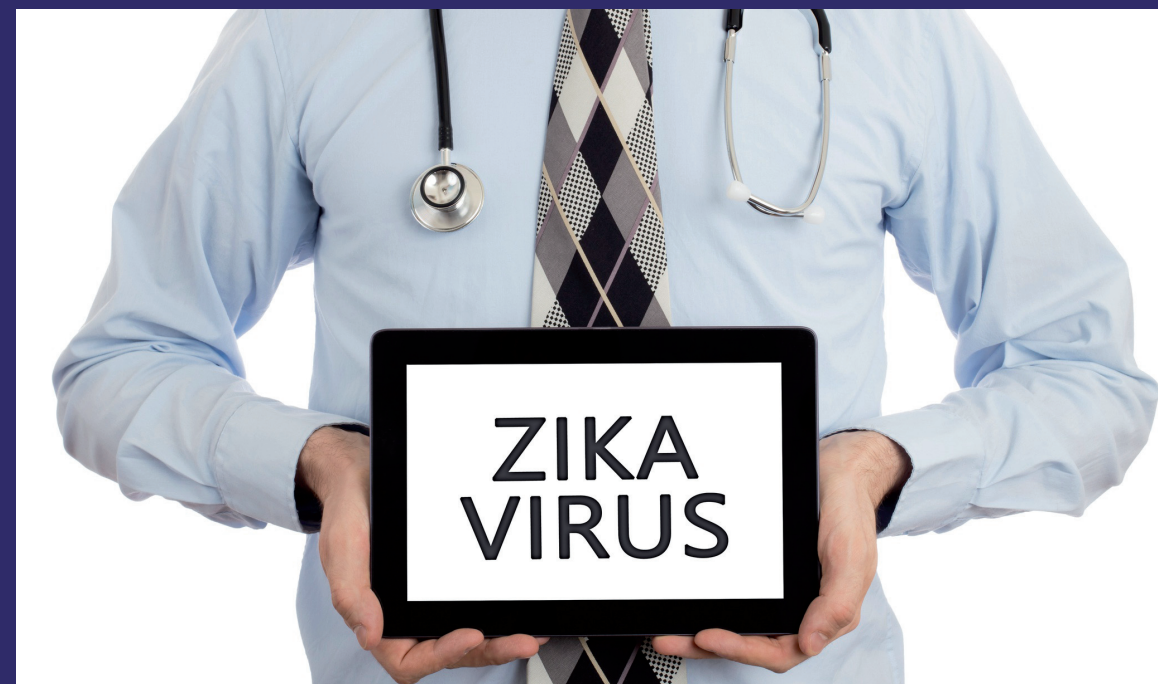


Peer's Review and Endorsement: "The Author has the ability to convey in depth research on Zika virus and its relationship to midwifery in a most passionate and professional manner. Student midwives can find this book most relevant, easy to read and apply in the Framework of Health Promotion and thus enhance their sphere of midwifery practice". Evelyn Collison, Senior Lecturer, Department of Adult Nursing and Midwifery, London South Bank University

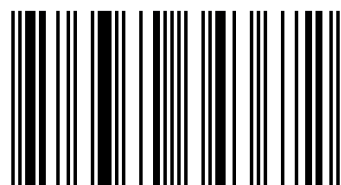


Vincent Icheku



Dr. Vincent Icheku is self-motivated, competent, and awarding winning academic with track record of publications. This present book is an attempt to answer the question, if Zika virus is the definitive culprit in the cases of microcephaly, why are there no similar birth defect epidemics in Africa where Zika virus existed for 70 years.

Is Zika virus the definitive culprit in the cases of microcephaly?



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Propose title:

If Zika virus is the definitive culprit in the cases of microcephaly, why are there no similar birth defect epidemics in Africa where Zika virus existed for over 70 years?

Foreword

This book is seeking to investigate and uncover the conundrum of why the Zika virus, though first identified in 1947 in Uganda, apparently had no links to microcephaly, thus raising the question of whether infections by mosquito caused those defects.

The book both provides an evaluation of current evidence for that link between Zika virus and microcephaly and attempts to explain the absence of microcephaly in Africa between 1947 -2016.

The book is evidenced based, examining the current literature in the field and will provide a much needed direction of travel for policy makers, researchers and potential management of this virus.

The book's conclusion hints that both man made chemical intervention and socio economic factors may have played a part in the rise of cases of microcephaly, which will be of enormous interest to researchers and the global bodies responsible for the management of this virus.

It will be a valuable global public health resource for practitioners in the field, academics, researchers and policy makers in their various fields of practice. ***Dr Annette Chowthi-Williams, Senior Lecturer in the School of health and social care, London South Bank University***

Peer Review and Endorsement

"The Author has the ability to convey indepth research on Zika virus and its relationship to midwifery in a most passionate and professional manner. Student midwives can find this book most relevant, easy to read and apply in the Framework of Health Promotion and thus enhance their sphere of midwifery practice". ***Evelyn Collison, Senior Lecturer, Department of Adult Nursing and Midwifery, London South Bank University***

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Introduction

The World Health Organisation (WHO) situational report shows that 62 countries and territories have reported cases of mosquito-borne Zika virus transmission since 2007. The report added that cases of person-to-person transmission of the Zika virus were reported in 11 countries from February 2016 (WHO, 2016). The world was alarmed at the beginning of 2016 by the sudden and explosive emergence of a Zika virus outbreak in the majority of Latin American and Caribbean countries, with estimated cases of 440 000–1 300 000 in Brazil alone (PAHO, 2016). Zika virus is thought to have led to more than 11,000 deaths and nearly 4,000 cases of microcephaly in Brazil since the start of the outbreak in May 2015 (WHO, 2016). The American Centers for Disease Control and Prevention (CDC) reported 150 cases of Zika virus in 2014, which is a very small number for its population, compared to the outbreak in 2015. The outbreak in May 2015 was unprecedented and is reported to have resulted in more than 1 million cases, with 4,000 suspected cases of microcephaly, and 270 confirmed cases that health officials believe are linked to the Zika virus (CDC, 2016).

Microcephaly is described as a rare congenital disease that is linked with incomplete brain development and causes babies to be born with unusually small heads and, in the majority of cases, brain damage (Gyawali, et al., 2016). Zika virus related microcephaly has now been reported in 20 countries or territories and WHO recently predicted that as many as four million people might be infected with the virus (WHO, 2016). By January 2016, A total of 3,530 suspected microcephaly cases had been reported by January 2016 compared to 4,000 suspected cases of microcephaly reported in May 2015, many of which occurred in infants born to women who lived in or had visited areas where Zika virus transmission was occurring. The birth prevalence of microcephaly in Brazil increased sharply during 2015–2016 with the largest increase occurred in the Northeast region, where Zika virus transmission was first reported in Brazil (CDC, 2016).

The Zika virus, linked in Brazil to the birth defect microcephaly, was first identified in the Ugandan Zika forest in 1947. The initial review of literature for this book shows that the Zika virus spread slowly to other parts of Africa, and eventually appeared in Southeast Asia. The evidence from the review also shows the current globalization of the Zika epidemic began on the Pacific island of Yap in the Federated States of Polynesia. The virus subsequently spread into French Polynesia where microcephaly and other congenital abnormalities were observed in the infants of women who were pregnant when they contracted the disease. The epidemic rapidly spread to the Cook Islands and Easter Island, Brazil, Caribbean Islands, the Americas and many other parts of the globe. In May 2016, the WHO tests confirmed two hundred cases of Zika virus with 7,557 suspected cases in the African island chain of Cape Verde. Cape Verde is an Atlantic archipelago that is about 350 miles (570km) west of Senegal and which has historic ties to Brazil (Icheke, 2016, who, 2016, Davis, 2016).

Aim and objective of the book

Until the recent WHO reported cases, there was no documented evidence of Zika-associated to microcephaly in any part of Africa, where the virus originated. This raises the question as to what is the connection between Zika virus and microcephaly. In other words, is mosquito-borne infection actually *the cause of the defects in babies born to Zika-virus-infected mothers*? The answer to that question could provide essential clues as to why microcephaly leading to birth defects suddenly appeared in Africa 70 years after Zika virus was first discovered in 1947. The aim of this book is to provide a single document that evaluates current evidence linking Zika virus to microcephaly in an epidemiological context of the disease and thus provide possible explanations as to why there was no microcephaly in Africa between 1947 and 2016. The objective is divided into the following five chapters of the book:

Chapter 1 focuses on Zika virus transmission by exploring the scientific studies that implicated *Aedes aegypti* mosquitoes *the main vector transmitting the Zika virus*. The chapter discussed the most common symptoms of Zika virus but noted that most people infected with Zika virus would have no symptoms or fall ill; only one in five of the people infected with the disease become symptomatic. Thus, the chapter argues that the asymptomatic nature of Zika virus has public health implication. For example, those who are asymptomatic and those who are in the incubation period of Zika virus could potentially donate infected blood or exchange contaminated body fluid, thereby, increasing human to human transmission of the disease.

The chapter also uses Table 1.1 to illustrate four categories of Zika virus transmission. For example, category 1 shows area with new introduction or re-introduction with ongoing Zika virus transmission; category 2 identified area either with evidence of virus circulation before 2015 or area with ongoing transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption; category 3 involves area with interrupted transmission and with potential for future transmission and category 4 shows area with established competent vector but no known documented past or current transmission.

Also, chapter 1 explores the modes of Zika virus transmission (Vector-borne and non- vector-borne transmission) and reinforces the view that mosquitoes are not the only means of Zika virus transmission. Thus, the chapter uses figure 1.3 to illustrate the vector and non-vector modes of Zika virus transmission cycle. The cycle starts when humans are bitten by an infected mosquito followed by viral replication in humans and viremia. The transmission cycle shows that Zika virus can spread to the reproductive organs and can be transmitted during sexual intercourse. Pregnant women who are infected with the Zika virus can also transmit the virus to their unborn child or the fetus during pregnancy. The Zika virus can then be transmitted from an infected person back to mosquitoes through subsequent mosquito bites. Lastly, the cycle continues when the Zika virus replicated in the mosquitoes and transmitted back to humans.

Chapter 2 focuses on the epidemiology of Zika virus with a view to documenting the incidence and geographical distribution of the virus. The chapter traced the origin of Zika virus to the first isolated in 1947 from a febrile sentinel rhesus monkey in the Zika forest in Uganda, where it got its name. The virus spread slowly to other parts of Africa and eventually appeared in Southeast Asia before the current globalization of the Zika virus epidemic, which started on the Pacific island of Yap in the Federated States of Polynesia in 2007. The chapter demonstrates that the Zika virus epidemic that started on the Pacific island of Yap was the first known presence of the Zika virus case outside of Africa and Southeast Asia. The chapter uses figures and tables to show that the wide geographical distribution of the Zika virus and demonstration that the disease spread to French Polynesia, New Caledonia, Cook Islands, and Easter Islands before cases were reported in Brazil in 2015.

Chapter 2 also explores globalisation and the risk for Zika virus spread and argued that increased globalisation continues to pose a risk for Zika virus spread. For example, there is clear evidence of a well-established association between global travels and the acquisition or transmission of infectious diseases. The chapter demonstrated that in 2015, there were 9.9 million flights from Brazilian to destinations in North America, Europe, Asia, and Africa. This has public health implication given that the incubation period for Zika virus is 3 to 14 days from the bite of Aedes species mosquito. Travelers and humanitarian health workers returning from affected areas in Brazil may be incubating the virus and become infectious after returning to their home countries.

Chapter 3 reviewed the evidence linking Zika virus to microcephaly and Guillain–Barré syndrome (GBS) given that the World Health Organization report of March 2016, claimed that there was a scientific consensus that the mosquito-borne Zika virus was a cause of the neurological disorder Guillain–Barré syndrome (GBS) and of microcephaly and other congenital brain abnormalities. The review is important given that the decisions about causality require a clear understanding of the association of Zika virus complications to guide public health actions. The chapter demonstrated there had been a remarkable increase in cases of microcephaly and other congenital abnormalities in Brazil between 2015 and mid-2016. The table 3.7 was used in the chapter to demonstrate that as of March 2017, 31 countries or territories reported microcephaly and other congenital abnormalities potentially linked to Zika virus infection.

Chapter 4 reviewed the evidence linking Microcephaly to birth defect in Africa and found that other factors may play in the Zika virus related microcephaly. The chapter discussed the evidence, which suggested that the emergence in 2014 of the microcephaly increase in Brazil occurred within certain "contexts and contingencies." Environmental degradation, poor sanitation and continued use of larvicidal chemicals in the drinking water of families were blamed for the sudden increase microcephaly. These evidence may provide a clue as to why the increase cases of Microcephaly were mostly reported in the Northwest of Brazil where the factors mainly prevalent.

As for the absence of microcephaly in Africa, Chapter 4 examines a phenomenon called herd immunity that seems to offer the most plausible explanation. Herd immunity becomes a type of indirect protection from infectious disease, occurring when a significant percentage of a population has become immune to an infection, thereby providing a measure of protection for individuals who are not immune and thus decreasing the number of new infections. Given that the virus is unable to infect the same person twice; the presence of immune system generating antibodies to kill the virus and the epidemic reaching a stage where there are too few people left to infect for transmission to be sustained. The chapter concluded with a warning that until the apparent association between Zika virus infection and microcephaly is either established or disproved, women should be cautious in planning to conceive a baby or to travel to a Zika-endemic country if already pregnant (Gyawali et al. 2016).

Chapter 5 will start with the premise that the World Health Organisation is better placed to identify critical areas of public health research; implementation and coordination of global fight against the Zika virus epidemic. Thus, it will explore WHO's Zika Virus Research Agenda that sets out to support the generation of evidence needed to strengthen essential public health guidance; actions to prevent; limit the impact of Zika virus and its complications. The chapter is also based on the premise that research and evidence are the foundations for sound health policies. It will, therefore, explore systematic review of evidence and the use of research evidence to inform Zika virus related public health policies and practices. The readers of this book may be delighted to know that both the American Centers for Disease Control and Prevention (CDC) and the World Health Organisation (WHO) are driving and encouraging the use of research evidence to underpin public health policy in the global fight against the Zika virus epidemic.

Chapter 6 discussed recommendations for public health interventions to prevent the global spread of Zika virus infection, given that there is no cure, no vaccine or prophylactic treatment for the disease. The chapter recommended primary preventive interventions such as promotion of avoidable travel to countries where Zika virus is prevalent especially pregnant women or those planning to get pregnant; use of mosquito repellent; practicing safe sex, etc. The chapter also recommended secondary interventions such as reduction of mosquito breeding sites in outdoor and indoor and symptomatic treatment based on good hydration, pain relief, and anti-histamines for the pruritic rash. Lastly, the chapter examined the scope of current research to develop Zika virus vaccines and argues that effective vaccine development is crucial in the fight against the Zika virus infection.

In conclusion, the book provided a summary of the current evidence linking Zika virus to microcephaly in historical context, 1947 to 2016 and offered possible explanations as to why there were no cases of microcephaly in Africa for 70 years. The summary of the possible explanations are: the possibility of chemical, Pyriproxyfen, used in a State-controlled programme aimed at eradicating disease-carrying mosquitoes; possibility of existence of inequalities in the low-income countries in the Americas, which are currently ignored in the microcephaly narrative and the possibility of herd immunity occurring in Africa that may have provided protection against the Zika virus infection.

Lastly, tables and maps were used in this book to reinforce and add value to the textual information. They were also used to draw attention to spatial relationships in the global distribution of Zika virus. Their use allows lengthier information in the book to be described in pictures and tabular forms and more memorable because they have colours and in shapes. Also, the tables and maps helped to present spatial relationships in a way that is more striking; given that they show the intensity of the Zika virus transmission and global spread. Once the spatial relationships were established, the book was then able to analyse them and used texts to explain the underlying causes of the disease and its complications, which in turn informed the recommended public health interventions.

Chapter 1:

Zika virus transmission

The Zika virus is a Flavivirus from the family Flaviviridae, which has emerged as a global mosquito-borne pathogen of growing public health concern (Icheke and Icheke, 2016). The *Aedes aegypti* mosquito was implicated in a study by Boorman and Porterfield (1956) as the main vector transmitting the Zika virus. This finding was confirmed by a later experimental study that demonstrated the competence of the *Aedes aegypti* mosquito to transmit the Zika virus. The *Aedes aegypti* mosquito, shown in figure 1.1, is one of the two mosquitoes (*Aedes aegypti* and *Aedes albopictus*) that spread the dengue and chikungunya viruses (CDC, 2016). Table 1.1 below offers a comparison of the two main *Aedes* mosquitoes, *Aedes aegypti*, and *Aedes albopictus*, species that transmit Zika virus.

Figure 1.1: *Aedes aegypti* mosquito



Source: Public Health England (2017), Travel Health Website:
<http://travelhealthpro.org.uk/news/4/zika-virus--update-and-advice-for-travellers-including-pregnant-women-and-those-planning-pregnancy>

The World Health Organisation (2016) recently reported that Zika virus had been isolated in numerous other species of the *Aedes* mosquito family, as well as in *Anopheles coustani*, *Mansonia uniformis* and *Culex perfuscus*, none of these species has been proven to acquire the Zika virus and transmit it in a laboratory setting. The report added that other *Aedes* species such as *Aedes atropalpus*, *Aedes koreicus*, *Aedes triseriatus*, and *Aedes japonicus* are known to be able to transmit other flaviviruses, but there is presently no evidence to show that these *Aedes* species can transmit Zika virus or adapt to urban environments. Contrary to this supposition, a study published by the medical journal, *The Lancet* warned that to assume that *Aedes aegypti* is the only mosquito involved in Zika virus transmission in areas where other mosquito species coexist naively and could be catastrophic if other species are found to have important roles in Zika virus transmission (Ayres, 2016). WHO emphatically maintained that *Aedes aegypti* is responsible for the current transmission of Zika virus in the Americas (WHO, 2016).

