Chikungunya that have entered various clinical trial stages [55,56,137]. Other authors have similarly reviewed promising vaccines for RVFV including inactivated vaccines, virus like particles, recombinant viral vectors, life attenuated vaccines and DNA vaccines [16,62]. Momattin., *et al.* [81] review therapeutic options for the treatment of MERS. Some authors have reviewed potential therapeutic targets [79,138] and promising vaccines [78,139] against SARS. There are currently no licensed vaccines for melioidosis [63], but Dance [64] review available drugs for the treatment of the disease, though the bacteria have developed resistance to multi anti-microbial agents.

Priorities for the management of emerging zoontic diseases

From this review, it is therefore evident that no single approach can be used to effectively control all the high impact priority emerging and re-emerging zoontic infections. The reasons for this situation are many including lack of specific drugs and vaccines, most of the diseases are circulating and being maintained in the forest via the sylvatic cycle, mosquito vectors and bats. In the case of malaria, adequate treatment drugs are available and pesticides for the control of the mosquito vector. Only partial successes have been recorded thus far, because mosquitoes were only successfully eradicated in some Western countries and malaria controlled in the US. Though some

5 countries have received malaria free certification, many countries have also reported mosquito resistance to pesticides and malaria resistance to ACT. The presence of different species (Ebola), strains (CHIKV) and serotypes (dengue fever) has for a long time slowed down the development of effective vaccines.

From the foregoing, in order to tackle the many emerging and re-emerging zoonotic infections challenging humanity, health care policy should focus on the following approach simultaneously:

- Focus on regions where majority of disease pathogens emerge or are endemic especially the tropical world particularly Africa.
- Specifically focus on resource poor countries that lack the expertise and capacity for the early detection of emerging pathogens before an outbreak occurs.
- Prioritize diseases with high case fatality rates such as Ebola, Marburg, HIV, RVF, Avian influenza and melioidosis.
- Focus on RNA viruses particularly of the family *Filoviridae*, *Bunyaviridae*, *Coronaviridae* and *Flaviviridae*
- Specifically focus on diseases with high infection rates per annum such as dengue fever, malaria and HIV/AIDS
- Focus on category A diseases (e.g., Marburg, Ebola, Lassa fever, and RVFV), B (*Burholderia pseudomalei*) and C (CCHF, SARS-CoV, MERS-CoV, Npah, CHIKV, SFTSV), which could also be easily weaponized and used for bioterrorism.
- Control or eradicate mosquito vectors particular members of the general *Aedes*, *Anopheles* and *Culex* linked to many emerging pathogens including malaria, West Nile virus, Japanese encephalitis, RVF, dengue fever, yellow fever and Zika fever.
- Focus on disease that cause major health complications such as hemorrhagic fevers (Ebola, Marburg, CCHF, RVF, dengue fever, yellow fever and Lassa fever), respiratory disorders (MERS, SARS), central nervous system disorder (Zika) and renal failure (MERS).
- Routinely monitor the movement and virus shedding by bats particularly of the genera *Rousettus*, *Eidolon* and *Rhinolopus*) that spread many high priority pathogens.
- Attempt to eliminate diseases that have been discovered over 100 years ago but are still ravaging humanity (e.g., malaria and melioidosis).
- Focus on diseases that have thus far spread to more than 30 countries such as HIV/AIDS, malaria, dengue, tuberculosis, CCHF, RVF, SARS, MERS, CHIK, influenza, Zika.
- Focus on disease that have no specific cure or licensed prophylactic vaccines (virtually all the eleven high priority emerging pathogens).
- Focus on emerging pathogens that have recently increased in virulence such as Zika virus.
- Focus on pathogens that are re-emerging either seasonally (RFVF, Lassa) or sporadically (Ebola, Marburg, Zika, SFTSV, CHIKV)
- Focus in pathogens that have multiple species (Ebola) strains (CHIKV) or serotypes (dengue) causing the same diseases.
- Generally, focus on pathogens of zoonotic origin, because most of them increase in virulence when they spill over to humans.
- Prioritize diseases that are hosted or amplified by several secondary reservoirs e.g. CCHF, RVF.

- Prioritize diseases with outbreak in 2016 (Zika, Lassa fever and yellow fever) that have the potential to spread to other parts of the world.
- Focus and prioritize pathogens that are transmitted by multiple vectors e.g. RVF which is transmitted by over 30 different species of mosquitoes including member of the genera *Aedes*, *Anopheles* and *Culex* and by other vectors such as ticks and flies.
- Use different combination of diagnostic tools such as virus isolation, molecular and serological approaches to distinguish some diseases that present similar symptoms such as CHIKF, Zika fever and dengue fever, all transmitted by mosquitoes.
- Attention should also be focused on many other emerging infections that have not expanded significantly beyond endemic areas or area of discovery or has not caused major global epidemics such as Hendra virus, Majaro virus, SFTSV.
- Pay particular attention to organisms resistant to multiple antimicrobial agents such as *Burkholderia peudomallei*.
- Develop better predictive tools and models that can lead to early disease detection and control before major outbreaks or epidemics occurs.
- Focus on known disease reservoirs such as bat and rodents that are commonly consumed as "bushmeat".
- Other disease vector that are capable of transmitting zoonotic viral diseases such as ticks, sand fly, tsetse flies should be closely monitored.
- Other potential disease reservoirs particularly cockroaches, rodents and house flies should also be closely monitored.
- Finally, a single disciplinary approach will not be successful hence a multidisciplinary approach involving several professionals is required involving experts such as virologist, microbiologist, medical and veterinary doctors and nurses, public health expert, laboratory technologist, ecologists, pharmacists, vaccine experts, entomologists, wildlife expert, and socio-economists.

Conclusion

Emerging infectious diseases of zoonotic origin has become a major threat to humanity. The number of emerging diseases is increasing. The causative organisms are mostly RNA viruses. Emerging viruses appears to be expanding their range and host, with increasing virulence and frequency of outbreaks. The WHO organization met in 2015 to assess diseases that are likely to cause major outbreaks in 2016. WHO ranked the diseases as most dangerous (Ebola virus disease, Marburg, severe acute respiratory syndrome, Middle East respiratory syndrome, Nipah, Lassa fever, Rift Valley fever, and Crimean Congo haemorrhagic fever), serious (chikungunya, severe fever with thrombocytopaenia syndrome and Zika) and important (HIV/AIDS, tuberculosis, malaria, avian influenza and dengue). In this study, we assessed emerging diseases of public health importance and found some commonalities upon which healthcare policy and prioty should focus in order to eradicate or control emerging infectious diseases.

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