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EBOLA AND ZIKA VIRUS

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ABSTRACT

Ebola haemorrhagic fever (EHF) is a zoonosis affecting both human and non-human primates (NHP).The virus causing the outbreak has been characterized as Zaire Ebolavirus (EBOV). EBOV belongs to the genus Ebolavirus which together with the genus Marburgvirus forms the family of Filoviridae. Managing Ebola patients in the African setting was a major challenge since there was no effective antiviral drug and no specific vaccine available. Only supportive care could be administered, to sustain cardiac and renal functions with prudent use of perfusion. Zika virus is usually spread to people through the bite of an infected mosquito. The virus can also be spread from a man to his sexual partner during unprotected sexual contact and from a pregnant woman to her baby during pregnancy or around the time of birth. The symptoms of Zika are similar to that of dengue and chikungunya, which are diseases caused by other viruses spread by the same type of mosquitoes. No specific treatment available for Zika. Symptoms are treated by getting rest, drinking fluids to prevent dehydration and taking medicines such as acetaminophen or paracetamol to relieve fever and pain.

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INTRODUCTION

Ebola virus

The Ebola virus causing the devastating outbreak in West Africa 38 years ago when it first surfaced and caused a mysterious illness among villagers in Zaire, now the Democratic Republic of Congo. The international team of scientists who were done with investigating that 1976 Ebola outbreak were shocked at the sight of the virus and the disease it caused. The scientists had looked at blood samples sent from Africa under the microscope and the virus looked like a worm or a long string. Once the team got on the ground in Zaire, they saw how rapidly the virus spread and how quickly it killed its victims.On 8 August 2014 the World Health Organisation (WHO) declared the Ebola virus disease (EVD) outbreak in West Africa a Public Health Emergency of International Concern (PHEIC). (Briand *et al*., 2014) Ebola haemorrhagic fever (EHF) is caused by five genetically distinct members of the Filoviridae family: Zaire ebolavirus (ZEBOV), Sudan ebolavirus (SEBOV), Côte d'Ivoire ebolavirus (CEBOV), Bundibugyoebolavirus (BEBOV) and Reston Ebolavirus (REBOV). The virus causing the Zaire Ebolavirus (EBOV), belongs to the genus *Ebolavirus*which together with the genus *Marburgvirus*forms the family of the *Filoviridae*.

Disease agent characteristics

- Family: *Filoviridae*; Genus: *Ebolavirus*
- Virion morphology and size: Enveloped, helical, cross-striated nucleocapsid, filamentous or pleomorphic virionsthat are flexible with extensive branching, 80 nm in diameter and 970-1200 nm in length
- Nucleic acid: Linear, negative-sense, single-stranded RNA, ~18,900 kb in length
- Physicochemical properties: Stable at room temperature and can resist desiccation; inactivated at 60°C for 30 minutes; infectivity greatly reduced or destroyed by UV light and gamma irradiation, lipid solvents, b-propiolactone, formaldehyde, sodium hypochlorite, and phenolic disinfectants.

For the West Africa outbreak the total number of cases is subject to change due to ongoing reclassification, retrospective

investigation and the availability of laboratory results. A second, non-related, EVD o utbreak has been reported in the DemocraticRepublic of Congo with currently a total of 62 confirmed and suspected cases. (http://apps.who.int/iris/bitstream/10665/133833/1/roadmapsitrep4_eng.pdf?ua=1; Nunes-Alves, 2014)