Table 1.1: Comparison of *Aedes aegypti* and *Aedes albopictus*:

<i>Aedes aegypti</i>	<i>Aedes albopictus</i>
bites primarily humans (anthropophilic)	bites primarily wild and domestic animals (zoophilic) but also humans
tends to bite indoors	tends to bite outdoors
feeds multiple times per cycle of egg production	feeds once per cycle of egg production
adapts well to human urban settlements	inhabits rural areas especially

Source: WHO (2016) Zika virus vectors and risk of spread in the WHO European Region
http://www.euro.who.int/__data/assets/pdf_file/0011/304211/Zika-virus-and-risk-of-spread-in-European-Region.pdf?ua=1

The most common symptoms among symptomatic patients include macular or papular rash (90 per cent); typically low grade fever (70 per cent) arthralgia (between 60 and 70 percent); fatigue (70 percent); non-purulent conjunctivitis or conjunctival hyperaemia (55 percent); myalgia (45 percent) and headache (45 per cent), while other symptoms, such as retro-orbital pain, oedema, vomiting,

sore throat, uveitis, and lymphadenopathy, are less frequent (Barzon, et al. 2016, Icheku, 2016).Brasil et al. (2016b) show that maculopapular rash is a typical feature of Zika virus infection; often pruriginous and starts on the face Andor the trunk and then spreads throughout the body but may also be focal and fugacious.

Figure 1.2



Adopted from: Dr. Bhagyashri (2016), Zika Virus article in Medscape.com

The above figure 1.2 shows pictures of rashes in a patient with Zika virus infection. These sort of rashes are called “maculopapular rashes” that is a compound word used to describe two terms, “macule” and papule.” Macule is flat discoloration or blemishes that measure smaller than 1 centimeter. Papule, on the other hand, is an elevated lesion that also measures smaller than 1 centimeter. When the two terms are combined, one can determine that maculopapular rashes are those that are composed of redness or smooth skin rash, with elevated bumps (Carteaux, 2016). Maculopapular rashes such as those highlighted in figure 1.2 are often felt itchy and uncomfortable but do not require any specific treatment as they tend to subside after few days without leaving any scar or spots (Oakley, 2016). A health writer for NBC News citing a team of New York doctors who treated Zika patients explains that Zika infection starts off with a headache; within a day, a red rash formed on his hands and arms and spread to his whole body by the third day. Thus, America doctors are therefore implored to be proactive in identifying the distinctive symptoms of the disease (Fox, 2016).

Most people infected with Zika virus are asymptomatic. In other words, people infected with Zika virus will have no symptoms or fall ill; only one in five of the people infected with the disease become symptomatic (CDC, 2016). One study estimated that up to 80 per cent cases of Zika virus infection are asymptomatic (Duffy et al. 2009). This result in only 20 per cent of those people infected with the virus seeking medical treatment (Swanson, 2016). Duffy et al. (2009) maintained that symptoms of Zika virus infection occur after an incubation period of 3–12 days. They added that the symptoms are usually mild and last for 4–7 days without severe complications (Duffy et al. 2009). The public health implication of this is that those who are asymptomatic and those who are in the incubation period of Zika virus could potentially donate infected blood or exchange contaminated body fluid, thereby, increasing human to human transmission (Icheku and Icheku, 2016).

Although Zika virus infection is not life-threatening in healthy person, severe symptoms and sequelae were reported, including Guillain-Barré syndrome and other neurological disorders, haemorrhagic complications and even death during the recent outbreaks (Barzon, e al. (2016). The first death from Guillain-Barré syndrome, a paralysis condition that developed from a Zika infection was in Puerto Rico in August 2016. The victim, aged between 35 and 45 years old and from the San Juan area of Puerto Rico, a US territory in the Caribbean died from Guillain-Barré syndrome (Coto, 2016). This prompted a public health expert to ask, “What does this first death tell us? That all of us are susceptible” (Agerholm, 2016). The World Health Organisation recent report on Zika virus and complications linked Guillain-Barré syndrome to Zika virus transmission (WHO, 2017). As discussed elsewhere in this chapter, Zika virus can be transmitted from an infected pregnant woman to her unborn child then can cause microcephaly leading to a birth defect and other severe brain anomalies in the infant. Zika infections in adults can result in Guillain-Barré syndrome, which has been described in this chapter as a condition that can cause temporary paralysis and in rare instances, death.

The World Health Organisation (2017) also recently reported that geographical distribution of Zika virus had expanded globally with 31 countries and territories including reported cases of microcephaly and other central nervous system malformations associated with Zika virus infections. WHO added that there are significant gaps in knowledge concerning Zika virus as a vector, the disease's transmission dynamics, and geographical distribution. These challenges notwithstanding, there is a need to have a clear description of the epidemiology of Zika virus transmission in a given place and at a given time to allow an assessment of the possibility of Zika virus infection for various populations or communities and to adapt public health recommendations accordingly for country residents and travelers alike. Subsequently, the World Health Organisation (WHO) and the United States Pan American Health Organization (PAHO) developed a new Zika virus categorisation scheme (WHO and PAHO, 2017). The aims of the following four categories of Zika virus transmission defined for the classification are:

- Category 1: To identify the area with new introduction or re-introduction with ongoing Zika virus transmission.
- Category 2: To identify area either with evidence of virus circulation before 2015 or area with an ongoing transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption.
- Category 3: To identify the area with interrupted transmission and with potential for future transmission.
- Category 4: To identify the area with established competent vector but no known documented past or current transmission (WHO, 2017).

Table 1.2:

Zika Virus classification by WHO Regional Office, Countries, Territories or Sub-national areas

WHO Regional Office Country / territory / sub-national area			
Category 1:	AFRO	Angola; Cabo Verde; Guinea-Bissau	3

	AMRO/PAHO	Anguilla; Antigua and Barbuda; Argentina; Aruba; Bahamas; Barbados; Belize; Bolivia (Plurinational State of); Bonaire, Saint Eustatius; Saba; Brazil; British Virgin Islands; Cayman Islands; Colombia; Costa Rica; Cuba; Curaçao; Dominica; Dominican Republic; Ecuador; El Salvador; French Guiana; Grenada; Guadeloupe; Guatemala; Guyana; Honduras; Jamaica; Martinique; Mexico; Montserrat; Nicaragua; Panama; Paraguay; Peru; Puerto Rico; Saint Barthélemy; Saint Kitts and Nevis; Saint Lucia; Saint Martin; Saint Vincent and the Grenadines; Saint Maarten; Suriname; Trinidad and Tobago; Turks and Caicos Islands; United States of America; United States Virgin Islands; Venezuela and Bolivarian Republic	47
	SEARO	Maldives	1
	WPRO	American Samoa; Fiji; Marshall Islands; Micronesia (Federated States of); Palau; Papua New Guinea; Samoa; Singapore; Solomon Islands; Tonga	10
Subtotal			61
Category 2:	AFRO	Burkina Faso; Burundi; Cameroon; Central African Republic; Côte d'Ivoire; Gabon; Nigeria; Senegal; Uganda	9
	AMRO/PAHO	Haiti	1
	SEARO	Indonesia; Thailand; Bangladesh	3
	WPRO	Cambodia; Lao People's Democratic Republic; Malaysia; Philippines; Viet Nam	5
	Subtotal		18
Category 3:	AMRO/PAHO	ISLA DE PASCUA – Chile	1
	WPRO	Cook Islands; French Polynesia; New Caledonia; Vanuatu	4
Subtotal			5
Category 4:	AFRO	Benin; Botswana; Chad; Comoros; Congo; Democratic Republic of the Congo; Equatorial Guinea; Eritrea; Ethiopia; Gambia; Ghana; Guinea; Kenya; Liberia; Madagascar; Malawi; Mali; Mauritius; Mayotte; Mozambique; Namibia; Niger; Réunion; Rwanda; Sao Tome and Principe; Seychelles; Sierra Leone; South Africa; South Sudan; Togo; United Republic of Tanzania; Zambia; Zimbabwe	33
	AMRO/PAHO	Uruguay	1
	EMRO	Djibouti; Egypt; Oman; Pakistan; Saudi Arabia; Somalia; Sudan; Yemen	8
	EURO	Georgia; Região Autónoma da Madeira – Portugal; Russian Federation; Turkey	4
	SEARO	Bhutan; India; Myanmar; Nepal; Sri Lanka; Timor-Leste	6
	WPRO	Australia; Brunei Darussalam; China; Christmas Island; Guam; Kiribati; Nauru; Niue; Northern Mariana Islands (Commonwealth of the); Tokelau; Tuvalu; Wallis and Futuna	12
Subtotal			64
Total			148

Source: WHO and PAHO (2017) Latest Global Situation Report on Zika: Zika virus, Microcephaly, and Guillain-Barré syndrome, World Health Organization and Pan American Health Organization, http://www2.paho.org/hq/index.php?option=com_content&view=article&id=11669:latest-global-situation-report-zika&catid=8444:news&Itemid=41716&lang=en

Zika virus transmission has been recorded in Africa, the Americas, Asia and the Pacific. Table 1. 2 presents a classification of the areas with ongoing Zika virus transmission in categories 1 and 2. This amounts to a total of 61 and 18 countries, territories or areas respectively. A total of 5 countries,

territories or areas with interrupted transmission but with potential for future transmission were presented in Table 1.2 as category 3. Category 4 in the table presents a total of 64 countries, territories or areas with established competent vector but no known documented past or current transmission as category 4 (WHO and PAHO, 2017). According to WHO (2017) some countries, territories or areas are currently not at risk of present vector borne Zika virus transmission due to the absence of a competent vector and favourable climate. Such countries, territories or areas are not included in the classification scheme and therefore uncategorised.

The European Region Office (2016) of the World Health Organisation recently claimed that *Aedes albopictus* is native to Southeast Asia. In the European Region, the virus established itself primarily in the Mediterranean basin particularly in Albania, Bosnia and Herzegovina, Bulgaria, Croatia, France, Germany, Georgia, Greece, Israel, Italy, Malta, Monaco, Montenegro, Romania, San Marino, Slovenia, Spain, Switzerland, Turkey and Vatican City. WHO (2016) also claimed that *Aedes aegypti* originates from Africa and has been identified in Europe in the past and recently reported in limited areas of the European Region, namely Madeira Island and the north-eastern Black Sea coast (Georgia and the southern part of the Russian Federation). This evidence suggests that the European Region may be at the risk of global health threat from the Zika virus.

The transmission of the Zika virus, which first started in Africa, then Asia and the Pacific Islands have now spread far beyond the affected areas where dozens of cases have been identified in America and its territories. Some health experts have warned that Zika virus could trigger global health threat, but this writer in an earlier study found that Zika virus transmission is unlikely to transmit in some countries given that the condition necessary for *Aedes aegypti* mosquitoes to breed is not fully present in such countries. The *Aedes aegypti* mosquito that produces Zika virus survives year round in tropical and subtropical climates; extremely common in areas lacking in pipe borne water systems, and depend greatly on water storage containers to lay their eggs (Confalonieri, et al., 2007, Icheku, 2016). This supposition is line with the finding of a study published in the medical journal *The Lancet*, which found that the mosquito-borne disease transmission is climate sensitive for several reasons. The mosquitoes require standing water to breed, and a warm ambient temperature is critical to adult feeding behaviour and mortality, the rate of larval development, and speed of virus replication. One study cited by Icheku (2016) added that if the climate is too cold, viral development is slowed down and the mosquitoes are unlikely to survive long enough to become infectious (Hales, et al., 2016). However, another study also cited by Icheku (2016) found that vector-borne diseases have been moving into more northern latitudes in response to global warming. The global warming hypothesis seems to reinforce the health experts' view that present Zika virus outbreak could trigger global health threat (Confalonieri, et al., 2007). Imperato (2016) argued that globalisation of the Zika virus transmission will be made possible by the widespread presence in various parts of the world of *Aedes* vectors and increased human travel that facilitated geographic spread. The vector-borne transmission will be explored in the following section.

Vector-borne transmission

As noted earlier, Zika virus has been isolated from *Aedes aegypti* mosquitoes, and experimental infections show that this species is capable of transmitting Zika virus. Other *Aedes*' mosquito species, notably *Aedes-Africanus*; *Aedes-albopictus*; *Aedes-Polynesians* is; *Aedes-unilinear*; *Aedes-vittatus* and *Aedes-hensilli* are considered potential vectors of Zika virus. These species bite during the day (ECDC, 2016). Barzon, et al., (2016) reviewed several other studies and posited that these viruses have been isolated or detected by Polymerase Chain Reaction (PCR) in Africa, while in Asia it has been detected in *Aedes aegypti*, which has been known to be the main Zika virus epidemic vector outside the continent of Africa. *Aedes hensilli*, which was considered the most common mosquito species in Yap Island and the competent vector for Zika virus transmission was conceivably the main vector for ZIKV transmission during the 2007 outbreak, even though the virus could not be

detected in any mosquito samples. *Aedes aegypti* and *Aedes Polynesians* are considered the most common mosquito species in French Polynesia; were most likely the vector involved in the local Zika virus transmission, while *Aedes-aegypti* and probably also *Aedes albopictus* were considered the vectors responsible for transmission in the Brazil and other countries in South and Central America. However, the reports on Zika virus isolation from field mosquitoes lacked as of the time of the outbreaks. Barzon, et al., (2016) citing Di Luca et al. (2016) added that both *Aedes-aegypti* and *Aedes-albopictus* were competent vectors for the Zika virus transmission but transmission from *Aedes-albopictus* is less efficient than from *Aedes aegypti* due to a longer extrinsic incubation period.

As illustrated in figure 1.3 below, Zika virus is mostly transmitted to individuals through bites from infected *Aedes aegypti* mosquitoes. The mosquito becomes infected when it feeds on a person already infected with the virus; it cannot be caught from merely coming into contact with the infected person (PHE, 2016). In addition to vector-based transmission via mosquitoes, other routes of transmission have been reported and studied. In other words, while the vast majority of Zika virus infections in humans are transmitted through mosquito vectors, other modes of transmission such as sexual transmission, transplacental and prenatal transmission, blood transfusion, and laboratory acquired infections have been documented (Marrs, et al., 2016). These and other route of transmission will be subsequently examined in greater depth.

Non-vector-borne transmission

Zika virus was always believed to be transmitted to humans only through the bites of *Aedes* mosquitoes, until about a decade ago (Basuand_Tumban, 2016). The last few years, there has been increasing numbers of documented confirmed cases of Zika virus infection resulting from non-mosquito-borne transmission. One of the first reports of sexual transmission Zika virus occurred in 2008 when an American man who is a resident of Colorado; a researcher who returned from Senegal and had sexual contact with his wife. He developed Zika symptoms, and so did his wife. Their Zika virus status was confirmed by serologic tests in the man and his wife (Foy, et. al, 2011). Although the man's wife tested positive for Zika virus, no effort was made at the time to check if the virus was in the husband's semen, which would be evidence of sexual transmission of Zika virus (Lowes, 2016).

As of February 2016, the Centers for Disease Control (CDC) recorded 14 suspected cases of sexual transmission of Zika virus in the United States, out of which 3 had laboratory confirmation. In the United Kingdom, Zika virus was isolated by RT-PCR in the semen sample of a 68-year-old man 62 days after having had acute Zika virus infection (Antunes de Britoand Cordeiro, 2016). A recent report by the Lancet Medical Journal shows that researchers in France found that viral loads were 100,000 times greater in the semen than in blood or urine two weeks after the onset of the symptoms (Mansuy, et al., 2016). Several studies cited by Barzon, et al., (2016) described cases of sexual transmission of Zika virus infection that are associated with viral shedding in semen and vaginal fluids. These include Zika virus that was recovered in semen up to 24 days after symptom onset; viral RNA has been detected for over six months after onset and cases of sexual transmission occurring weeks after the index case have been described. The CDC and the UK government recommended in the light of the over whelming evidence of sexual related Zika virus transmission that partners returning from countries where Zika virus are active to abstain from sex or use condoms for at least 8 weeks if they had no symptoms of Zika infection or for 6 months if they had clinical features or confirmation of Zika virus infection. These recommendations were extended for the duration of pregnancy for those with pregnant partners (Antunes de Britoand Cordeiro, 2016).

Blood transfusion and organ transplantation are also potential risks for non-vector-borne Zika virus transmission (ECDC, 2016). Reuter (2016) reported two cases of Zika virus transmission by blood

transfusion during the Zika virus outbreak in Brazil. Before Reuter's (2016) report, one study found that during the Zika virus outbreak in French Polynesia between 2013 and 2014, 1,505 blood samples were taken from blood donors and analysed. Zika virus was detected by RT-PCR in 42 samples, amounting to 3 per cent of the total samples. Eleven patients, amounting 26 percent of the total sample were found to have developed symptoms of Zika virus infection between three and ten days after donating blood. This finding has implication for public health given the fact that a majority of Zika virus infected patients do not show symptoms. The 3 per cent of the blood donors in French Polynesia who tested positive for Zika virus were asymptomatic (Musso, 2014). This is compounded by the fact that Zika virus can thrive in the body of an infected person for up to 2 months. This makes it very easy for the Zika virus to spread through blood transfusion, that is, transmission from blood donors to blood recipients (Musso, 2014, Basuand Tumban, 2016).

