West of England Medical Journal

Formerly Bristol Medico-Chirurgical Journal

The e-journal of the
Bristol Medico-Chirurgical Society

WEMJ Volume 115 No.1 Article 7 March 2016

Little and Large
Editorial: Viruses in the News

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PART ONE: ZIKA VIRUS

INTRODUCTION

Having just returned from Brazil the Zika virus is very much in the mind of the first author on this paper. The association between microcephaly and Zika virus is in the news constantly and Brazil is the worst affected country.
So what is the Zika virus, what does it do and how is it transmitted?

THE FLAVIRIDAE FAMILY

Zika virus is of the the Flaviviridae family and is specifically from the Flavivirus genus. There are over one hundred members of the same family of viruses and they include the pathogens that cause a large number of diseases ranging from Hepatitis C to classical swine fever.
The flavivirus genus that Zika belongs to are mostly spread by mosquito vectors. Flavus means yellow in Latin and the family and genus are named after Yellow Fever. There are sixty-seven already identified viruses in the Flavivirus genus group causing diseases in humans and animals including Yellow fever, Dengue Fever, West Nile Virus and Zika virus.
They are small viruses icosahedral or spherical in shape with a diameter of around 40-50nm [1].
Yellow fever, which results in rapid death from liver damage and subsequent jaundice, was the first virus to be shown to be transmitted by mosquitoes [2].
Yellow fever has historically killed millions of people and still causes 200,000 infections and 30,000 deaths every year. Although most common in Africa and Central America it has, in the past, caused outbreaks in North America and Southern Europe. There are effective vaccines against Yellow Fever.

ZIKA VIRUS

Zika was first isolated in April 1947 from a rhesus macaque monkey in the Zika forest of Uganda. Immunity to the virus was, however, detected in Indian patients in the early 1950s indicating that the virus was already present endemically in Asia as well as Africa.

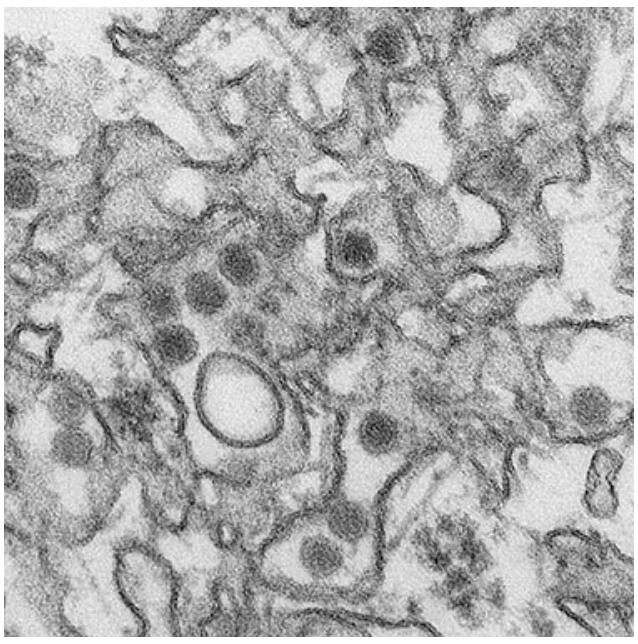

Figure 1. Zika Virus: Electron Micrograph
Virus particles are 40 nm in diameter, with an outer envelope, and an inner dense core
(Author:CDC/ Cynthia Goldsmith [3])

The virus is transmitted by daytime-active mosquitoes. It has been isolated from a number of species in the genus Aedes, such as A. aegypti and arboreal mosquitoes such as A. africanus and a variety of other similar mosquitoes [3].
Until 2015 Zika virus outbreaks had occurred in Africa, Southeast Asia, and the Pacific Islands. Recently considerable numbers of cases have been reported throughout many of the countries in South and Central America. A recent case in Spain occurred in a pregnant woman who had just returned to Spain from Colombia. It is rumoured that transmission via sexual intercourse has occasionally occurred and the virus has been isolated from bodily fluids including breast milk.

SYMPTOMS AND SIGNS OF ZIKA FEVER

In adults the common case history is that of headache, progressing to a maculopapular rash, fever, and back pain. In addition there has recently been a strong link between Zika fever and the Guillain–Barré syndrome [3,4] and an association with microcephaly in newborn babies by mother-to-child transmission [3,5,6,7].
Since the Zika outbreak first occurred in Brazil in May 2015 there have been around 4,000 cases of microcephaly compared with just two hundred per annum previously [8].
There is presently no vaccination against the disease and no specific treatment. The mainstay in management is bed rest and fluid balance plus symptom control [9].
The greatest damage to the fetus probably occurs during the first trimester of pregnancy and may be mediated by an effect on stem cells. A reliable antibody test is difficult because of cross reaction with Dengue fever. In the absence of a satisfactory serological test other techniques are required. Ultrasound can pick up microcephaly at between eighteen and twenty weeks gestation [10].