Virology

The virus causing the outbreak has been characterized as Zaire Ebolavirus (EBOV). EBOV belongs to the genus *Ebolavirus*which together with the genus *Marburgvirus* forms the family of *Filoviridae*. This family belongs to the order of the *Mononegavirales*which further contains members of *Bornaviridae*, *Paramyxoviridae* and *Rhabdoviridae*. *Ebolaviruses*a re l inear, n egativestranded, RNA viruses with a genome of approximately 19 kilobases. Morphologically, when studied under an electron microscope, the viral particles look like long stretched filaments with some particles tending to curve into an appearance looking like the number 6. At this moment the genus *Ebolavirus*consists of five species: EBOV, Sudan ebolavirus (SUDV), Tai forest ebolavirus (TAFV), Bundibugyoebolavirus (BDBV) and Reston ebolavirus (RESTV). RESTV is considered to be non-pathogenic to humans. (Feldmann and Geisbert, 2011) The *Filoviridae*family in the order Mononegavirales is separated from other Mononegavirales on the basis of morphological, physiochemical, and biological features (Feldmann *et al*., 2003; Kiley *et al*., 1982) and more latterly genomic analyses (Carroll *et al*., 2013). Filoviruses are non-segmented, negative-strand RNA viruses. The viruses are filamentous (Filo- derived from the Latin *filum*or thread) enveloped particles of variable length. The filovirus genomes are typically approximately 19 kb in length (Feldmann *et al*., 2003; Sanchez *et al*., 2007). The proteins expressed by the filoviruses are: nucleoprotein (NP), glycoprotein (GP), RNA-dependent RNA polymerase (L), and four structural proteins: VP24, VP30, VP35, and VP40 (Sanchez *et al*., 2007; Feldmann and Kiley, 1999). *Ebolavirus*is able to express a truncated soluble glycoprotein (sGP) through RNA editing. The ribonucleoprotein is derived from the RNA genome, NP, VP30, VP35, and L protein, though *Marburgvirus*is reported to be able replicate in the absence of VP30. The VP35 protein is known to block interferon induction in both Marburg and Ebola viruses (Brauburger *et al*., 2012), and the discovery of the open reading frame for this protein integrated into bat genomes is an area for future research exploration to better understand host-virus interactions and immunity (Taylor *et al*., 2011).

Filovirus Outbreaks in Humans—Brief History Including Known Links to Bat Exposure

Lake Victoria marburgvirus was the first filovirus discovered in 1967, when laboratory workers in Marburg, Germany and Belgrade, Yugoslavia (now Republic of Serbia) were contact with infected, imported green monkeys (Chlorocebus spp.) Subsequently, a number of small human outbreaks of Marburgvirus (both Marburg virus and Ravn virus) occurred sporadically between1975–1997, some of which had some link to bat caves (Taylor *et al*., 2011; Brauburger *et al*., 2012). The two largest outbreaks of Marburg virus happened in the Democratic Republic of Congo (DRC) 1998–2000 where 128/154 infected people died in Angola in 2004–2005 where 227/252 patients succumbed to the virus (Brauburger *et al*., 2012). The DRC outbreak was linked to gold mining in Goroumbwa cave (Bausch *et al*., 2003), and origins of the Angola outbreak are not certain. Both Kitaka and Python cave are known to harbor large bat populations, and have been sites for follow up studies on Marburg ecology (Towner *et al*., 2009; Amman *et al*., 2012). The history of Ebolavirus outbreaks in Africa including an excellent summary of outbreaks up until 2005 (Pourrut *et al*., 2005).

Transmission

Natural reservoir of Ebola virus has not yet been identified, it is unknown how the virus first appears in a human at the start of an outbreak. However, researchers believe that the first Person becomes infected through contact with an infected animal, such as a fruit bat or nonhuman primate. Ebola is transmitted through direct contact (through broken skin or unprotected mucous membranes in, for example, the eyes, nose, or mouth) with

1. Blood or body fluids (including but not limited to feces, saliva, sweat, urine, vomit, breast milk, and semen) of a person.
2. Objects (like needles and syringes) that have been contaminated with the virus,
3. Infected fruit bats or primates (apes and monkeys), and
4. Possibly from contact with semen from a man who has recovered from ebola (for example, by having oral, vaginal, or anal sex)

Ebola is not spread through the air, water or in general, by food. In Africa, Ebola may be spread as a result of handling bush meat (wild animals hunted for food) and contact with infected bats. There is no evidence that mosquitos or other insects can transmit Ebola virus. Only a few species of mammals (for example, humans, monkeys, and apes) have shown the ability to become infected with and spread Ebola virus.

Signs and symptoms

A person infected with Ebola virus is not contagious until symptoms appear. Signs and symptoms of Ebola include:

1. Fever
2. Severe headache
3. Fatigue
4. Muscle pain
5. Weakness
6. Diarrhea
7. Vomiting
8. Stomach pain
9. Unexplained bleeding or bruising

Symptoms may appear anywhere from 2 to 21 days after exposure to the virus, but the average is 8 to 10 days.