Materno foetal transmission can occur most probably by trans-placental transmission and during delivery when the mother is infected by Zika virus (ECDC, 2016). A recent review of several studies on Zika virus pathogenesis established that transplacental transmission of Zika virus in human has been extensively reported in cases of foetal microcephaly by detection of the virus in the amniotic fluid; in foetal and placental tissues (Barzon, et al., 2016). Another recent study published in the medical Journal Lancet found Zika virus genome in the amniotic fluid of two pregnant women, which was not detected in their urine or serum. The researchers argued that this finding strengthens the putative association between Zika virus and cases of microcephaly in neonates. They added that their results suggest that the Zika virus can cross the placental barrier and as such should be considered as a potentially infectious agent for human foetuses (Calvet, et al. 2016).

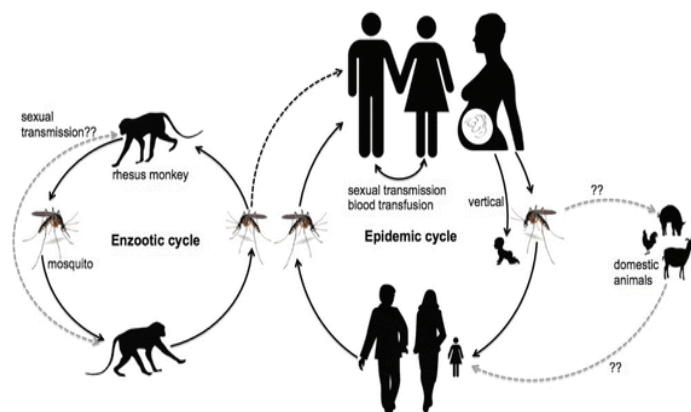
An additional mode of Non-vector-borne transmission of Zika virus has been identified by one study. The study found that prenatal transmission of Zika virus was reported during the outbreak in French Polynesia in 2013 from two mothers who acquired the infection a few days before delivery. Zika virus RNA was detected in their breast milk, while no infectious virus was isolated in cell culture, making this an unlikely route of transmission (Besnard et al. 2014). This probably explains why Barzon, et al., (2016) citing Centers for Disease Control and Prevention (CDC) reported that mothers were encouraged to continue to breastfeed their babies even in areas of endemic activity of the Zika virus. Breastfeeding is encouraged because of its numerous health benefits to the baby.

Zika virus transmission cycles

WHO (2016) stated that the ability of the *Aedes* mosquito to transmit Zika virus is based on the combination of its competence and capacity. A vector competence is vector's biological capability to transmit a virus. A vector capacity, on the other hand, is the efficiency with which the vector transmits a disease, which is based on its preferred host, the number of bites (feedings) per cycle of egg production, its longevity, the density of the mosquito population and other factors. The vector competence of *Aedes aegypti* and *Aedes albopictus* is similar. *Aedes albopictus* is considered to have lower vector capacity than *Aedes aegypti* for transmitting arboviruses (viruses transmitted by insects), including Zika virus (WHO, 2016).

As noted earlier, Zika virus is transmitted to humans by mosquitoes, especially the *Aedes aegypti* species. The virus is transmitted to an individual mostly through bites from an infected *Aedes aegypti* mosquito. The mosquito becomes infected when it feed on a person already infected with the virus and cannot be caught from coming into contact with the infected person. In other words, *Aedes aegypti* mosquitoes are conceivably the main vector for Zika virus natural transmission. However, as illustrated in figure 1.3, there are also non-vector Zika virus transmission modes. The figure is an adaptation of illustrated summary of both the vector and non-vector modes of Zika virus transmission from a study published in Virology Journal by Basuand Tumban (2016):

Figure 1.3: Vector and non-vector modes of Zika virus transmission



Source: Basu, R. and Tumban, E. (2016) Zika Virus on a Spreading Spree: what we now know that was unknown in the 1950's, *Virology Journal* 13:165

Basu and Tumban (2016) stated that Zika virus is transmitted in sylvatic habitats in an enzootic cycle by infected mosquitoes to rhesus monkeys and vice versa. Human beings can be infected with the Zika virus in sylvatic habitats following a mosquito bite or if there is a spill over of an infected mosquito from sylvatic habitats as illustrated in the middle dotted black line in the figure 1.3. Basu and Tumban (2016) further explained that an epidemic cycle starts when humans are bitten by an infected mosquito followed by viral replication in humans and viremia. The Zika virus can spread to the reproductive organs and can be transmitted during sexual intercourse. Pregnant women who are infected with the Zika virus can also transmit the virus to their unborn child or the fetus during pregnancy. The Zika virus can then be transmitted from an infected person back to mosquitoes through subsequent mosquito bites. The cycle continues when the Zika virus is replicated in the mosquitoes and transmitted back to humans. However, there is no documented evidence to show that the Zika virus can be transmitted by mosquitoes between domestic animals and humans as illustrated by the right dotted gray lines with question mark in figure 1.3 or whether the virus can be transmitted sexually between monkeys as represented by the left dotted gray line with question mark also in the figure (Basu and Tumban, 2016).

In summary, this chapter has shown that Zika virus is primarily a vector-borne disease and is transmitted mainly by *Aedes aegypti*. The chapter also discussed non-vector or secondary modes of transmission such as mother-to-child, during sexual intercourse, blood transfusion, and organ transplantation. The health risks and global distribution of Zika virus represents a real challenge to world public health as well as the scientific community (Rodriguez-Morales and Villamil-Gomez, 2016). The current spread of Zika virus in Caribbean Islands and the American countries constitutes a significant development in the epidemiology of this emerging vector-borne disease. There is now a well-established evidence of an association between travels and the acquisition or transmission of infectious diseases (Musso, et al, 2015). For example, a review carried out by Ihekweazu (2016) found 31 reported cases of travel-associated Zika virus in 11 states in the United States of America and the District of Columbia and 5 cases of travelers diagnosed with the Zika virus in the United Kingdom. Also, Westcott, (2016) reporting for Newsweek stated that many people in the U.S state of Florida,

Illinois, New Jersey, Texas, Arkansas and other several other states who recently traveled to countries where Zika virus is present have tested positive for the virus. There is now enough compelling evidence, as will be read in chapter 2 of this book, to suggest that Zika virus spread from Africa to these countries through travel (Icheke, 2016). Thus it is imperative that Zika virus prevention and control should consider all the above modes of transmission, providing strategies to checkmate the spread of the disease and carry out further epidemiological and clinical assessment to provide a better understanding of the virus and its real impact on human health (Rodriguez-Morales et al. 2016).

Chapter 2

Epidemiology: Geographical distribution of Zika virus

In this chapter, the incidence and geographical distribution of Zika virus are discussed. The Zika virus was first isolated in 1947 from a febrile sentinel rhesus monkey in the Zika forest in Uganda, where it got its name. The forest at the time was the hub of scientific research in East Africa and, while carrying out tests on wild African monkeys in the Zika forest, scientists, whose research had been funded by the Rockefeller Foundation, unexpectedly discovered a previously unknown microorganism, which they later named Zika (Byaruhanga, 2016).

One study shows that over the next six decades, the virus spread slowly to other parts of Africa, and eventually appeared in Southeast Asia, transmitted by *Aedes aegypti* and other *Aedes* mosquito species (Imperato, 2016). The prevalence of Zika virus infection in Uganda where the disease originated was 6.1 per cent in 1952 among a population of 99 residents and 7.1 per cent in Java, Indonesia, from 1977-1978 among patients who were hospitalized for fever (Bhagyashri, 2016). The study added that only 14 cases of illness associated with the Zika virus were reported before 1981. The study argued that the current globalization of the Zika virus epidemic started on the Pacific island of Yap in the Federated States of Polynesia in 2007 (Imperato, 2016). Similarly, another study reported that there were sporadic cases of Zika virus infections that were reported in several entomological and Serological surveys in 14 countries across Africa, Asia, and Oceania before 2007 (Ioos, et al., 2014).

According to Imperato (2016), the Zika virus epidemic that started on the Pacific island of Yap was the first known presence of the Zika virus case outside of Africa and Southeast Asia. The outbreak infected an estimated 73 per cent of the island's population. The virus spread to French Polynesia, New Caledonia, Cook Islands, and Easter Islands between 2013 and 2014. An estimated 28,000 cases were reported in a population of 270,000 inhabitants. In the same period microcephaly and other congenital abnormalities were observed in the infants of women who were pregnant when they contracted the virus. However, it was not known if cases of the microcephaly resulted from Zika virus infection amongst pregnant women or infection plus some other co-factor (Imperato, 2016, Bhagyashri, 2016).

In May 2015, Brazil reported a major and the first outbreak of Zika virus infection in the Americas. The Brazil Ministry of Health reported nearly 7000 cases of illness with skin rash between February 2015 and 29 April 2015 (Kindhauser, et al., 2016). In December 2015, the Brazil Ministry of Health reported between 440,000 and 1,300,000 suspected cases of Zika virus infection, which was attributable to *Aedes aegypti* and *Aedes albopictus* as the vectors for the transmission of the disease (Bhagyashri, 2016). Subsequently, Bahia State Laboratory in Brazil notified WHO that samples taken from some of the patients have tested positive for Zika virus. The Brazilian Authority stressed that the result is not conclusive until full laboratory test is carried out. It was not until 7 May 2015 that Brazil's National Reference Laboratory confirmed, by Polymerase Chain Reaction (PCR) test, that

there is Zika virus circulation in the country. PCR is used to reproduce (amplify) selected sections of DNA or RNA for analysis and reasonable to conclude that the confirmation by PCR is the first report of locally acquired Zika disease in the Americas (WHO, 2016).

The outbreak demonstrated a high attack rate with thousands of people affected culminated in more than 1 million cases as well as 4,000 suspected cases of microcephaly, with 270 confirmed cases that health officials believe are linked to the Zika virus. The Brazil Ministry of Health has since reported a remarkable increase in the number of babies born with microcephaly. However, it was not conclusive how the microcephaly cases are linked with Zika virus infection and what factors increase risk of the disease to the foetus (WHO, 2016). Thus, it was not surprising that both WHO (2016) and CDC (2016) reported that the outbreak of the disease in May 2015 was unprecedented. This may have prompted the Pan American Health Organization (PAHO) and WHO to issue an epidemiological alert on Zika virus infection (PAHO, 2015, Kindhauser, et al., 2016).

A decision was reached at the first meeting of the Emergency Committee (EC) convened by the Director-General under the International Health Regulations (2005) (IHR 2005). The Committee advised that the recent cluster of microcephaly cases and other neurological disorders reported in Brazil and French Polynesia in 2014 constitutes a Public Health Emergency of International Concern (PHEIC) (WHO, 2016, Imperato, 2016). The Committee provided the following advice to the Director-General for her consideration:

- Surveillance for microcephaly and GBS should be standardized and enhanced, particularly in areas of known Zika virus transmission and areas at risk of such transmission.
- Research into the aetiology of new clusters of microcephaly and other neurological disorders should be intensified to determine whether there is a causative link to Zika virus and other factors or co-factors.
- As these clusters have occurred in areas newly infected with Zika virus, and in keeping with good public health practice and the absence of another explanation for these clusters, the Committee highlights the importance of aggressive measures to reduce infection with Zika virus, particularly among pregnant women and women of childbearing age (WHO, 2016).

The Emergency Committee also made the following additional recommendations as a precautionary measure:

- Zika virus transmission
- Surveillance for Zika virus infection should be enhanced, with the dissemination of standard case definitions and diagnostics to at-risk areas.
- The development of new diagnostics for Zika virus infection should be prioritized to facilitate surveillance and control measures.
- Risk communications should be enhanced in countries with Zika virus transmission to address population concerns, enhance community engagement, improve reporting, and ensure application of vector control and personal protective measures.
- Vector control measures and appropriate personal protective measures should be aggressively promoted and implemented to reduce the risk of exposure to Zika virus.
- Attention should be given to ensuring women of childbearing age and particularly pregnant women have the necessary information and materials to reduce risk of exposure.
- Pregnant women who have been exposed to Zika virus should be counselled and followed for birth outcomes based on the best available information and national practice and policies.
- Longer-term measures
- Appropriate research and development efforts should be intensified for Zika virus vaccines, therapeutics, and diagnostics.

- In areas of known Zika virus transmission health services should be prepared for potential increases in neurological syndromes and congenital malformations.
- There should be no restrictions on travel or trade with countries, areas, and territories with Zika virus transmission.
- Travelers to areas with Zika virus transmission should be provided with up to date advice on potential risks and appropriate measures to reduce the possibility of exposure to mosquito bites.
- Standard WHO recommendations regarding disinfection of aircraft and airports should be implemented.
- National authorities should ensure the rapid and timely reporting and sharing of information of public health importance relevant to this PHEIC.
- Clinical, virologic and epidemiologic data related to the increased rates of microcephaly and/or Guillain-Barré syndrome, and Zika virus transmission, should be rapidly shared with WHO to facilitate international understanding of these events, to guide international support for control efforts, and to prioritize further research and product development(WHO, 2016).

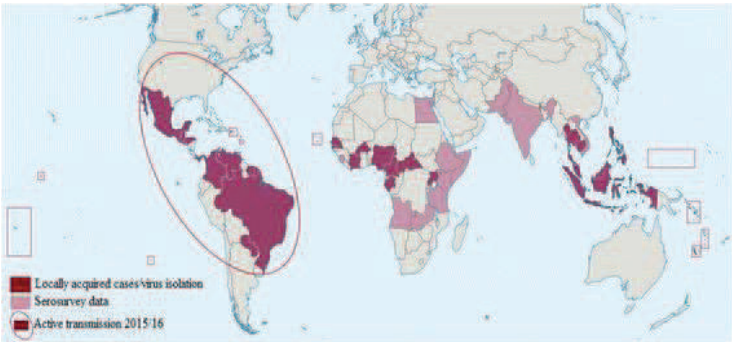
Adoption of this long list of recommendations in this chapter is imperative as most of it will inform public health interventions that will be recommended in the later chapters of this book. It is also important to stress at this juncture that the Declaration of Public Health Emergency of International Concern (PHEIC) on 1 February 2016 by the WHO Director-General has based the above committee's recommendations (WHO, 2016).

The declaration in March 2016 by the World Health Organisation that Zika virus was actively circulating in 38 countries and territories has global public health implications. For example, of the 38 countries and territories, 12 were reported to have increased cases of Guillain-Barré syndrome or laboratory evidence of Zika virus among patients identified as having Guillain-Barré syndrome (WHO, 2016). Guillain-Barré syndrome was described in a fact sheet published by USA National Institutes of Health (NIH) as a disorder that allows the body's immune system to attack part of the peripheral nervous system (NIH, 2017). In the United States alone, a total of 591 laboratory-confirmed travel-associated cases of Zika virus infections were reported as of June 2016. None of these cases were acquired through local vector-borne transmission (WHO, 2016, CDC, 2016). However, 11 cases out of the 591 confirmed travel-related cases had been transmitted through Sexual transmission and out of the 11 cases that were reported only one of the cases was attributed to Guillain-Barré syndrome (CDC, 2016, Bhagyashri, 2016). As of 20 July 2016, there were 62 countries and territories with reported cases of mosquito-borne transmission. There was a consensus among scientists that Zika virus is the main cause of microcephaly and Guillain-Barré syndrome (ECDC, 2016).

However, it is important to stress at this juncture that there had been few published studies on Zika virus before 2014 because cases of the disease occurred sporadically and followed by oligosymptomatic clinical presentation (Cordeiro and de Brito 2016). Dr. Bhagyashri, in his article published in Medscape, argued that the global prevalence of Zika virus infection has not been widely reported due to difficulty in confirming diagnosis asymptomatic nature of the disease and clinical resemblance to other infection with other flaviviruses such as dengue, chikungunya (Bhagyashri, 2016). The paucity of published studies notwithstanding, Zika virus infection, had been reported in various hosts, including humans, primates, and mosquitoes in 14 countries across Africa, Asia, and Oceania, as of 2014 (Ioos, et al., 2014). As noted earlier, the virus has since spread outside of Africa, the continent where it was first isolated in the Zika Forest of Uganda. As reported earlier, the virus was discovered by chance in a rhesus monkey that had been placed in a cage on a sentinel platform in the forest by the Virus Research Institute in 1947. According to Catherine Byaruhanga (2016), a BBC African reporter, Zika virus was discovered in the forest by Ugandan, American and European

scientists. The forest was then the hub of scientific research in East Africa and while testing monkeys in the forest the scientists, whose research had been funded by the Rockefeller Foundation, accidentally came across a new microorganism, which they later named Zika (Byaruhanga, 2016).

Figure 2.4: Current regions of known Zika virus endemic



Source: Gyawali, et al., (2016).The global spread of Zika virus: Is public and media concern justified in regions currently unaffected?

Figure 2.4 provides a chronological map of the presence of Zika only in those countries for which there is evidence of autochthonous or indigenous transmission by mosquitoes, excluding the many countries that have notified imported Zika infections.