Clinical Features of Zika fever

Common
- maculopapular rash,
- fever
- back pain
- fatigue

Uncommon
- Guillain–Barré syndrome
- microcephaly

THE WHO AND ZIKA

The World Health Organisation response has been as follows [11]:
"WHO is supporting countries to control Zika virus disease through:

1. *Define and prioritize research into Zika virus disease by convening experts and partners.*
2. *Enhance surveillance of Zika virus and potential complications.*
3. *Strengthen capacity in risk communication to help countries meet their commitments under the International Health Regulations.*
4. *Provide training on clinical management, diagnosis and vector control including through a number of WHO Collaborating Centres.*
5. *Strengthen the capacity of laboratories to detect the virus.*
6. *Support health authorities to implement vector control strategies aimed at reducing Aedes mosquito populations such as providing larvicide to treat standing water sites that cannot be treated in other ways, such as cleaning, emptying, and covering them.*
7. *Prepare recommendations for clinical care and follow-up of people with Zika virus, in collaboration with experts and other health agencies."*

More significantly the WHO has declared the Zika infection outbreak in South America to be a public health emergency [12] and Brazil has despatched hundreds of thousands of troops on mosquito eradication. The outbreak overshadows the forthcoming Olympics in Rio de Janeiro. Pregnant women and those trying

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to become pregnant have been advised not to travel to Brazil[13].

A programme to develop a vaccine against Zika virus has been started but will probably take several years to come to fruition. A vaccine for Dengue fever has recently been approved after twenty years of development and is based on an attenuated Yellow Fever virus. It is intended to give immunity against all four types of Dengue fever [14].

MICROCEPHALY

Figure 2. Microcephaly. Note the underdevelopment of the forehead compared with the rest of the face (with permission, courtesy of Professor Peter Dunn).

Underdevelopment and lack of growth of the brain leads to microcephaly with a small cranium. It can be arbitrarily defined as an occipito-frontal head circumference of more than three standard deviations below the mean for the age and sex of the subject. [15]

CAUSES AND TYPES OF MICROCEPHALY
(Adapted from the Mayo Clinic website [16])

- Chromosomal abnormalities. Down syndrome and other conditions may result in microcephaly.
- Decreased oxygen to the fetal brain (cerebral anoxia). Certain complications of pregnancy or delivery can impair oxygen delivery to the fetal brain.
- Infections of the fetus during pregnancy. These include toxoplasmosis, cytomegalovirus, German measles (rubella) and chickenpox (varicella).
- And now....ZIKA VIRUS
- Exposure to drugs, alcohol or certain toxic chemicals in the womb. Any of these put your baby at risk of brain abnormalities.
- Severe malnutrition. Not getting adequate nutrition during pregnancy can affect the baby's development.
- Uncontrolled phenylketonuria, also known as PKU, in the mother. PKU is a birth defect that hampers the body's ability to break down the amino acid phenylalanine.

Microcephaly due to brain damage must be distinguished from the various forms of craniostenosis (or craniosynostosis) in which the premature fusing of the joints (sutures) between the bony plates that form an infant's skull keeps the brain from growing. Skull x-rays and CT scans can demonstrate the premature fusion. Treating craniostenosis usually means that the infant needs surgery to separate the fused bones. If there are no underlying problems in the brain, this surgery allows the brain adequate space to grow and develop.

Controversy in Brazil

A report by an Argentinian group "Physicians in Crop Sprayed Towns" has suggested that Zika is not responsible for the rise in cases of microcephaly. They claim that the larvicide pyriproxyfen, added to water to control mosquitoes, is the real cause. Other groups have blamed vaccination programmes but the WHO says that a definitive link between Zika and microcephaly is within weeks of being confirmed [17].

PART TWO: GIANT VIRUSES

The Flaviviruses are small but that is not the case with all viruses. In 1992 researchers discovered an unusual microbe in a water tower in Bradford, England. They were looking for Legionella bacteria subsequent on an outbreak of pneumonia but came across a structure that stained positive with the gram stain. It was a hairy-looking polyhedron 400nm across and it was initially assumed to be an unusual gram-positive bacterium because it was ten times the diameter of most viruses.

In 2003 researchers from the University of the Mediterranean Aix-Marseille II identified the organism as a virus [18,19,20]. Named the Mimivirus because it mimicked a bacterium, this was the first giant virus to be identified. Since that time many more giant viruses have been found and according to the New Scientist... "giant viruses are basically everywhere". Latest discoveries include the massive Pithovirus discovered in a 30,000 year old Siberian ice core [20]. The Pithovirus, at 1500nm in length, is nearly as large as common bacteria such as E. coli.

The giant viruses can also be found inside our bodies and have been detected in human blood and even in a contact lens case. Studies have linked them with pneumonia, which was, as mentioned above, the precipitating factor in the original investigation in Bradford.