The public can prevent the spread of ebola virus disease within the community by

1. Taking all persons with any of these signs and symptoms of Ebola Virus Disease to the health facility immediately for medical attention.
2. The isolation of persons suffering from Ebola Virus Disease to avoid the spread of the disease within the community.

3. Wear protective clothing such as gowns, gloves, face mask and goggles each time you visit an Ebola virus disease patient in the health facility to protect you from getting infected with Ebola virus disease
4. Reporting the death of suspected Ebola Virus Disease patients to the nearest health facility.
5. Avoiding traditional burial practices such as embalming and washing of the dead body of suspected Ebola virus disease patient.
6. Informing family members, neighbours and friends about the signs, symptoms and simple preventive measures against Ebola Virus disease such as:

    i. Keeping the house and environment clean always;
    ii. Maintaining good personal hygiene practices such as washing the hands with soap and water always
    iii. Avoiding eating improperly cooked "bush meat"
    iv. Avoiding contact with the blood, saliva, faeces and urine of animals such as fruit bats, chimpanzees, gorillas, monkeys, forest antelope, etc (dead or alive)
    v. Avoiding contact with the blood, saliva and urine of an infected person (dead or alive)

7. Ensuring that everyone in your community is educated on the signs, symptoms and how to prevent Ebola Virus Disease through the mosques, churches, schools, market places, Associations, Town hall meetings, etc

Zika virus

Zika is a viral infection transmitted by the bite of an infected mosquito. It can sometimes be spread by having sex with an infected man. Anyone who gets bitten by an infected mosquito, or who has unprotected sex with an infected man can become infected with Zika. On 1 February 2016, the World Health organization (WHO) declared that the recent cluster of microcephaly cases and other neurological disorders reported in the America's, where an outbreak with Zika virus (ZIKV) is ongoing, constitutes a Public Health Emergency of International Concern (PHEIC) (WHO, 2016). Zika virus (ZIKV) is a mosquito-borne virus (genus *Flavivirus,* family *Flaviviridae*) related to yellow fever, dengue, ZIKV was first isolated in 1947 from Rhesus macaques living in the eponymous forest in Uganda (Dick *et al*., 1952). Up to 2006, only sporadic cases of ZIKV human infections were reported in literature (Hayes, 2009). Accordingly, ZIKV was long considered a low-impact human pathogen, which might explain the limited, compared to other mosquito-borne viruses such as dengue virus (9187 references), West Nile virus (5949 references) or chikungunya virus (2183 references) (Martinez-Pulgarin *et al*., 2015) Virions of ZIKV are 40–60 nm in diameter, spherical in shape and contain a lipid envelope. Its genome consists of a positive sense RNA of approximately 11 kb. The virions consist of a single capsid (C) and two membrane-associated envelope proteins (M, E). The nonstructural proteins (NS1-NS5) contain sequence motifs

Table 1. Diagnosis of diease: This is done by using ELISA, PCR

Virus	Bat Species	Detection Method	References
Marburgvirus	*Epomopsfranqueti*	Antibodies	(Pourrut *et al*., 2009)
	Hypsignathusmonstrosus	Antibodies	(Pourrut *et al*., 2009)
	Miniopterusinflatus	Antibodies; PCR	(Swanepoel
	Rhinolophuseloquens	Antibodies; PCR	*et al*., 2007)
	Rousettusaegyptiacus	Viral Isolation	(Swanepoel *et al*., 2007; Pourrut *et al*., 2009) (Swanepoel *et al*., 2007; Towner 2009; Pourrut *et al*., 2009; Kuzmin *et al*., 2010)
Lloviu virus	*Miniopterusschreibersii*	PCR; HTS	(Negredo *et al*., 2011)
Reston ebolavirus	*Cynopterus sphinx*	Antibodies	(Yuan *et al*., 2012)
	Hipposiderospomona	Antibodies	(Yuan *et al*., 2012)
	Miniopterusschreibersii	Antibodies	(Kuzmin *et al*., 2010)