Table2.3: Early reported cases of Zika virus infection

Year	Countries/Territories/areas	Reported cases
1947	Uganda's Zika Forest	Scientists researching yellow fever in Uganda's Zika Forest identify the virus in a rhesus monkey
1952	Uganda and Tanzania	First human cases detected in Uganda and Tanzania
1954	Nigeria	The first virus found in Nigeria
1960s-80s	Equatorial Africa	Zika detected in mosquitoes and monkeys across equatorial Africa
1969–83	Asia: India, Indonesia, Malaysia and Pakistan	Zika found in equatorial Asia, including India, Indonesia, Malaysia and Pakistan
2007	Senegal and Pacific island of Yap	First large outbreak on Pacific island of Yap and Senegal
2008	Colorado, USA	A US scientist conducting field work in Senegal falls ill with Zika infections upon his return home to Colorado.
2012	African and Asian	Researchers identify two distinct lineages of the virus, African and Asian
2013–14	French Polynesia: Easter Island,	Zika outbreaks in French Polynesia. Retrospective

	The Cook Islands and New Caledonia.	analysis shows a possible link to birth defects and severe neurological complications in babies.
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Adapted from: Kindhauser, et al. (2016), Bulletin of the World Health; WHO (2016) Zika virus situation reports and U.S. Centers for Disease Control and Prevention, also cited in Reuters (2016)

The above table 2.4 illustrates Zika virus timeline from its discovery 1947 to May 2014, to which detailed information is available. The table shows that the rise in cases of microcephaly did not necessary followed the rise in the spread of the virus in human. It also shows that Zika virus strains have a wide geographical distribution. As noted in chapter 1, human cases of the Zika virus have been sporadically reported in Asia and Africa, since the 1960s. The first large documented outbreak occurred in 2007 in Yap Island, Micronesia, in the North Pacific. Marta Zaraska (2015) reporting for Washington post, Health and Sciences estimated that three-quarters out of 11,000 or so residents of the Yap Island older than three years, were infected by the Zika virus. The Island's residents that were infected showed common symptoms, which resolved within few days and none of the residents died and until 2007 when scientists knew only fourteen human cases of the disease (Icheku, 2016). It is also noted in the chapter that in 2008, the virus showed up Colorado, USA when US scientist conducting field work in Senegal fell ill with Zika infection upon his return home to Colorado and infected his wife in what is probably the first documented case of sexual transmission of Zika virus (Foy, 2011). In 2012, researchers published their findings on the characterisation of Zika virus strains collected from many countries including Cambodia, Malaysia, Nigeria, Senegal, Thailand, and Uganda. They constructed phylogenetic trees to assess the relationships and found two geographically distinct lineages of the virus, African and Asian (Haddow, et al. 2012, Kindhauser, et al., 2016).

Furthermore, Table 2.4 also shows that there were Zika virus outbreaks in 2013-2014, which affected four groups of Pacific Islands: French Polynesia, Easter Island, the Cook Islands, and New Caledonia. The virus first showed up in Tahiti and other parts of French Polynesia 2013; infecting an estimated 28,000 people, equals to about 11 per cent of the population of the islands. By 2014, the virus showed up in several South Pacific islands such as New Caledonia, east of Australia and the Cook Islands. The disease popped up in the Easter Island, and as the island is part of Chile, the arrival marks the first confirmed cases of the disease in the Americas (Icheku, 2016). One study shows that an increase in the incidence of Zika virus infection in the Islands was followed by an increase in the incidence of Guillain-Barré syndrome. However, this was a suggestive view given that the Islands were also experiencing an outbreak of dengue, a disease that is associated with Zika infection and Guillain-Barré syndrome (Oehler, et al., 2014). This does preclude or challenge the notion that Zika virus infection causes of mild illness (Kindhauser, et al., 2016).

Table 2.4 shows that the first scientific proof of human cases of Zika virus was in 1954 when the virus was isolated from a young girl in Eastern Nigeria and in 1964 when a researcher in Uganda fell ill while working with Zika strains isolated from mosquitoes. The researcher suffered from a pink non-itchy rash that covered most of his body, including the palms of his hands (see figure 1.2) and soles of his feet. He noted that the clinical picture of the infection was that of a mild febrile illness, which lasted for five days duration (Bushak, 2016). It is interesting to note, however, that in Uganda where the virus was first discovered only one human case was confirmed in 1952. Icheku and Icheku, (2016) argued that human cases may have been documented much earlier if not for the lack of testing facilities for Zika virus especially in the rural areas with poor or lack of health facilities. For example, the Uganda Virus Research Institute happens to be the only place in the whole country

where Zika blood test can be carried out. The Institute is owned by the Uganda government and carries out research on communicable diseases in human and animal, with emphasis on transmitted viral infections. It has its base in Entebbe and out of reach of many rural communities (Byaruhanga, 2016).

It is important to note at this juncture that the evidence of Zika virus origin discussed in chapter 1 above, showed that the virus is transmitted mainly by *Aedes* mosquitoes that were first discovered in Zika Forest of East Uganda in 1947 (Kindhauser, et al., 2016). One study alerted the world to the presence of other Zika virus strain found in other species of mosquitoes that are indigenous to Africa. For example, in 1968 Zika virus strain was isolation from *Aedes-Leptocephalus* found in Saboya forest, 187 km from Dakar, in the western part of Senegal. The study added that in the following year (1969), Zika virus was further isolated from *Aedes-Luteocephalus*, *Aedes-furcifer-taylori* and An-Gambia. In the same year, the virus was also isolated from a human being living in Bandia located 65 km from Dakar. Furthermore, between 1972 and 2011, 381 Zika virus isolates were collected as part of an entomological surveillance program, mainly from *Aedes-Africanus*, *Aedes-Luteocephalus*, *Aedes-furcifer* and *Aedes-Taylori*. In the same period, Zika virus isolates were also collected seven times from humans and twice from nonhuman primates (NHPs) such as *Cercopithecus aethiops* and *Erythrocebus patas* (Diagne, et al. 2015). As shown in Table 2.3, researchers identify two distinct lineages of the virus, African and Asian (WHO cited in Reuters, 2016). Vorou (2016) agreed with the distinction and claimed Zika virus was first isolated from *Aedes africanus* mosquitoes collected in Zika Forest but outside Africa, *Aedes aegypti* is the principal vector. Table 2.4 illustrates mosquitoes in which Zika virus has been detected.

Table 2.4: Mosquitoes in which Zika virus has been detected

Year of sampling	Location	Mosquito genus and species	Study/assay
Africa			
1947	Zika Forest, Uganda	<i>Aedes africanus</i>	Mosquito catches in Zika Forest, and first isolation of ZIKV from <i>Aedes africanus</i> pooled specimens
1958	Zika Forest, Uganda	<i>Aedes africanus</i>	Virus isolation
1964	Zika Forest, Uganda	<i>Aedes africanus</i>	Virus isolation
1969	Uganda, Bwamba County, Zika Forest	<i>Aedes africanus</i> , <i>Aedes apicorgenteus</i>	Virus isolation from pooled specimens of mosquitoes trapped in Zika Forest
1976–1980	Central African Republic	<i>Aedes africanus</i> , <i>Aedes opok</i>	Retrospective entomological study with RT-PCR and sequencing
1968–2002	West Africa: Côte d'Ivoire, Senegal, Burkina Faso, Central Africa	<i>Aedes dalzieli</i> , <i>Aedes africanus</i> , <i>Aedes aegypti</i> , <i>Aedes furcifer</i> , <i>Aedes grahamii</i> , <i>Aedes luteocephalus</i> , <i>Aedes vittatus</i> , <i>Aedes opock</i>	Retrospective study; phylogenetic analysis, reverse transcription PCR, nucleotide

	Republic		sequencing; numerous recombination events were detected
1962–2008	Senegal	<i>Aedes aegypti</i> , <i>Aedes dalzieli</i> , <i>Aedes fowleri</i> , <i>Aedes furcifer</i> (known as <i>Aedes taylori</i>), <i>Aedes luteocephalus</i> , <i>Aedes vittatus</i> , <i>Aedes neoafricanus</i> , <i>Aedes metallicus</i> , <i>Aedes minutus</i> , <i>Anopheles africanus</i> , <i>Anopheles coustani</i> , <i>Anopheles coustani</i> , <i>Anopheles gambiae</i> s.l., <i>Mansonia uniformis</i> (the higher number of ZIKV isolation events was detected in <i>Aedes furcifer</i> (known as <i>Aedes taylori</i>), <i>Aedes luteocephalus</i> , and <i>Aedes dalzieli</i>)	Virus isolation in the mosquito cell line AP61 (<i>Aedes pseudoscutellaris</i>) Identification of isolates by immunofluorescence with virus-specific immune ascitic fluid; this was confirmed by complement fixation or neutralization tests
2011	Southeastern Senegal	<i>Aedes africanus</i> , <i>Aedes hirsutus</i> , <i>Aedes metallicus</i> , <i>Aedes unilineatus</i> , and <i>Culex perfuscus</i> had the highest infection rates compared to <i>Aedes (Diceromyia) furcifer</i> , <i>Aedes (Fredwardsius) vittatus</i> , <i>Aedes taylori</i> , <i>Aedes luteocephalus</i> , <i>Aedes dalzieli</i> , <i>Aedes aegypti</i> , <i>Mansonia uniformis</i> , and <i>Anopheles coustani</i> , with the lower infection rates	Virus isolation, RT-PCR
2007	Gabon	<i>Aedes albopictus</i>	Retrospective sero-epidemiological and entomological study in 2014; RT-PCR and sequencing of pooled specimens
Asia			
1969	Malaysia	<i>Aedes aegypti</i>	Virus isolation
NA; experiment in 2012	Singapore	(Local in Singapore) <i>Aedes aegypti</i>	Inoculation of Ugandan ZIKV in (local in Singapore) <i>Aedes aegypti</i> and subsequent mosquito-borne transmission of the virus
NA; experiment in 2014	Yap Island, Federated States of Micronesia; human	Field collected <i>Aedes henselli</i> and <i>Culex quinquefasciatus</i> tested negative for Zika virus; <i>Aedes henselli</i> laboratory infection	Experiment; laboratory infection of <i>Aedes henselli</i>

	outbreak in 2007		
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Source: Vorou, R. (2016), Zika virus, vectors, reservoirs, amplifying hosts, and their potential to spread worldwide: what we know and what we should investigate urgently, Int J Infect Dis. 2016; Volume 48, Pages 85-90, [http://www.ijidonline.com/article/S1201-9712\(16\)31057-8/fulltext](http://www.ijidonline.com/article/S1201-9712(16)31057-8/fulltext)

As Vorou (2016) illustrated in Table 2.4, Zika virus was isolated from different species of mosquitoes collected in different parts of Africa between 1947 and 2011. The table shows that in *Aedes aegypti* is predominant in Asia between 1969 and 2014. *Aedes henselli*, which is also shown on the table, is described as experiment or laboratory infection (Vorou, 2016). Finally, the awareness of mosquitoes in which Zika virus has been detected is critical to the understanding of the distinction between Zika viruses in Africa and those in Asia. It is also a public health imperative to describe species of-of mosquitoes associated with Zika virus transmission as the description gives insight into the geographic distribution of Zika virus along with the indicated global timing and scale of public health interventions that will be discussed in subsequent sections.

Table 2.5: Timeline of first reported cases and geographical distribution of Zika virus in 2015

Timeline of first reported cases of Zika virus in Countries and Territories	
2 March:	Brazil notifies WHO of reports of an illness characterized by skin rash in north-eastern states.
7 May:	Brazil's National Reference Laboratory confirms, by PCR, Zika virus circulation in the country. This is the first report of locally acquired Zika disease in the Americas.
16 October:	Colombia reports PCR-confirmed cases of locally acquired Zika infection.
21 October:	Cape Verde confirms, by PCR, the country's first outbreak of Zika infection.
2 November:	Suriname reports two PCR-confirmed cases of locally acquired Zika infection.
11 November:	Brazil declares a national public health emergency as cases of suspected microcephaly continue to increase.
12 November:	Panama reports cases with symptoms compatible with Zika.
24 November:	El Salvador reports its first 3 PCR-confirmed cases of locally acquired Zika infection.
25 November:	Mexico reports three PCR-confirmed cases of Zika infection, of which two were locally acquired. The third case had a travel history to Colombia.
26 November:	Guatemala reports its first PCR confirmed case of locally acquired Zika infection
27 November:	Paraguay reports six PCR-confirmed cases of locally acquired Zika infection.
27 November:	The Bolivarian Republic of Venezuela reports seven suspected cases of locally acquired Zika infection. Four samples test positive by PCR
2 December:	Panama reports its first 3 PCR-confirmed cases of locally acquired Zika infection.
16 December:	Honduras reports two PCR-confirmed cases of locally acquired Zika infection.
21 December:	French Guiana and Martinique report their first two PCR-confirmed cases of locally acquired Zika infection.
31 December:	The United States reports the first PCR confirmed case of locally acquired Zika infection in the Commonwealth of Puerto Rico, an unincorporated territory of the United States.

Source: Kindhauser, et al. (2016), Bulletin of the World Health and U.S. Centers for Disease Control and Prevention cited in Reuters (2016)

An unusual increase in the number of central nervous system malformations in foetuses and infants from March 2014 to May 2015 in French Polynesia alerted the world to the public health risks posed by the Zika virus. In Brazil Zika virus genome was detected in the blood and tissue samples of a baby with microcephaly and other congenital anomalies that died within 5 minutes of birth. Brazilian researchers publish evidence, drawn from case reports in several countries, that depiction of Zika as "a mild cousin of dengue" may not be accurate due to the possibility of more serious disease symptoms, especially in immune compromised patients (Marcondes and Ximenes, 2015). Figure 2.4 and Table 2.5 have been used to show that Zika virus has been steadily on the increase. The geographical spread of Zika virus includes Colombia and Cape Verde, both countries reported PCR-confirmed cases of locally acquired Zika infection in October; Suriname, Panama, El Salvador, Mexico, Guatemala, Paraguay and Bolivarian Republic of Venezuela reported PCR-confirmed cases of locally acquired Zika in November, 2015 (Reuters, 2016). These unusual increases in the number of new cases in 2015 and uncertainty of accurate detection of the virus prompted the Pan American Health Organization and WHO to issue an alert to the association of Zika virus infection with the neurological syndrome and congenital malformations in the Americas. The alert includes guidelines for laboratory detection of the virus (PAHO, 2015). The timeline of first reported cases and geographical distribution of Zika virus illustrated in Table 2.6 shows that the virus continued to spread into many more countries in the Americas beyond 2015.

Table 2.6: Timeline of first reported cases and geographical distribution of Zika virus in 2016

Timeline of first reported cases of Zika virus in Countries and Territories	
January 14:	Guyana reports its first PCR confirmed case of locally acquired Zika infection.
January 15:	Ecuador reports its first two PCR-confirmed cases of locally acquired Zika infection. The next day, the country confirms an additional 6 cases, of which two are locally acquired, three imported from Columbia, and one from the Bolivarian Republic of Venezuela.
January 15:	Barbados reports its first three PCR-confirmed cases of locally acquired Zika infection.
January 15:	The Hawaii Department of Health (USA) reports a case of microcephaly in Hawaii, born to a woman who had resided in Brazil early in her pregnancy.
January 16:	The Plurinational State of Bolivia reports its first PCR confirmed case of locally acquired Zika infection.
January 18:	Haiti reports its first five PCR-confirmed cases of locally acquired Zika.
January 18:	France reports the first PCR confirmed case of locally acquired Zika in Saint Martin.
January 23:	The Dominican Republic reports its first 10 PCR-confirmed cases of Zika infection, of which eight were locally acquired, and two were imported from El Salvador.
January 25:	The United States reports the first PCR confirmed case of locally acquired Zika infection in St Croix, one of the three main islands in the United States Virgin Islands.
January 27:	Nicaragua reports its first two PCR-confirmed cases of locally acquired Zika infection.
January 28:	Curacao reports its first PCR confirmed case of locally acquired Zika.
January 29:	Suriname reports 1,107 suspected cases of Zika, of which 308 are confirmed, by PCR, for Zika virus.
January 30:	Jamaica reports its first PCR confirmed case of locally acquired Zika.
February 1:	WHO declares that the recent association of Zika infection with clusters of

	microcephaly and other neurological disorders constitutes a Public Health Emergency of International Concern.
February 1:	Cape Verde reports 7081 suspected cases of Zika between end September 2015 and 17 January 2016.
February2:	The first case of Zika transmission in the United States; local health officials say likely contracted through sex, not mosquito bite
February5:	U.S. Centers for Disease Control and Prevention says virus being actively transmitted in 30 countries, mostly in the Americas
February18:	CDC adds Aruba and Bonaire bringing total to 32
February23:	CDC adds Trinidad and Tobago and Marshall Islands bringing total to 34
February27:	France detects first sexually transmitted case of Zika
March 19:	CDC adds Cuba bringing total to 38
March 22:	CDC adds Dominica bringing total to 39
April 1:	CDC adds Kosrae, Federated States of Micronesia bringing total to 40
April 4:	CDC adds Fiji bringing total to 41
April 13:	CDC adds St. Lucia bringing total to 42
April 18:	CDC adds Belize bringing total to 43
April 25:	Canada confirms first sexually transmitted Zika case
April 29:	Puerto Rico reports first death related to Zika, according to the CDC.
May 4:	Panama confirms four microcephaly cases tied to Zika
May 6:	Spain has the first case of Zika-related brain defect in a fetus
May 9:	CDC adds Papua New Guinea, Saint Barthelemy and Peru bringing total to 46
May 12:	CDC adds Grenada bringing total to 47
May 26:	CDC adds Argentina bringing total to 48 WHO confirmed cases of Zika virus in the African island chain of Cape Verde
June 30:	CDC adds Anguilla bringing total to 49
July 14:	CDC adds Saint Eustatius bringing total to 50
July 26:	CDC adds Saba bringing total to 51
July 27:	Paraguay reports first cases of microcephaly linked to Zika
Aug. 2:	CDC adds Antigua, Barbuda, and Turks and Caicos bringing total to 54
Aug. 11:	CDC adds the Cayman Islands bringing total to 55
Aug. 25:	CDC adds The Bahamas and the United States bringing total to 57
Aug. 26:	Nicaragua confirms first microcephaly birth linked to Zika
Aug. 31:	CDC adds Singapore and the British Virgin Islands bringing tally to 58 (The CDC groups together Antigua and Barbuda in its updated official count)
Sept. 3:	Malaysia detects the first case of locally transmitted Zika
Sept. 5:	The Philippines confirms the first case of Zika virus likely to have been transmitted locally
Sept. 13:	Thailand said it had recorded 200 cases of Zika since January, 2016
Sept. 26:	CDC adds St. Kitts and Nevis bringing tally to 59
Oct. 27:	Myanmar confirms fist case of Zika virus infection
Nov. 16:	CDC adds Singapore and Palau bringing tally to 61
Nov. 21:	CDC adds Montserrat pushing total to 62
Dec. 15:	France reported symptoms compatible with Zika virus infection from a traveler returning from Angola.
Dec. 29	Saint Martin reporting Guillain-Barré syndrome (GBS) cases associated with Zika virus infection for the first time in the past week

Source: WHO (2016) Zika virus situation reports and U.S. Centers for Disease Control and Prevention cited in Reuters (2016)

The above timeline charts shows that in 2016 the global prevalence of Zika virus infection has been widely reported in 62 countries and territories in Americas and other parts of the world. The situation is clearer with the use of the map as shown in figure 2.5 below. The map allows for lengthier information to be described in picture and more memorable because the information is in coloured and in shape. The map helps to present spatial relationships in a way that is more striking; given that it shows the intensity of the Zika virus transmission. It draws attention to spatial relationships, for example, the distribution of Zika virus in the United States of America and its territories.