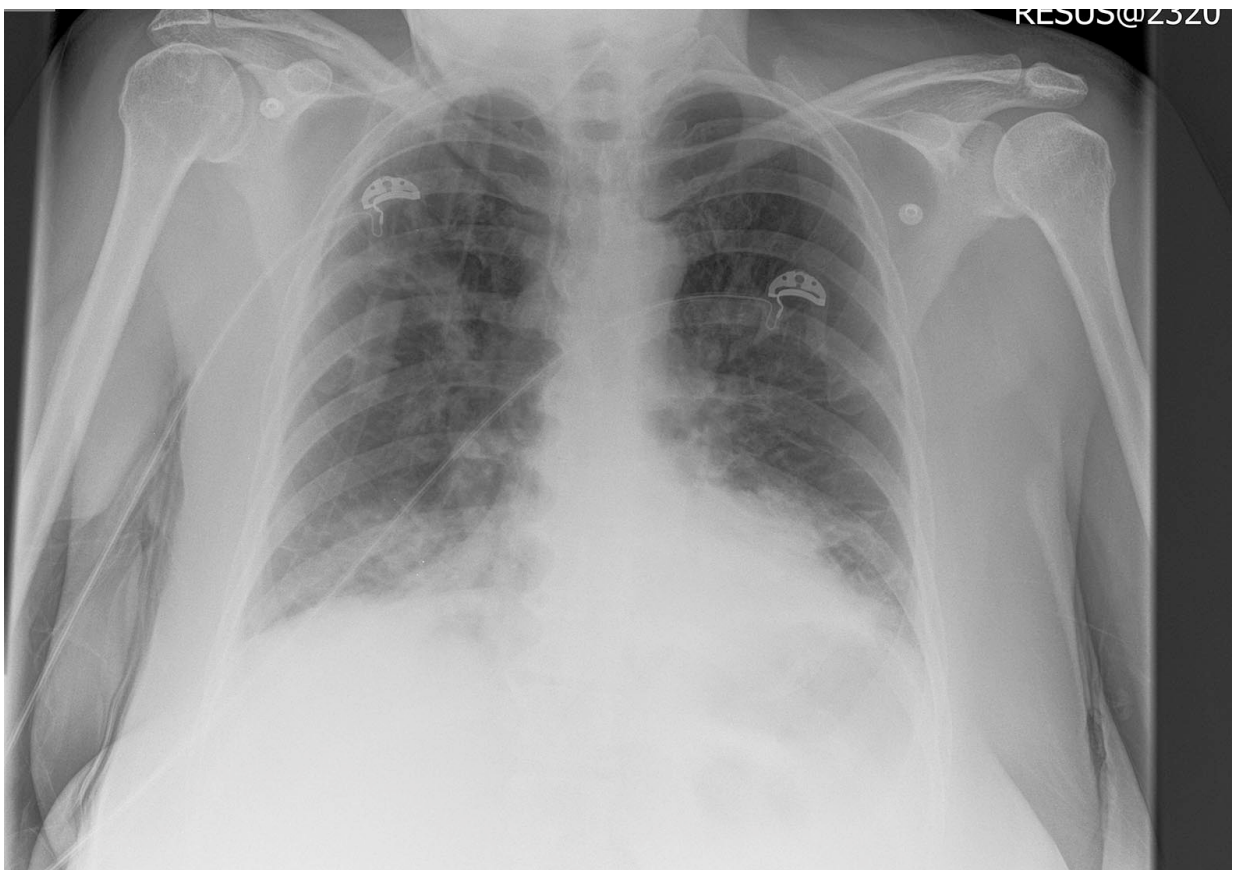

Figure 3. Viral pneumonia
Admitted with difficulty in breathing and a cough productive of green sputum associated with fever and chest tightness. Her symptoms had begun four days prior to admission She had a background of asthma and was a non smoker. On admission she was febrile and her AP Chest x-ray revealed a bilateral lower lobe pneumonia. Bloods showed a raised inflammatory response.

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CONCLUSION

The recent outbreaks of Ebola and now Zika virus are a reminder that pathogenic organisms can and will spread in epidemic proportions when we least expect them to do so. Research into vaccines should be undertaken as soon as the pathogens are discovered rather than waiting until the outbreak occurs.

The controversy over insecticides serves to remind us that toxic chemicals can also cause birth defects and harm the very people that the user is trying to protect.

The giant viruses show us that our understanding of the world of microbes is certainly not complete and may shake up our very understanding of life. The giant viruses may even predate all other life and possibly represent the remnants of the most ancient lifeforms. In addition it is clear that viruses often transmit genes to their hosts as well as steal them. Bacteriology and Virology have suddenly become a lot more interesting but to live in "interesting times" is an old Chinese curse.

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