Clinical anagement and treatement

Besides activity against influenza virus infection, this drug also has documented activity against RNA viruses including *Ebolaviruses*. (Smither *et al*., 2014; Furuta *et al*., 2013) Favipiravir prevented death in mice infected with EBOV when treatment was started six dayspost infection. (Oestereich *et al*., 2014) BCX-4430 is also a nucleoside analogue with broad spectrum activity against RNA viruses and has proven to be effective against the Marburg virus in a non-human primate model and Ebola virus in a mouse model. (Warren *et al*., 2014) characteristic of a serine protease, RNA helicase and RdRp (NS5). The genomic RNA contains a single long ORF flanked by 5'- and 3'-terminal non-coding regions (NCRs) that form specific secondary structures required for genome replication and translation. Translation-initiation of genomic RNA is cap-dependent. Viral proteins are synthesized as part of a polyprotein that is co- and post-translationally cleaved by viral and cellular proteases. RNA synthesis occurs in the cytoplasm in association with modified cellular membranes via synthesis of full-length negative-strand intermediates. Virion assembly, including acquisition of the glycoprotein-containing lipid

Table 2. Drug and Mode of Action

S.No	Drug	Drug Type	Mode of Action
1.	Favipiravir(T-705) (FujifilmHoldings Corp)	Nucleoside analogue – broad spectrum Activity against RNAviruses	RNA chain termination and/or lethal mutagenesis
1.	TKM-Ebola (Tekmira Pharmaceuticals Corp)	Lipid nanoparticle With siRNA –Ebolavirus specific compound	Gene silencing
2.	BCX-4430 (BioCryst Pharmaceuticals)	Nucleoside analogue – broad spectrum Activity against RNA Viruses	RNA chain termination
4.	AVI-6002 (Sarepta Therapeutics)	Phosporodiamidate Morpholinooligomer –Ebolavirus specific compound	Gene silencing

envelope, occurs by budding through intracellular membranes. Viral particles are transported in cytoplasmic vesicles through the secretory pathway before they are released by exocytosis (Daep *et al*., 2014; Leyssen *et al*., 2000).

More information on Zika virus disease can be found in the previous risk assessments (European Centre for Disease Prevention and Control, 2014; European Centre for Disease

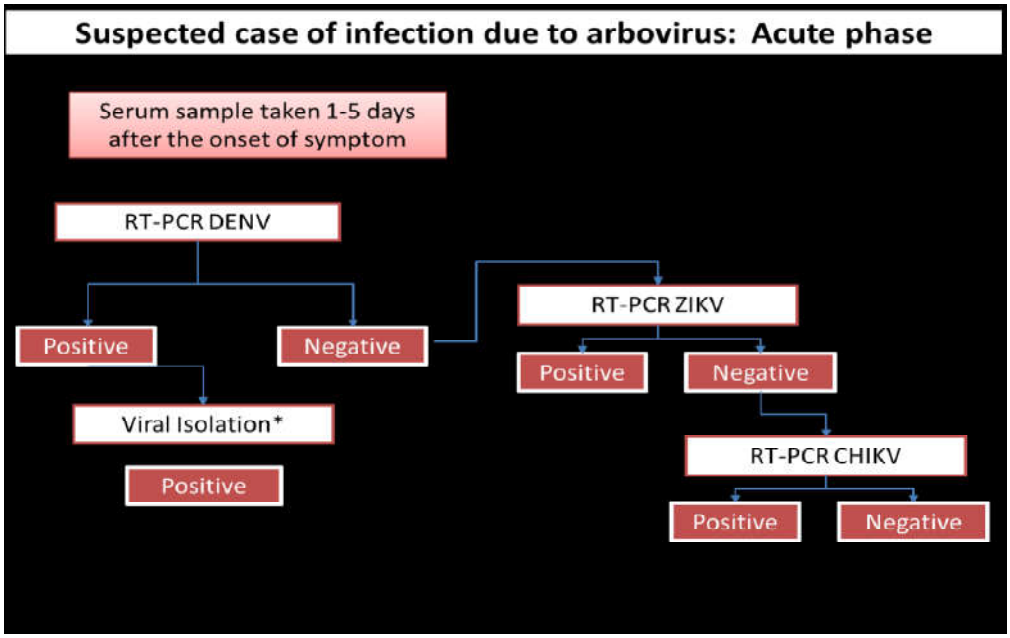

Table No.3 Characteristics of reported cases of congenital malformation potentially linked with zika virus infection in Brazil (AS OF 18 JANUARY 2016)