Figure 2.5:
Laboratory confirmed Zika virus disease cases reported to ArboNET by state or territory as of March 22, 2017.

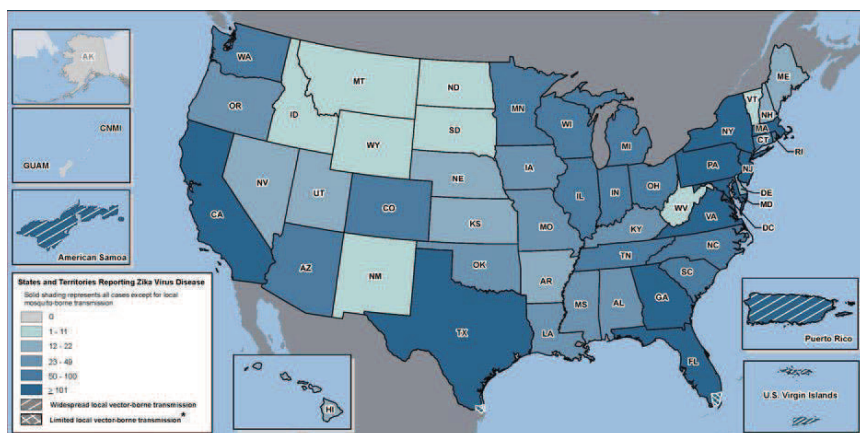


Figure 2.5 shows the magnitude of Zika virus distribution is now a nationally notifiable condition in the United States of America and its territories. For example, as of March 30, 2017 the Centers for Disease Control and Prevention Zika virus Case Counts in the US shows that of the 5,182 total Zika cases reported in the United States, 4,886 cases in travelers returning from affected areas, 222 cases acquired through presumed local mosquito-borne transmission in Florida (N=216) and Texas (N=6)74 cases acquired through other routes, including sexual transmission (N=45), congenital infection (N=27), laboratory transmission (N=1), and person-to-person through an unknown route (N=1). Of the 38,303 cases reported in the US territories, 147 cases were in travelers returning from affected areas, and 38,156 cases were acquired through presumed local mosquito-borne transmission. There were no sexually transmitted cases reported in areas with local mosquito-borne transmission of Zika virus because it is not possible to determine whether infection occurred due to mosquito-borne or sexual transmission (CDC, 2017).

The magnitude of the geographical distribution of Zika virus cases in the States and its territories is alarming given that the above data contains provisional data reported to ArboNET for January 1, 2015 – March 22, 2017. The data are for laboratory-confirmed symptomatic Zika virus disease cases and viremic blood donors. Viremic blood donors are people who reported no symptoms at the time they donated blood, but whose blood tested positive when screened for the presence of Zika virus RNA by the blood collection agency. In most cases, viremic blood donors develop symptoms after

they had donated blood or may have had symptoms before the blood donation uptake. These are individuals presented on the above set as both Zika virus disease cases and viremic blood donors (Kaiser Family Foundation, 2017, CDC, 2017).

The above timeline charts and maps present a grim picture with clear implication for imported cases of the Zika virus around the world. Basu, and Tumban, (2016) citing several other studies posited that imported cases of Zika virus had been reported across the globe in 2016. For example, 1265 cases in August 2016 in Europe; more than 279 cases were reported Canada in September 2016; in Eurasia/Asia, 6 imported cases have been reported in Russia, and more than 21 cases have been reported in China; more than 300 and 200 cases have been reported in Singapore and Thailand, respectively; in-between the Pacific and Indian Oceans, 12 and more than 44 imported cases have been reported in Hawaii and Australia respectively. Basu, and Tumban, (2016) drawing from the evidence of their review literature concluded that there had been imported cases of Zika virus to at least one country on every continent except Antarctica, making this the first Zika pandemic the world has ever experienced. The implication of this finding is that Zika virus poses a global health risk, especially through travel (Icheke, 2016).

Globalisation and the public health risks of Zika virus spread

Increased globalisation continues to pose a risk for Zika virus spread. For example, there is clear evidence of a well-established association between global travels and the acquisition or transmission of infectious diseases (Icheke, 2016). Travelers may be exposed to infectious disease depending on their travel destination, the purpose of the visit and presence of infectious agents in the area visited (Richens, 2006). In 2015, the breakdown of the destination of international travellers for which data is available amounts to 9.9 million, flight from Brazilian airports (Zika virus most affected country) to North America is 65 percent, Europe is 27 percent, Asia is 5 per cent and 3 per cent to Africa (Gyawali, 2016). According to Icheke (2016), an estimated 1.4 million UK citizens traveled to areas where Zika virus is prevalent, and 5 UK travelers were diagnosed with the disease between 2010 and 2014. A total of 153 travel-associated and 107 locally acquired Zika cases had been reported in the USA and its territories as at March 2016 (Gyawali, 2016). Thus, CDC (2016) information for clinicians includes warning that incubation period for Zika virus is 3 to 14 days from the bite of *Aedes* species mosquito. This raises the concern that travelers and humanitarian health workers returning from affected areas in Brazil may be incubating the virus and become infectious after returning to their home countries.

Sikka et al., (2016) argued that, although, mobilization of economic and medical resources is on-going, the full burden of the Zika virus outbreak has not yet to be felt by the global community. They further argued that although it is difficult to predict the trajectory of global Zika virus spread, previous experiences with dengue and chikungunya viruses point toward a close link between globalization, urbanization, and the behaviour of emerging viruses in today's world. They, therefore, recommended that any approaches to such a potential global health security threat should be consistent, proactive, and should involve coordinated, multi-pronged, multilateral collaborative efforts that actively engage local, regional, national, and global agencies and resource pools. There is no doubt that Zika virus has emerged as a global public health threat over the last decade and as such the ultimate goal of the world, public health community should be the containment and the subsequent elimination of the virus as a global health security threat (Sikka et al., (2016).

Lastly, as stated earlier, Zika virus has been identified in Africa, Asia and recently in the Americas where concurrent neurologic conditions such as microcephaly and Guillain-Barré syndrome (GBS) were occurring at alarming rates. Fellner (2016) maintained that Zika virus infection has emerged as the world's newest health threat that is linked to microcephaly in infants and Guillain-Barré

syndrome in adults. Thus, examination of the health risks posed by microcephaly and GBS remain a top priority.

Chapter 3:

Microcephaly and Guillain-Barré syndrome

A global Zika virus spread modelling study published in the Medical Journal; Lancet predicted substantial international spread of Zika virus by travelers from Brazil to the rest of the world (Bogoch, et al, 2016). Fellner(2016) suggests that Zika virus linked to microcephaly and Guillain-Barré syndrome has emerged as the world's newest health threat. Thus, this chapter aims to examine cases of microcephaly and Guillain-Barré syndrome being reported from countries affected by Zika. The objective is to highlight the importance of surveillance for timely detection and monitoring of Zika infection and screening for microcephaly and Guillain-Barré syndrome, which are essential to guide the public health response (Kandel, et. al, 2016).

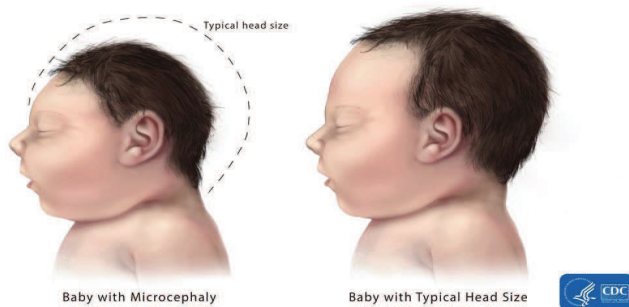
Microcephaly leading birth defects

As stated earlier, the World Health Organization maintained that there is association between Zika virus, microcephaly and birth defects (WHO, 2016). The following section analyses the evidence linking Zika virus to microcephaly and birth defect. Such analysis is particularly necessary given the purpose of this book, which is to provide a single document that discusses Association of Zika virus to microcephaly that leads to birth defects and examine evidence that may offer vital clues as to why there was no documented case of microcephaly in Africa where the disease originated for 70 years.

Microcephaly is referred to as a birth defect where a baby's head is smaller than normal and in comparison to babies of the same age and sex. In normal pregnancy, a baby's head grows because the baby's brain grows. Microcephaly results in birth defect because a baby's brain did not develop properly during pregnancy or has stopped growing after birth culminating a smaller head size (CDC, 2016).The outcome of Zika virus infection during pregnancy ranges from miscarriage to the delivery of healthy babies (Brasil *et al.* 2016c). Complications from Zika virus infection have been known to include hearing loss, vision problems, intellectual disability such as decreased ability to learn and function in daily life, developmental delays such as problems with speech or other developmental milestones, including sitting, standing and walking (CDC, 2016). These problems can range from mild to severe, are often life-long and, in some cases, can be life-threatening (CDC, 2016, Icheke and Icheke, 2016).

Not all children born with congenital Zika syndrome will have all the above conditions or display symptoms of microcephaly. However, some with congenital Zika virus syndrome who do not have microcephaly at birth may later develop smaller head and other complications of microcephaly (CDC, 2017). The Michigan Department of Health and Human Services (2016), recent article explains that "when microcephaly is present before or after birth, it is called congenital microcephaly. When microcephaly develops later in infancy or childhood, it is called acquired microcephaly. Proportional microcephaly means that the head size, length (or height), and weight are all less than expected in proportion to each other. Relative microcephaly is when the head size is small compared to height and weight, but inside of the normal range for age and sex." The explanations of these themes help clarify the use of the congenital in this book.

Figure 3.6: Baby with microcephaly and baby with normal head size



Source: CDC (2016) Birth Defects: Facts about Microcephaly

Figure 3.6 above compares a typical head size of a baby with a head size of a baby with microcephaly. Measuring a baby's head circumference whose mother has been exposed to Zika virus infection is a primary way to determine the presence of microcephaly (CDC, 2016). Some scholars attributed the small head size to central nervous system (CNS) malformations (Sarno, et al., 2016). Other scholars described congenital Zika syndrome as a pattern of congenital anomalies associated with Zika virus infection during pregnancy, which includes microcephaly (Russell, 2016).

The World Health Organisation (2017) recently reported in addition to congenital microcephaly, a range of manifestations has been reported among babies up to 4 weeks old where there has been exposure to Zika virus in utero. However, failure to detect signs of congenital Zika virus syndrome, especially when assessment is carried out in utero, does not inevitably mean that the foetus or new born does not have abnormalities. Hearing abnormalities, for instance, could only be assessed after birth and in the in utero. Some signs such as seizures, malformations of the head, involuntary movement, seizures, irritability, brainstem dysfunction such as swallowing problems, limb contractures, hearing and sight abnormalities and brain anomalies may only manifest the child's birth (WHO, 2017).

The WHO (2017) report added that Zika virus replicates and persists for several months in the placenta and the brain tissue of a fetus. This result in an increase in fetal loss, growth retardation and birth defects are common in babies born to mothers with Zika virus infection during pregnancy. The report identified the following as birth defects:

- Fatal microcephaly (small head)
- Intracranial calcifications (calcium deposits in the brain)
- Brain damage (WHO, 2017)

World Health Organisation (2017) recently reported that "congenital Zika virus syndrome" is all the known spectrum of congenital abnormalities associated with Zika virus exposure of fetuses during pregnancy. Similarly, Centers for Disease Control and Prevention (2017), report entitled "Microcephaly and Other Birth Defects," described Congenital Zika syndrome as the type of birth defects found among fetuses and babies infected with Zika virus during pregnancy. The organisation outlined the following five features of congenital Zika syndrome:

- Severe microcephaly where the skull has partially collapsed
- Decreased brain tissue with a specific pattern of brain damage
- Damage to the back of the eye
- Joints with limited range of motion, such as clubfoot
- Too much muscle tone restricting body movement soon after birth (CDC, 2017)

Zika virus infection is generally mild and self-limited; as a result over 80 per cent of Zika virus infection cases mostly go unnoticed. However, serious concern is emerging over Zika virus due to remarkable increase in cases of microcephaly and other central nervous system malformations between 2015 and mid-2016 in Brazil (Basil, et al. 2016, Malone, et al., (2016). As of 10 March 2017, 31 countries or territories have reported microcephaly and other central nervous system (CNS) malformations potentially associated with Zika virus infection, or suggestive of congenital infection (WHO, 2017). The countries and territories are outlined in table 3.6 below:

Table 3.7:
The countries and territories that have reported microcephaly and central nervous system (CNS) malformation cases potentially associated with Zika virus infection.

WHO Regional Office Country or territory			
Countries and territories that have reported microcephaly and CNS malformation cases potentially associated with ZIKV infection	AFRO	Cape Verde	1
	AMRO/PAHO	Argentina, Bolivia (Plurinational State of), Brazil, Canada*, Colombia, Costa Rica, Dominican Republic, El Salvador, French Guiana, Grenada, Guadeloupe, Guatemala, Haiti, Honduras, Martinique, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, Trinidad and Tobago, United States of America*	24
	EURO	Slovenia**, Spain***	2
	SEARO	Thailand	3
	WPRO	French Polynesia, Marshall Islands, Viet Nam	1
Total			31

*Probable locations of ZIKV infection are undetermined.

** Probable location of ZIKV infection is Brazil.

*** Probable locations of ZIKV infection are Colombia or the Bolivarian Republic of Venezuela.

Source: World Health Organisation (2017) Situational Report: Update,
<http://apps.who.int/iris/bitstream/10665/254714/1/zikasitrep10Mar17-eng.pdf?ua=1>

Guillain-Barré syndrome

Serious complications have been reported in many cases of Zika virus infection involving Guillain-Barré syndrome (Bhagyashri, 2016). The clusters of cases of the Guillain-Barré syndrome (GBS) that were observed during the outbreak of Zika virus infection in Colombia from November 2015 through March 2016 provided evidence linking Zika virus infection to the Guillain-Barré syndrome (Parra, et al., 2016). This section explored the clinical features of cases of Guillain-Barré syndrome in the context of Zika virus outbreaks and examined their relationship with Zika infection.

There have been several descriptions of Guillain-Barré syndrome. Dr. Michael Andary in a recent article published in Medscape described Guillain-Barré syndrome as a collection of clinical syndromes that manifests as an acute inflammatory polyradiculoneuropathy with resultant weakness and diminished reflexes (Andary, 2017). A recent medically reviewed article that was published in MedicineNet (2016) states that Guillain-Barré is called a syndrome or disorder rather than a disease because it is not clear that a specific disease-causing agent is involved. A syndrome,

on the other hand, is a medical condition characterised by a collection of signs and symptoms. Signs are what the doctors can observe or measure. Whereas, symptoms what the patient feels. GBS syndrome can affect anybody and can strike at any age, and all sexes are equally vulnerable to the disorder. However, the disorder is rare and afflicts only about one person in a 100,000 (NIH, 2017).

A typical patient with Guillain-Barré syndrome suffers from acute inflammatory demyelinating polyradiculoneuropathy (AIDP); presents 2-4 weeks following a relatively benign respiratory or gastrointestinal illness with complaints of finger dysesthesias and proximal muscle weakness of the lower extremities (Andary, 2017). The weakness is often progressive from about an hour to days involving the arms, truncal muscles, cranial nerves, and muscles of respiration (Andary, 2017). The American National Institutes of Health (2017) elaborated on this view when it stated that the early symptoms of this GBS disorder include varying degrees of weakness or tingling sensations in the legs. In most cases, the people affected by the disorder experience symmetrical weakness; abnormal sensations that spread to the arms and upper body. In severe cases, these symptoms increase in their intensity until certain muscles in the patient's body cannot be used at all culminating in total paralysis. The severe cases of the disorder become life threatening when it starts interfering with breathing, high blood pressure or heart rate and thus considered a medical emergency. The patients at an advanced or severe stage of the disorder are often put on a ventilator to assist with breathing and are watched closely for problems such as an abnormal heart beat, infections, blood clots, and high or low blood pressure. However, most patients have full recovery from the most severe cases of the disorder while some patients continue to have a certain degree of weakness (NIH, 2017).

It is not clear why some people are more vulnerable to the disorder that is not contagious than the others. It is equally not clear what sets the disease in motion. However, scientists do know that the body's immune system begins to attack the body itself, causing what is known as an autoimmune disease. The cells of the immune system attack only foreign material and invading organisms in a healthy person. The immune system in a GBS afflicted person starts to destroy the myelin sheath that surrounds the axons of many peripheral nerves, or even the axons themselves. The axons are the long thin extensions of the nerve cells that carry nerve signals. The myelin sheath, on the other hand, surrounds the axon and speeds up the transmission of nerve signals and allows the transmission of signals over long distances. In afflicted person, the peripheral nerves' myelin sheaths are either injured or degraded and thus prevent the nerves from transmitting signals efficiently. This results to inability of the person's muscles to respond to the brain's commands through the nerves' network (NIH, 2017).