No.	Date of report location	Clinical findings	Laboratory findings
1.	17 November 2015 Paraíba state	Foetus with microcephaly at ultrasound exams (US) 30.1 weeks' gestation Head circumference <2.6 SD Observed lesions (US): - Brain atrophy with coarse calcifications involving the white matter of the frontal lobes, including the caudate, lentostriatal vessels and cerebellum. - Corpus callosal and vermian dysgenesis. - Enlarged cisterna magna Mother: symptoms compatible with Zika virus infection at week 18-19 of gestation*	RT-PCR Zika virus positive in amniotic fluid (Instituto Oswaldo Cruz) (Melo *et al*., 2016; Ministério da Saúde, 2015)
2.	28 November 2015 Ceara state	Newborn Born the 18 November 2015 (residing Tejuçuoca, Ceara State) No measurement of head circumference at birth Weight: 945 grams at birth Died within 5 min after birth Observed lesions (US, 13 Nov 2015): -microcephaly (head circumference 190 mm) - fetal anasarca - polydramnios	Presence of Zika viral genome in blood and tissue samples of the newborn (Evandro Chagas Institute) (Centro de operações de emergências em saúde pública sobre microcefalias 2015; Pan American Health Organization, 2015)
3.	15 January 2016 Hawaii (USA)	Case: baby with congenital microcephaly who was born recently on Oahu island, Hawaii. Mother had a probable exposure to Zika virus when she was residing in Brazil in May 2015 (no further details provided)	Laboratory confirmation of a past Zika virus infection (no details) (US CDC laboratory) (Hawaii Department of health, 2016)

Transmission

Zika virus disease is caused by an RNA virus transmitted to humans by the Aedes aegypti species. Up to eighty per cent of infections are asymptomatic (Duffy *et al*., 2009). Symptomatic infections are characterised by a self-limiting febrile illness of 4–7 days duration accompanied by maculopapular rash, arthralgia, conjunctivitis, myalgia and headache. Zika virus has not been noted to cause death in the past, nor has it been linked to intra-uterine infections and congenital CNS anomalies. Zika virus infection can be confirmed by direct detection of Zika virus RNA or specific viral antigens in clinical specimens. There are no validated assays for serology.

Prevention and Control, 2015) and in the ECDC factsheet for health professionals (Kuno *et al*., 1998)

- Zika virus is spread to people primarily through the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*).
- A pregnant woman can pass Zika virus to her fetus during pregnancy or around the time of birth. We are studying how Zika affects pregnancies.
- To date, there are no reports of infants getting Zika through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where Zika virus is found.

- Although mosquito bites are the main way that Zika virus is spread, Zika virus can also spread when an infected man has sex with his partners.

Zika virus genetics: There are two lineages of Zika virus, the African lineage and the Asian lineage (Kuno *et al*., 1998; Faye *et al*., 2014). Presently, only two full genome sequences of Zika virus from Brazil and Suriname have been published (Haddow *et al*., 2012). Molecular analysis of the Zika virus isolated from the travel-related case from the Maldives and diagnosed in Finland in showed that it too belonged to the Asian lineage. Recent preliminary findings from molecular investigations of 17 whole genome sequences in the public domain stressed a possible change in the fitness of the Asian lineage through an adaptation of the NS1 codon usage. The researchers suggest that these modifications may have an impact on viral replication rates and viral titres in humans. The authors also reported structural and immunological similarities in the NS1 antigen between Zika and dengue viruses. Both preliminary findings should be further studied and verified on larger whole genome panels (Enfissi *et al*.,).

Symptoms: The most common symptoms are fever, rash, joint pain or red eyes. Other common symptoms include muscle pain and headache. Symptoms usually begin two to seven days after being bitten by an infected mosquito and last several days to a week. Hospitalization and deaths from Zika are unusual, but a nerve disorder, Guillain-Barré Syndrome, can rarely follow an infection. The biggest concern is related to birth defects that have been seen when pregnant women become infected.

Algorithm for detecting zika virus (ZIKV) (Gourinat *et al*., 2015): This algorithm is addressed to laboratories with established capacity (molecular, antigenic and/or serological) to detect dengue (DENV), Zika (ZIKV) (Hayes, 2009), and chikungunya (CHIKV) as part of the differential diagnosis for arbor viruses. A BSL2 containment level is required to handle suspected samples.

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