According to USA Mayo Clinic (2016), the exact cause of Guillain-Barré syndrome is not known but a recent article published by NHS Choices (2017), a United Kingdom Government's website, states that the syndrome is thought to be caused by a problem with the immune system, the body's natural defence against illness and infection. Much as great deal of mystery still surrounds the syndrome; there are some known risk factors with public health implications:

- The risk of the disorder increases with age
- Males are slightly more prone to Guillain-Barré syndrome than female
- *Campylobacter* infection (often from uncooked meat) sometimes precedes Guillain-Barré syndrome
- HIV (human immunodeficiency virus)
- Influenza or Epstein-Barr virus
- *Mycoplasma pneumonia* - a bacterial infection of the lungs
- Hodgkin's lymphoma - an uncommon cancer of the lymphatic's
- Influenza or, rarely, childhood vaccinations.
- Surgery (Newman, 2016)

Other possible triggers for Guillain-Barré syndrome include injury cause by medical procedures such as a bone marrow transplant, bacterial and viral, glandular fever and some travel infections such as dengue and the Zika virus(NHS Choices, 2017).

A recent study published in the medical Journal Lancet analysed blood samples from 42 patients diagnosed with Guillain-Barré syndrome (GBS) during the Zika virus outbreak in French Polynesia provided the first evidence that linked Zika virus to GBS (Cao-Lormeau, et al., 2016). The 42 patients represent a 20-fold increase in incidence of GBS in the French Polynesia compared with the previous four years (WHO, 2016). Similarly, a retrospective study in Colombia evaluated 68 patients with GBS between fall 2015 and spring 2016, 97 percent of whom had symptoms of Zika virus infection within one month before onset of GBS symptoms (Parra, et al., 2016). The study found that out of 37 patients who were tested with serology, 86 percent had evidence of recent Flavivirus infection; of 42 patients who were tested with reverse-transcription polymerase chain reaction (RT-PCR), 40 percent had positive results. Among those tested with nerve-conduction studies and electromyography, 78 percent had the acute inflammatory demyelinating polyneuropathy subtype of GBS (Parra, et al., 2016). These studies provided evidence linking Zika virus to Guillain-Barré syndrome.

The current Zika outbreak in the Americas was followed by increased reports of cases of microcephaly and GBS. The table 3.7 below shows 23 countries or territories that have reported an increased incidence of Guillain-Barré syndrome and laboratory confirmation of a ZIKV infection among GBS cases (WHO, 2017). Given that Zika virus is spreading rapidly across the Americas, there is need for countries prepare for adequate intensive care beds capacity to manage patients with Guillain-Barré syndrome (Cao-Lormeau, et al., 2016).

Table 3.8: Countries and territories that have reported Guillain-Barré syndrome (GBS) potentially associated with Zika virus infection

WHO Regional Office Country or territory			
Reported increase in incidence of GBS cases, with at least one GBS case with confirmed ZIKV infection	AMRO/PAHO	Brazil, Colombia, Curaçao, Dominican Republic, El Salvador*, French Guiana, Guadeloupe, Guatemala, Honduras, Jamaica, Martinique, Puerto Rico, Suriname**, Trinidad and Tobago, Venezuela (Bolivarian Republic of)	15
	WRPO	French Polynesia	1
No increase in GBS incidence reported, but at least one GBS case with confirmed ZIKV infection	AMRO/PAHO	Bolivia (Plurinational State of), Costa Rica, Grenada, Haiti, Mexico, Panama, Saint Martin	7
Total			23

*GBS cases with the previous history of ZIKV infection were reported by the United States of America.

**One case living in continental Netherlands was diagnosed in January 2016 and reported by the Netherlands.

Source: World Health Organisation (2017) Situational Report: Update,
<http://apps.who.int/iris/bitstream/10665/254714/1/zikasisrep10Mar17-eng.pdf?ua=1>

The knowledge of cause and course of Guillain-Barré syndrome is limited but has now become an active area of neurological investigation, incorporating the cooperative efforts of neurological scientists, immunologists, and virologists. Although there have been major steps in the right direction, there is need to intensify effort aimed at resolving issues around pathogenesis of Guillain-Barré syndrome, particularly for the acute inflammatory demyelinating polyneuropathy form of the syndrome. The newly emerging forms of Guillain-Barré syndrome, which are associated with Zika virus, need to be closely monitored to checkmate the global transmission. There is also uncertainties surrounding the incubation period of Zika virus, and also the long-term health consequences of the virus infection still remain unclear (WHO, 2017 NIH, 2017).

Finally, it is evident from the discussion in this chapter that both microcephaly and Guillain-Barré syndrome allegedly linked to Zika virus pose global health threat. Thus, surveillance for timely detection and monitoring of Zika infection and screening for microcephaly and Guillain-Barré syndrome will be essential to guide the public health response (Kandel, et. al, 2016). Also, adherence to national and international protocols related to Zika virus, Guillain-Barré syndrome and microcephaly is of utmost importance, wide training and education of healthcare workers, including travel medicine practitioners, are also of high relevance about the threats. It is also imperative to increase personal protection measures when visiting endemic areas and enhanced vector control by health authorities in countries where Zika virus and other arboviruses are prevalence (Rodriguez-Morales, 2016).

Chapter 4

Reviewing the evidence linking Microcephaly to birth defect in Africa

The outbreak of Zika virus in Brazil, beginning in May 2015, was unprecedented culminating in 4,000 suspected cases of microcephaly, and 270 confirmed cases that health officials believe are linked to the Zika virus (CDC, 2016). Since the outbreak of the Zika virus in the north-east of Brazil in 2015, the virus has spread rapidly throughout the Americas. Microcephaly came into the scene in the same year (2015) when physicians in the country began to report that there was a surge of the number of the disorder among newborns, which was suspected to have a link to Zika virus infection during the mothers' pregnancy (Butler, 2016). Zika virus became a suspect in the increased microcephaly following the World Health Organization statement in March 2016 that there was a scientific consensus that the mosquito-borne Zika virus causes microcephaly that leads to the birth defect (WHO, 2016). This chapter will explore this view given that the decisions about causality require a clear understanding of the association of Zika virus complications to guide public health actions.

As noted in Chapter 3, serious concern is emerging over Zika virus due to remarkable increase in cases of microcephaly and Guillain-Barré syndrome (Kandel, et. al, 2016, Malone, et al., 2016). The link between Zika virus and microcephaly during pregnancy first came to light when a test carried out by the Brazilian Ministry of Health identified Zika virus RNA (ribonucleic acid) in the amniotic fluid of two women whose fetuses had been found by prenatal ultrasound to have microcephaly (Campos et al. 2015). Zika virus related microcephaly has since then emerged as the world's newest health threat given an increasing globalisation (Bogoch, et al., 2016, Fellner, 2016). For example, WHO (2016) in May 2016 confirmed an outbreak of the Zika virus on the African island chain of Cape Verde, linking it to first cases of microcephaly Africa. This raises the question as to what is the connection between Zika virus and microcephaly (Icheke, 2016).

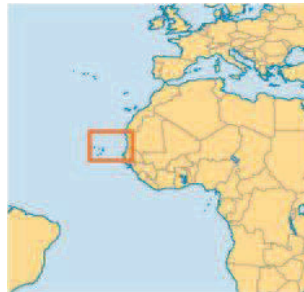
Figure: 4.6

African island chain of Cape Verde

island chain of Cape Verde



Map of African



Source: Google maps (2017)

Cape Verde or Cabo Verde as shown in figure 4.6 is officially country an archipelago of 10 volcanic islands in the central Atlantic Ocean, which has historic ties to Brazil (Davis, 2016). The Islands are located 570 kilometers (350 mi) off the coast of Senegal West Africa and cover a combined area of slightly over 4,000 square kilometers (1,500 sq mi) as shown in figure 4.6. The WHO finding is of particular concern because Zika virus that first discovered in East Africa in 1947 had no known link to brain disorders or birth defect until the WHO recent findings (Icheke, 2016, Basu, 2013). Thus, the aim of this chapter is to examine available evidence that associates Zika virus to microcephaly as such evidence may provide possible explanations for why there was no documented case of microcephaly leading to a recent birth defect in Cape Verde.

Causal relationship between Zika infection during pregnancy and microcephaly

As noted in chapter 2 of this book, Zika virus has a widespread distribution in Africa, the Indian subcontinent, Southeast Asia, Micronesia and French Polynesia, and most recently the American continent. The WHO (2016) Global Situation Report shows that 72 countries and territories have reported evidence of Zika virus transmission since 2007. The report further shows that since February 2016, 20 countries or territories have reported microcephaly potentially associated with Zika virus infection. Four of the 20 countries reported microcephalic babies born from mothers in countries with no endemic Zika virus transmission but who reported recent travel history to Zika-affected countries. Subsequently, the World Health Organisation's Director-General in a recent statement indicated that a causal relationship between Zika infection during pregnancy and microcephaly is strongly suspected, though not yet scientifically proven (WHO, 2016). The evidence is therefore required to supports the likelihood that Zika virus infection during pregnancy will have a broad range of effects on the developing fetus.

The WHO (2016) in its statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations called for intensified research into the etiology of new clusters of microcephaly and other neurological disorders to determine whether there is a causative link to Zika

virus and/or other factors or co-factors (WHO, 2016). One of the earliest responses to epidemiological data suggesting that microcephaly cases in Brazil might be associated with the introduction of Zika virus was a study published in the medical Journal Lancet. The study was designed to detect and sequence the Zika virus genome in amniotic fluid samples of two pregnant women in Brazil whose fetuses were diagnosed with microcephaly. The study found that the Zika virus genome in the amniotic fluid of both pregnant women. The credibility of the findings was not in any doubt and strengthens the presumed association of Zika virus and cases of microcephaly in neonates in Brazil (Calvet, et al., 2016).

Falcao et al. (2016) citing CDC supported the view of the causal relationship between prenatal infection by the Zika virus and microcephaly and other cerebral abnormalities. This view was based on evidence concerning Zika virus infection during prenatal development that was consistent with the defects observed, with the occurrence of a rare and specific phenotype involving microcephaly and cerebral abnormalities in fetuses (Falcao et al. 2016). One study documented an increase in reported prevalence of microcephaly in infants born to women living in areas with confirmed Zika virus transmission during the first trimester of pregnancy (de Oliveira, et al., 2016). Another study that was carried out about 35 children with microcephaly found that 74 per cent of the mothers in northeastern Brazil who were suspected of having had Zika during their pregnancies reported that they had had a skin rash during the first and second trimesters (Schuler-Faccini, et al., 2016). The study also showed that since the Zika virus outbreak in the country, the incidence of microcephaly increased more than 20 times higher than what would otherwise have been expected (Paixão, et al., 2016). Further association between Zika virus and microcephaly was supported by several case reports and case series of laboratory-confirmed or presumed Zika virus infection during pregnancy (Barzon, et al., 2016).

The above studies suggest that Zika virus can infect fetus, but WHO (2016) experts caution that the link is not proven that Zika virus causes of microcephaly leading birth defect. Some public health experts also called for caution and for further research to clarify the biological mechanism linking Zika virus to microcephaly. For example, Dr Ana de Filippis, from the Oswaldo Cruz Institute in Rio de Janeiro, Brazil, (one of the authors of the research published in Lancet confirming the presence of Zika virus in the amniotic fluid of two Brazilian women who had had Zika-like symptoms during their pregnancies) said that the study cannot determine whether the Zika virus identified in the two women was the cause of microcephaly in their babies. "Until we understand the biological mechanism linking Zika virus to microcephaly we cannot be certain that one causes the other and further research is urgently needed." Commenting on the study, Jimmy Whitworth, professor of international public health at the London School of Hygiene and Tropical Medicine, said: that the researchers have shown that the virus crossed the placental barrier during the first and second trimesters of pregnancy in the two Brazilian but did not provide any clear evidence that Zika virus causes microcephaly. He added that such study can show an association between Zika and microcephaly but cannot show that Zika virus caused the microcephaly. He, therefore, calls for accumulation of evidence from a variety of studies from different perspectives to confirm that Zika virus caused microcephaly that leads to birth defects (BBC, 2016, Press Association, 2016). One important view that emerged from these experts' views that caution should be exercised until the evidence linking Zika virus to microcephaly is made conclusive through further research.

Also, some scholars suggested that what is known about Zika virus is limited at the present moment (Wu, et al., 2016). Similarly, Gyawali, et al., (2016) stressed that while the evidence associating Zika virus to microcephaly is compelling, extensive scientific study is needed to confirm the association. Rasmussen, et al., (2016) added that despite accumulated evidence that supports the link between Zika virus infection and microcephaly; cautious approach should be taken towards ascribing Zika virus as a cause of birth defects. One study published in Nature International Journal of Science

demonstrated that the accurate size of Brazil's surge in microcephaly leading to birth defects is elusive. The study shows that Brazil's Health Ministry reported 6,398 'suspected' cases of microcephaly and central nervous system malformations since November 2015 but investigated only 2,197 so far. The study also shows, out of 854 cases that were confirmed as microcephaly, only 97 cases were confirmed by laboratory tests as having a link to Zika virus. The study added that Brazil is likely to have under-reported its past microcephaly cases. The country recorded just 147 in 2014 (around 0.5 cases per 10,000 births), but experts say that they would have expected to see around ten times that number by typical frequencies seen elsewhere. It is therefore difficult to draw conclusion given that Brazil lacks reliable historical baselines for comparison (Butler, 2016).

As alluded earlier, Brazil reported a higher prevalence of microcephaly in 2015 Zika virus outbreak than previous years. Wu, et al., (2016) citing Kleber de Oliveira, et al., (2016) argued that the higher prevalence of microcephaly in Brazil was found in 15 states among the 19 states that had Zika virus infections as reported by laboratory confirmation. However, Wu, et al., (2016) warned that the study cannot generate causal reference because it does not rule out unknown and uncontrolled confounders. Kleber de Oliveira, et al., (2016) showed that since late 2014, clusters of febrile rash illness had been reported from the Northeast region of Brazil. These cases were attributed to Zika virus, a flavivirus transmitted by Aedes mosquitoes. The high incidence microcephaly in Brazil is found to be driven purely by states in the Northeast, in particular, Pernambuco with 14.62 cases and Paraíba with 10.82 per 10,000 births respectively. Thus, it is impossible to establish, from the epidemiological data available, the true size of the surge in microcephaly, and whether there is any link with the Zika virus (Butler, 2016). The question, therefore, is why the epidemiological signal of a link between Zika and microcephaly seems to be strongest only in the northeast of the Brazil? It is most likely to be that local factors involved increased cases of microcephaly in North East of Brazil.

Other factors that may be involve in the recent increase cases of microcephaly

The World Health Organisation's declaration of Zika virus as an important Public Health Emergency of International Concern (PHEIC) on 1st of February 2016 is mainly driven by the support for increase cases of microcephaly found in new born babies is linked to the on-going Zika virus outbreak in Brazil (WHO, 2016). However, the prevailing uncertainty about Zika virus infection and its link to microcephaly leading to birth defect may provide a vital clue as to question as to why the absence of microcephaly in Africa 70 years after the discovery of Zika virus in East Africa. The association between the viral infections and pregnancy has long been recognized. This section of this book will explore other factors at play in the Zika virus related microcephaly that may provide a possible explanation of the absence of macrocephaly in Africa.

One study on viral infections and pregnancy found that pregnant women suffer worse outcomes during viral epidemics and pandemics than the general population and non-pregnant women. The researchers stated that women go through an immunological transformation during pregnancy. They added that adverse pregnancy outcomes might result when the immune system required for promoting and supporting the pregnancy and growing fetus is compromised due to infection (Silasi, et al., 2015). CDC (2017) agreed with the researcher's views by reporting that the causes of microcephaly in babies are mostly inconclusive and added that some babies have microcephaly because of other abnormalities. The abnormalities include severe microcephaly, can include exposures during pregnancy to certain infections such as rubella, toxoplasmosis or cytomegalovirus; also to lack of nutrients or not getting enough food, exposure to harmful substances, such as alcohol, certain drugs, or toxic chemicals, and interruption of the blood supply to the baby's brain during development (CDC, 2017).

In a review of the literature, Icheke and Icheke (2016) found no conclusive evidence that Zika virus infection caused any of the abnormalities found in the babies with microcephaly. The review could

also not find any conclusive scientific evidence of the full spectrum of outcomes that might be associated with Zika virus infection during pregnancy or the factors that might increase risk of the disease infection to the foetus. Some scholars in support of the review finding posted that studies linking high incidence of human microcephaly to the presence of Zika virus were not supported by any experimental data that provide a direct link between microcephaly and Zika virus during fetal brain development (Garcez, et al., 2016). Other scholars added that there was no direct experimental causal evidence confirms that the Zika virus is the sole etiological agent responsible for the development of brain malformations in human fetuses during pregnancy. Also, the scholars stated that Zika virus might not be, per se, the only etiological agent responsible for microcephaly (Nogueira, et al., 2016). If Zika virus is the definitive culprit in the cases of microcephaly, why are there no similar epidemics in other countries also affected by the Zika virus? Perhaps, because there are other reasons for the increase cases of microcephaly in Brazil, which may also provide the most likely explanation why birth defects not, been documented in Africa 70 years after the discovery of the Zika virus.

A paper published in Science News is one of the many studies that first cast doubts on Zika virus as the cause of microcephaly. The paper also cited the New England Complex Systems Institute (NECSI) report and argued that in Brazil, the microcephaly rate soared with more than 1,500 confirmed cases. A recent study of nearly 12,000 pregnant women infected with Zika virus in Colombia; found zero microcephaly cases and asked if Zika virus is to blame for microcephaly, where are the missing cases? The number of missing cases in Colombia and elsewhere raises serious questions about the supposed connection between Zika and microcephaly (Science Daily, 2016). Another study reported three deaths association with Zika virus, one of them is a newborn, but a death of a teenager with sickle cell disease has been recently published Colombia, which suggested that comorbidities are also the risk factor (Arzusa-Ortega, et al., 2016). Other studies have shown that congenital malformations, including microcephaly, generally have complicated multifactorial etiology and may have been caused by infection during pregnancy or through chromosomal disorders, exposure to environmental toxins or metabolic diseases, as shown in Table 4.9 below (Rodriguez-Morales, 2016, Falcao et al. 2016).

Table 4.9: Etiological agents and risk factors for microcephaly

Period and types	Etiology
Congenital Genetic	Inherited genetic disorders, syndromes, and mutations
External, chemical agents	Brain injury due to teratogenic drugs, toxins and chemical products, including fetal alcohol syndrome, radiation
Metabolic diseases	Diabetes
Nutritional	Malnutrition (maternal malnutrition, maternal folate deficiency, placental insufficiency)
Vascular	Hypoxic-ischemic lesions
Infectious	Transplacental infections of the central nervous system STORCH infections; syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, HIV other viruses
Post-partum	Brain vascular and non-vascular injuries Meningitis Encephalitis Congenital encephalitis due to HIV Copper intoxication Chronic renal failure

Source: Rodriguez-Morales, A.J. (2016) Zika and microcephaly in Latin America: an emerging threat for pregnant travelers. *Travel Med Infect Dis.*; 14(1):5.

The American Mayo Foundation for Medical Education and Research (MFMER) described Microcephaly as the result of abnormal brain development, which can occur in the womb (congenital) or during infancy. The organisation added that microcephaly might be genetic or other causes that may include the following:

- Craniosynostosis i.e. the premature fusing of the joints (sutures) between the bony plates that form an infant's skull keeps the brain from growing.
- Chromosomal abnormalities i.e. down syndrome and other conditions may result in microcephaly.
- Decreased oxygen to the fetal brain (cerebral anoxia) i.e. certain complications of pregnancy or delivery can impair oxygen delivery to the fetal brain.
- Infections of the fetus during pregnancy i.e. these include toxoplasmosis, cytomegalovirus, German measles (rubella) and chickenpox (varicella).
- Severe malnutrition i.e. not getting adequate nutrition during pregnancy can affect your baby's development.
- Uncontrolled phenylketonuria also known as PKU i.e. birth defect that hampers the body's ability to break down the amino acid phenylalanine
- Exposure to drugs, alcohol or certain toxic chemicals in the womb. Any of these put your baby at risk of brain abnormalities (Mayo Clinic, 2017, CDC, 2016).

Microcephaly has many causes, such as a group of infections known as STORCH (syphilis, toxoplasmosis, other infections, rubella, cytomegalovirus infection and herpes simplex). Cytomegalovirus, for instance, has been reported to cause birth defects in around 13 per cent of pregnant women who were infected by the virus; while rubella does so in between 38 percent and 100 percent of women who were not vaccinated and infected during their first trimester (Butler, 2016).

A recent report by Argentine doctors' organisation, "Physicians in the Crop-Sprayed" (2016) may provide a clue as to why most cases of Microcephaly were reported in the Northeast states in Brazil. The report challenges the theory that the Zika virus epidemic in Brazil is the cause of the increase in the birth defect microcephaly among newborns. The Physicians in the Crop-Sprayed Towns argued that the Brazilian Ministry of health failed to recognise that in the area where most sick people live, a chemical larvicide that produces malformations in mosquitoes was introduced into the drinking water supply in 2014. According to the Physicians, the poison, Pyriproxyfen, is used in a State-controlled program aimed at eradicating disease-carrying mosquitoes. The Physicians explain that pyriproxyfen is a growth inhibitor of mosquito larvae, which alters the development process from larva to pupa to adult, thus generating malformations in developing mosquitoes and killing or disabling them. It acts as an insect juvenile hormone or juvenoid and has the effect of inhibiting the development of adult insect characteristics such as wings and mature external genitalia and reproductive development. It is an endocrine disruptor and is teratogenic that causes birth defects. The Physicians added that malformations detected in thousands of babies from pregnant women living in areas where the Brazilian state added Pyriproxyfen to drinking water are not a coincidence, even though the Ministry of Health places a direct blame on the Zika virus for this damage (Bowater, 2016).

However, the Brazilian federal government was quick to dismiss the Physicians in the Crop-Sprayed's reports, insisting that there had been no scientific study that linked the chemical pyriproxyfen to

microcephaly that leads to the birth defects (Bowater, 2016). Contrary to the government denial, Brazilian doctors' and public health researchers' organisation (Abrasco) published a report, which concurs with the findings of the Argentine's doctors' organisation. For example, Robinson (2016) citing Abrasco's report stated that the emergence in 2014 of the microcephaly increase occurred within certain "contexts and contingencies." Environmental degradation, poor sanitation and continued use of larvicidal chemicals in the drinking water of families for more than 40 years must be assessed in any attempt to understand the phenomenon. Also, Robinson (2016) stated that both the Brazilian and Argentine doctors' and researchers' associations were in agreement that poverty is also a key factor that is ignored in Zika virus related microcephaly narrative. Abrasco accused the Brazilian government of deliberately concealing the social and economic factors in the microcephaly's narrative. "In Argentina and across America the poorest populations with the least access to sanitation and safe water suffer most from the outbreak." The Argentine Physicians supported this view by stating that inequality and poverty form the basis of the disease progression (Robinson, 2016).

Figure: 4.7



Source: Robinson, C. (2016) what did Brazilian public health researchers say about Zika, pesticides, and birth defects? <http://gmwatch.org/news/latest-news/16741>

ECDC (2016) supported the use aerial spraying with insecticides as shown in figure4.7 above as a means of eliminating adult mosquitoes during the Zika virus outbreak but added that the efficacy of such measure seems very limited. The organisation warned that if authorities implement such measure because of the supposed threat of Zika virus, it could increase children's risk of brain disorders, which is the opposite of what anti-Zika virus campaigns are supposed to achieve (ECDC, 2016). This view is supported by a study by American Academy of Pediatrics, published in Science Daily, which found that community's use of airplanes to spread pesticide each summer poses a greater risk of autism spectrum disorder and developmental disorders among children born in the area (Science Daily, 2016). The study compared children living in zip codes (post code) where aerial pesticide spraying was used each summer to combat mosquitoes with children living in non-aerial-spraying zip codes. The researchers found that children exposed to the aerial pesticide spraying were about 25 percent more likely to be diagnosed with autism or have a documented developmental delay than those living in areas that used other methods of pesticide application (Science Daily, 2016)

The chemical pyriproxyfen seems to provide the most plausible evidence that challenges the theory that the Zika virus is the cause of microcephaly leading to birth defects Brazil (Robinson, 2016). As for the absence of microcephaly in Africa, a phenomenon called herd immunity seems to offer the most plausible explanation (Icheke, 2016). According to Fine et al. (2011) the term herd immunity, referring to an entire population's immunity, which was used to describe naturally occurring phenomenon in the 1930s when it was observed that, after a large group of children had become immune to measles infection, new infections decreased in the short term (Fine, 2011). In other words, herd immunity becomes a type of indirect protection from infectious disease, occurring when a significant percentage of a population has become immune to the infection, thereby providing a measure of protection for individuals who are not immune and thus decreasing the number of new infections (Hinman, et al., 2016). Thus, Wighton, (2016) citing the findings of scientists at Imperial College London predicted that the current explosive Zika virus epidemic would burn itself out due to the phenomenon called herd immunity. Given that the virus is unable to infect the same person twice; the presence of immune system generating antibodies to kill the virus and the epidemic reaching a stage where there are too few people left to infected for transmission to be sustained.

However, Dawes, et al. (2016) argued that the current understanding of protective immune responses to Zika virus is limited, and is derived primarily from human data following infection and from comparison with other flaviviruses. Conversely, Geard, et al., (2016) succinctly explains how populations acquire protective immunity. In their view, when we are exposed to a pathogen (a virus, bacteria or parasite), our bodies produce an immune response to defend itself. This immune response not only clears the pathogen but often provides protection against further infection even after they recover, so they are not susceptible to being infected by the same disease again. They added that Infectious diseases spread when a pathogen is transmitted from an infectious person to a person or vector to a person who is susceptible to infection. During an outbreak, lots of people can become infected in a short time and develop immunity. As a result, the number of susceptible people left vulnerable to be infected is reduced, making it harder for the pathogen to keep spreading. Subsequently, the number of new infections declines and the outbreak ends, without it being necessary for everyone to have been infected. This may explain what happened in the early years of Zika virus transmission in Africa after the disease run its course, there may no longer be enough susceptible people in a population to allow a further outbreak to occur. If this was the case, the inability of the Zika virus to spread might have provided indirect protection for those who remain susceptible by protection known as "herd immunity" (Geard, et al., 2016).

While public health experts usually aim to achieve herd immunity through vaccination, in the case of Zika virus, experts predict that herd immunity will be achieved through natural process (Geard, et al., 2016). In line with this view, Baker (2016) argued that Africans have had decades to build up immunity to Zika virus through natural protective immunity, a disease that most South Americans are encountering for the first time. She predicted that even if there is a regular outbreak of Zika virus in Africa, it may even be that many women, once they reach childbearing age, have already been infected and are immune and thus have protection against the virus. The challenge, however, is that because many people infected with Zika virus will not become sick and those who do may experience symptoms that could be mistaken for those caused by other diseases such as dengue or chikungunya. Thus, better diagnostic tests are required to estimate the current level of herd immunity to Zika virus in different populations and identify those most vulnerable or at risk (Geard, et al., 2016).

Finally, this chapter reviewed the literature to identify existing evidence of the causal link between Zika virus infection and microcephaly and found that other factors may be at play. However, future studies are warranted to solidify the other factors that may be involved in the increased cases of

macrocephaly in Brazil. The understanding the factors may provide a possible explanation of the absence of macrocephaly in Africa. Until the apparent association between Zika virus infection and microcephaly is either established or disproved, women should be cautious in planning to conceive a baby or to travel to a Zika-endemic country if already pregnant. Also, safe sex until the mooted possibility of sexual and vertical transmission of Zika virus is substantiated.

Lastly, Gyawali et al., (2016) call for governments to establish stringent public health safety policy for managing blood and blood products in the effort to combat the Zika virus global health security threat. As Scriven and Garman (2007) postulated public health uses a variety of disciplines such as epidemiology, biostatistics, biology and biomedical science in its study of public health safety. McKee and Pomerleau (2005) added that public health depends on heavily on environmental sciences, social and behavioral sciences to deal public health safety. It involves applying scientific information to a range of realistic settings that require attention to problems such as health issues affecting the society, selecting intervention strategies and approaches to deal with the health issues (McKee and Pomerleau, 2005). Thus, the following chapter 5 and 6 will focus on public health research and intervention respectively.

Chapter 5

Public health research required to fill the gaps in Zika virus related research

The World Health Organisation recognised the importance of public health studies to fill the current gaps in Zika virus related research. This is evident in its Zika Virus Research Agenda Document (2017), which goal is to support the generation of evidence needed to strengthen essential public health guidance and actions to prevent and limit the impact of Zika virus and its complications. This chapter examines this goal; the WHO's role in health research and use of research evidence to inform Zika virus related public health policies and practices. Such examination is required, given the current worldwide Zika virus transmission and the need to consider what aspect of research should be prioritised to effectively combat the Zika virus global health security threat (Sikka et al., 2016, Gyawali, et al., 2016).

WHO (2017) also calls for an urgent need for research to address the unfolding human cost of the Zika virus epidemic. To reinforce this call, WHO used stories of families of infants born with microcephaly and other congenital syndromes whose conditions have been linked to Zika virus related maternal infection during pregnancy. In other words, research is required to establish conclusively the link between the Zika virus and microcephaly leading birth defect. Research evidence is also required to ascertain clearly how Zika virus is transmitted from mother to unborn child and through sexual intercourse. WHO (2017) had already warned that many infants affected by the Zika virus related microcephaly would develop learning and motor disabilities as they grow older and will require life-long care and social support. Also, asserts that it is better placed to identify critical areas of research; implement or coordinate global activities and subsequently identified the following research and development priority areas:

- Investigation into public health and clinical implications;
- description of the dynamics of arbovirus epidemics in the Americas region and characterisation of arbovirus vectors; and development and enhancement laboratory; platforms to support surveillance and piloting new vector control tools (WHO, 2017)

Gyawali, et al., (2016) stated that given the global scale of the current Zika virus transmission, public and private key stakeholders, funding agencies and public health experts worldwide should consider what issues need to be prioritised for research to produce effective approaches to combat the Zika virus public health threat. Furthermore, there is currently very limited knowledge about the virus; the shortfall in research includes epidemiological characteristics, surveillance and diagnostics, virus

reservoirs/vectors/transmission, disease manifestations and sequelae, clinical management and public health interventions. Gyawali, et al., (2016) citing Vogel, et al., (2016) added that the drivers responsible for Zika emergence and outbreak are evidently complex and multifactorial. Thus, the collective knowledge gap calls for urgent action to provide better knowledge of both the Zika virus itself and the pathologies it causes, especially microcephaly leading to a birth defect, which represents a serious public health challenge (Gyawali, et al., 2016).

The importance of public health research could be seen more specifically from the point of establishing the causal link between Zika virus infection and microcephaly leading to birth defects. Rodriguez-Morales (2016) recommended further studies to examine other aberrations in fetal development apart from microcephaly given that new evidence is indicating that Zika virus infection can cause other fetal brain abnormality (Oliveira Melo, et al. 2016). Although the importance of public health research in establishing the causal link between Zika virus infection and microcephaly is widely recognized, exploiting research optimally to resolve priority of any health problems is not a straightforward matter. This is because of the complex nature of health problems confronting societies in general; the rapid advances in knowledge and technologies related to health; the shifting expectations and concerns of the public in respect of research. This is in addition to the changes in the organization and management of research within and across countries, which pose an enormous challenge to member states (WHO, 2012).

WHO's role in public health research

The importance of research and the harnessing of knowledge, science, and technology are highlighted as priority areas in Article 2 of the Constitution of the World Health Organization and the Eleventh General Programme of Work 2006–2015 (PAHO, 2009). The WHO's role in health research, in general, is defined in the document, 'The WHO Strategy on Research for Health as "shaping the research agenda and stimulating the generation, translation, and dissemination of valuable knowledge." This is an addition to five functions that involve providing leadership, setting norms and standards, articulating evidence-based policy options, providing technical support and monitoring the health situation. These functions require strong research knowledge and experience among the staff of the World Health Organisation. This is because the World Health Organisation recognizes that research is central to progress in global health and the need to identify ways in which the organisation can work with member states and partners to harness science, technology, and broader knowledge in order to produce research evidence and tools for improving health outcomes (WHO, 2012).

The World Health Organisation also leads in the harmonization, collection, review, and analysis of data on Zika virus and prioritised the following five relevant public health research areas:

- Establish causality between Zika virus infection and neurological disorders (in the fetus, neonates, infants, and adults): development of a causality framework and a systematic review.
- The risk of adverse outcomes of pregnancy in women infected with Zika virus and follow-up of babies and infants: establish a cohort of pregnant women.
- Explore sexual transmission of Zika virus: establish a cohort of men and women and regularly test body fluids for the presence of Zika virus.
- Vector control research: evaluate interventions based on community and resistance of the vectors, develop surveillance system.
- Public health system research: evaluate the preparedness of health system to manage babies with microcephaly and assist their families, to manage patients with GBS; to evaluate the availability of contraception in health services to respond to the demand and assess abortion services (WHO, 2016).

By the five public health research priority areas, WHO (2016) established Strategic Response Framework and Joint Operational Response Plan with a clear objective to fast-track research and development of new products including diagnostics, vaccines, and therapeutics. To achieve this objective, the following activities need to be carried out:

- Identify research gaps.
- Support the conduct of research related to Zika virus diagnostics, therapeutics, vaccines and novel vector control approaches
- Convene research actors and stakeholders.
- Coordinate introduction of products after assessment and evaluation.
- Coordinate supportive research activities including regulatory support and data sharing mechanisms (WHO, 2016).

Some scholars added that, although mobilization of economic and medical resources is on-going, the full burden of the Zika virus outbreak has not yet to be felt by the global community. They further argued that although it is difficult to predict the trajectory of global Zika virus spread, previous experiences with dengue and chikungunya viruses point toward a close link between globalization, urbanization, and the behaviour of emerging viruses in today's world. They, therefore, recommended that any approaches to such a potential global health security threat should be consistent, proactive, and should involve coordinated, multi-pronged, multilateral collaborative efforts that actively engage local, regional, national, and global agencies and resource pools. There is no doubt that Zika virus has emerged as a global public health threat over the last decade and as such the ultimate goal of the world, public health community should be the containment and the subsequent elimination of the virus as a global health security threat (Sikka et al., (2016). Thus, the use of research evidence is crucial if the fight against global health security threat pose by the Zika virus is to be won.

Use of research evidence to informed Zika virus related public health policies and practices

As research and evidence are the foundation for sound health policies, WHO reported that all member states are increasingly placing demands on research to provide opportunities for resolving current and emerging health problems (WHO, 2012, WHO, 2017). Moreso, the global environment is characterised by competing demands for limited resources. Thus, to *ameliorate or eliminate the* global health security threat posed by the Zika virus, it is imperative that health policies and professional practices are informed by the best research evidence. Watts (2017) citing one of the world's leading virologists; reported in the UK Guardian Newspapers that there was "a strong possibility that pesticides could be involved in the microcephaly cases in Brazil but this needs to be studied." Dr. David Morens of the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health was also quoted as saying that the pesticide hypothesis is "plausible," but quite rightly called for more scientific evidence (Robinson, 2016). According to Calvet, et al., (2016), there is a need for further studies to create a clear understanding of the mechanisms of immune pathogenic that lead to congenital malformation due to Zika virus infection. These views are all in recognition that research evidence is central to progress in the global fight against the Zika virus epidemic.

The recognition of research evidence in the global fight against the Zika virus infection notwithstanding, one study found that there is widespread evidence of failure to apply health interventions that have been demonstrated to be cost effective by high-quality research evidence; this failure affects both high-income and low-income countries. Low-income countries, in particular, were found to be facing additional challenges in term of using research evidence, which include the weakness of their health systems, the lack of professional regulation and a lack of access to quality research evidence. Thus, some scholars recommended strengthening of institutions and

mechanisms that can promote interactions between researchers, policy-makers and other stakeholders who can influence the uptake of research findings (Haines, et al., 2004).

The aim of evidence-informed policy and professional practice is to promote communication, understanding, and advocacy around the information, knowledge management and knowledge translation challenges that would allow countries to:

- develop national policy and practice guidelines, and
- use these guidelines to support improvements in policy and practice at the local level and the front line of health care (HIFA, 2017)

World Health Organization (WHO) in recognition of the benefits of research evidence encouraged member states to develop a strategy on health policy and systems research that advocates for thoroughly embedding research into public health decision-making (Haines, et al., 2004).

There is no doubt that public health policy intervention by member states can contribute enormously to the fight against the spread of Zika virus epidemic. This is because, at a global community level, there is already a commitment to reducing health inequalities worldwide. For example, Member States signed up to the 65th World Health Assembly for the reduction health inequities through action on the social determinants of health (2011). WHO (2015) describes health inequality as the differences in health status, or the differences in the distribution of health determinants, between different groups in any society. Health inequalities, according to Marmot and Allen (2014) are those differences in health that are still prevalent even though they are realistically avoidable, which is unfair. This view is in line with the view of WHO (2008) Social Determinants of Health report that describes ill health as the outcome of unfair distribution of health determinants such as income, power, goods and services, access to healthcare, leisure, education, employment and other factors, all of which promote good health. As noted earlier, health experts in both Brazilian and Argentine argued that poverty is a key factor that is ignored in Zika virus related microcephaly narrative and accused their respective governments of deliberately concealing the social and economic factors in the microcephaly's narrative (Robinson, 2016). Thus, any attempt to tackle health inequity should be based on dealing with the wider determinants of health. On the other hand, to tackle health inequalities, it is essential to deal with inequities in the way that society is organised at the national level (WHO, 2008).

At the global level, Quinn and Kumar (2014) argued that infectious disease outbreaks can spread quickly across the world through travel and that poverty, inequality. They further argued that social determinants of health create conditions for the transmission of infectious diseases compounded by the existence of health inequalities, which can further contribute to unequal burdens of morbidity and mortality. Quinn and Kumar added that studies of influenza pandemic plans across multiple countries find little to no recognition of health inequalities or attempts to engage disadvantaged populations to explicitly address the differential impact of a pandemic on them. As Marmot (2010) postulated, to improve health for all and decrease unfair and unjust inequalities in health, action must be taken across the social gradient. Central to this is the acknowledgment that vulnerability to disease or ill-health starts before birth and accrues over a life time. Thus, without explicit attention to existing health inequalities and underlying social determinants of health, the global fight against the Zika virus epidemic is unlikely to succeed in its goals and objectives.

Some scholars have called for an urgent need for evidence to inform public health policy decision making to reduce health inequalities. The scholars argued that the use of research evidence to underpin public health policy is strongly promoted, but its implementation has not been straightforward. They, therefore, recommended that to effectively implement research evidence-informed public health policy, actions are required:

- To encourage two-way communication between researchers and decision makers.

- The environment within which decision makers work, regarding structure and rewards, should be adapted to encourage the use of research evidence.
- The decision makers should be trained to be able to increase their ability to access and interpret research outputs.
- The researchers should be trained to be able to increase their ability to produce evidence that will be of use to policy makers and to present the main findings and to effectively disseminate them to the relevant audience (Orton, et al., 2011).

Some scholars attributed the low uptake of research evidence to inform public health interventions, especially in low-income countries, to low priority accorded to health and systems research. The scholars argued that many stakeholders involved in implementing public health interventions do not appear to perceive investment in rigorous evaluation to be a priority: they believe that they know what should be done, and their main priority is to put their beliefs into practice. In doing so the opportunity to generate robust evidence about how to change policy and practice are lost. Thus, facilitating interactions between researchers and policy-makers may increase the uptake of research findings and lead to evidence-based health policies and practices. The following seven key processes during which interactions between research and policy should be considered:

- setting priorities for and commissioning of research
- carrying out the research
- synthesizing the evidence
- setting policy agendas
- formulating policies
- implementing policies
- evaluating the impact of policies (Haines, et al., 2004).

The WHO Zika Strategic Response Plan (2016) emphasized the importance of generating data and evidence needed to strengthen public health and community guidance and interventions to prevent, detect and control Zika virus infection and manage its complications. However, Black (2001) sounds a note of warning by adding that while there may be extensive research on the effectiveness of healthcare interventions, there is often less evidence on their cost effectiveness, implementation, cultural appropriateness and effects on health inequalities, all of which are important considerations for policy-making. Black (2001) warning notwithstanding, since there is the potential for health improvements gains, which results from the utilization of research evidence to inform public health policies, finding cost-effective ways of promoting the uptake of research evidence-informed interventions should be a priority for researchers, practitioners and policymakers alike (Haines, et al, 2004).

Also, a systematic review on the use of research evidence to inform public health policies and practice found that it is the most direct means of interaction with researcher practitioners and policymakers and most influential facilitator of research uptake for policy (Innvaer, et al., 2002). Systematic methods for appraising and collating evidence have been developed in recent decades in response to calls for evidence to support public policy decisions. The origin of systematic review of evidence could be traced to the late 1970s and early 1980s when a group of health service researchers in Oxford prepared the ground for evidence-based medicine by beginning a programme of systematic reviews on the effectiveness of health care interventions culminated in the Cochrane Collaboration. Cochrane opened its centre in Oxford in 1992 and has since become an international network of researchers, academics, practitioners and users committed to the principles of managing healthcare knowledge in such a way that it is quality assured, accessible, and cumulative (EPPI, 2017). The use of systematic review methods for appraising and collating evidence to support public health policy and practice decision is widely recognised. Some scholars have stressed the need for systematic reviews with frequent updating and open dissemination for the appraisal of the evidence

about Zika virus infection and for the next public health threats that will emerge (Krauer, et al., 2017).

Furthermore, the goal of CDC (2016) vector control/intervention in priority areas or populations at risk has been to suppress Zika virus transmission if local cases or an outbreak is detected. The following actions are recommended for State, Tribal, Local, and Territorial Health Officials to take in formulating public health policies and practices:

- Establish a communication network with vector control/surveillance partners.
- Develop and implement a plan to establish or enhance local vector surveillance and control, especially in jurisdictions where *Aedes aegypti* and *Aedes albopictus* are endemic.
- Identify, and train if necessary, partners to fill gaps in vector control coverage in the event local mosquitoes become infected with Zika virus.
- Educate communities on how to reduce vector populations through source reduction.
- Educate communities on how to protect themselves using personal protection and primary mosquito prevention methods.
- Provide vector guidance and vector control services to pregnant women in high-risk areas.

A synthesis of published literature with a focus on the evidence that would help determine the effectiveness of these proposed vector control measures is essential. For example, a meta-review aimed at assessing the effectiveness of any *Aedes* control measure as a means of tackling the public health threats posed by the Zika virus found that there is renewed interest in effective measures to control Zika and dengue vectors. The reviewer added that a synthesis of published literature with a focus on the quality of evidence is warranted to determine the effectiveness of any vector control strategies. The review authors argued that various strategies for the control of mosquito-borne diseases exist and have been used for decades. They added the effectiveness of the vector control measures had been evaluated in several systematic reviews, but their conclusions were contradicting. The reviewers further argued that the current Zika virus outbreak in the Americas renewed the global health community's interest in the control of *Aedes* transmitted diseases and called for evidence through a systematic review that would help determine the effectiveness of such control measures (Bouزيد, et al., 2016).

Another review study published in the New England Journal of Medicine demonstrated that availability of research evidence helped to progress the public health response to the outbreak of Zika virus disease in the following areas:

- the distribution of health messages about the importance of mosquito-bite prevention;
- recommendations by public health authorities in some of the most severely affected countries to delay pregnancy;
- and advise that pregnant women avoid travel to areas with active Zika virus transmission (Rasmussen et al., 2016).

Rasmussen et al., (2016) advocated for the use of research evidence to advance the course of public health but argued that there is some occasion where good evidence is totally ignored. For example, by the evidence from the literature reviewed for this book; it came to light that Zika virus may not be regarded as the only causative agent in cases of microcephaly in Brazil, Cape Verde and elsewhere. Despite the evidence that abounds in literature, the USA National Institutes of Health (NIH) recently announced that it launched a clinical trial of an experimental Zika virus vaccine (USA Health News, 2016). In a separate study, another team of scientists at Washington University School of Medicine identified a human antibody that prevents the fetus from becoming infected with Zika in pregnant mice. The antibody also prevented damage to the placenta and prevented adult mice from getting Zika infections. The research was in mice, so it can not directly translate to humans, but it does suggest that a vaccine against Zika could spur protective antibodies that not only prevent people from getting the virus but could protect a pregnant woman's fetus (Bhandari, 2016). However, these

studies are ignoring the emerging evidence and rushing to develop a vaccine before there is conclusive proof that Zika virus causes microcephaly leading birth defects. There is also clear evidence that experimental vaccines have real health risks, which are often down played in the wake of perceived global "emergencies" of a pathogen such as Zika virus (USA Health News, 2016).

The World Health Organisation is better placed to identify critical areas of public health research; implementation and coordination of global fight against the Zika virus epidemic. Thus, this chapter explored WHO's Zika Virus Research Agenda, which sets out to support the generation of evidence needed to strengthen essential public health policies; actions to prevent; limit the impact of Zika virus and its complications. Also, as research and evidence are the foundations for sound health policies, the chapter explored systematic review of evidence and the use of research evidence to inform Zika virus related public health policies and practices. The use of research evidence to underpin public health policy is strongly advocated by both CDC and WHO. Some scholars on the hand expressed the view that there is a pressing need for research evidence to underpin public health decisions, which should not ignore the complex effects on health inequalities but lamented over the limited implementation of the evidence inform public health decisions.

Lastly, the history of public Health could be traced to 1848 when the secretary of the Poor Law Commission; Edwin Chadwick produced a report, which highlighted the outbreak of the second cholera epidemic in 1848. The disease outbreak was the main influence for the Public Health Act 1848 to be introduced culminating in the modern public health movement. With Robert Koch providing support in regards to the germ theory and identifying the bacteria that caused diseases such as tuberculosis in 1882 and cholera in 1884 progression was made in taking the necessary steps in order to develop public health whilst acknowledging the study of epidemiology and microbiology in public health and its importance in the move towards the public health policies being implemented (Morley, 2007). Since the outbreak in Brazil in 2015, Zika virus has been a major public health issue that is affecting the global community and demands effective public Health policy interventions to combat the global threat posed by the disease. Thus, the following chapter focuses on policy interventions aimed at preventing, management and vaccine development.

Chapter 6

Public Health interventions to prevent transmission of Zika virus

Public health is defined as all organised measures to prevent disease, promote health and prolong life among the population as a whole; whether public or private. The focus of public health is on the population as a whole to ensure conditions are met for people to be of good health. This is achieved by assessing and monitoring the health of individuals within the community and identifying the risks and problems in place that could hinder them from obtaining good health (WHO, 2016). Public health has also been described as the science of protecting the safety of the population and has a goal of improving the health of the community through research, education and assembling new policies. It allows policies to be designed with the intentions to improve the health and well-being of the community, prevents disease, minimising the consequences of such diseases, prolong the population's life and above all reduce the inequalities within the health care environment (Orme et al. 2007).

As noted earlier, Zika virus became public health emergency of international concern on February 1, 2016 (WHO, 2016). The recently confirmed cases of Zika virus related microcephaly in the African island chain of Cape Verde has been linked to cases of microcephaly leading birth defect in Brazil calls for urgent public health policy intervention. Although, new evidence is suggesting that there are other causes of the abnormalities found in the babies with microcephaly studies have consistently

proved a link between Zika virus and microcephaly (WHO, 2016). Thus, the striking emergence of cases of Zika virus related microcephaly in Africa poses a threat for a worldwide outbreak of the mosquito-borne viral supposedly causing birth defects (Wong, 2013). As WHO (2006) postulated, the failure of market forces to address effectively the health needs of populations places a duty on all governments to intervene to promote and improve the health of the populace. Thus, National Governments have a lot of “levers” at its disposal to try to mitigate further transmission of the Zika virus. For example, the government could use laws and regulations and other policy intervention strategies at a variety of levels to secure safer healthy behavior among the population (Lawrence and Gostin, 2000).

Public health interventions are often very complex, programmatic, and context dependent and evidence for their effectiveness must be sufficiently comprehensive to encompass that complexity (Rychetnik, et al., 2006). Issel (2014) describes intervention in general as a set of actions with a coherent objective to bring about change or produce identifiable outcomes. The actions might include policy, regulatory initiatives, single strategy projects or multi-component programs. Public health intervention, in particular, is intended to promote or protect the health or prevent ill health in communities or populations. Health policy, on the other hand, is being referred to as decisions, plans, and actions that are undertaken to achieve specific health care goals within a society (WHO, 2017). Health policies are essential as they set a general plan of action used to guide desired outcomes and are fundamental guideline to help make decisions (Leachy, 2017).

It is imperative to consider public health interventions in this book given the global public health threat posed by Zika virus and its health complications. Wong (2013) has already warned that the nations that are endemic for dengue, yellow fever and chikungunya are potentially at risk for Zika virus. This is because *Aedes aegypti* and *Aedes albopictus* are well-known vectors for dengue, yellow fever and chikungunya and are also known to transmit Zika virus. Mackenbach and McKee (2013) postulated that public health policy interventions function on some different levels that affect population's health. For example, public health policies can influence primary prevention which aims to avoid the occurrence of a disease by reducing exposure to health risks or secondary prevention, which aims to avoid the development of a disease to a symptomatic stage by diagnosing and treating the disease before it causes significant morbidity of the disease. In line with Mackenbach and McKee's postulation, this chapter focuses on primary preventive interventions; case management interventions and Zika virus vaccines development.

Primary preventive interventions

The current evidence, though not conclusive, suggests that pregnant women who contract the virus during pregnancy may have an increased risk of giving birth to a baby with microcephaly (2016). In this book, the importance of controlling the *Aedes aegypti* mosquito population while no vaccine or antiviral is available is highly recommended as part of Zika virus control intervention policy. The people whose travel is unavoidable to countries where Zika virus is prevalent should be advised to take scrupulous insect bite avoidance measures, both during daytime and night time hours; especially during the mid-morning and late afternoon to dusk, when the *Aedes aegypti* mosquito mosquitos are most active (PHE, 2016, Icheku, 2016). They should also be advised to use insect repellent that contains N, N-diethyl-meta-toluamide (DEET) on exposed skin. The repellent is considered safe to use even if they are pregnant and could be applied to the skin after sunscreen is used. They should also include sleeping under a mosquito net and wearing loose clothing that covers the arms and legs (NHS Choices, 2016). Travelers with immune disorders or severe chronic illnesses are advised to consult their doctors or seek advice from a travel clinic before traveling, particularly about effective prevention measures. Similar protective measures should apply to symptomatic patients to prevent human-to-mosquito-to-human transmission (ECDC, 2016).

The people who are concerned about trying to get pregnant and have a history of travel to the Zika virus-affected countries should be advised to see their General Practitioner (GP) or midwife and mention their travel history even if they are feeling well. Given that there is clear evidence of a well-established association between travels and the acquisition or transmission of infectious diseases, individual who are concerned about travel to Zika affected area while pregnant should be advised to see their GP or midwife and mention their travel history; within two weeks of returning to the United Kingdom. The GP or the midwife should discuss the risk with them and arrange an ultrasound scan to monitor the growth of their baby. The GP or midwife may also make referral to a specialist foetal medicine service for monitoring or order for blood test if Zika virus infection is suspected. Referral should also be made to a maternal-foetal medicine or infectious disease specialist with expertise in pregnancy management. Those pregnant with laboratory evidence of Zika virus in serum or amniotic fluid should include serial ultrasounds to monitor fetal anatomy and growth every 3–4 weeks (Petersen, 2016, Icheke, 2016).

The US Centers for Disease Control and Prevention position is that all pregnant women should be advised to refrain from traveling to countries affected by Zika virus. This is based on the inconclusive evidence suggesting a link between Zika virus infection with microcephaly and other neurological disorders (Petersen, 2016). Similarly, the UK National Health Services current position is that women who are pregnant or planning to become pregnant should be advised to discuss their travel plans with appropriate health care professional (NHS Choices, 2016). All women who are pregnant or planning to become pregnant during impending travel to areas where Zika virus is prevalent should be strongly advised to seek pre-travel advice so that an informed decision can be made on whether or not to change the travel plans. Women who are not pregnant should be advised to consider using contraception during travel and for 28 days on their return to avoid an unplanned pregnancy occurring (NHS Choices, 2016, Icheke, 2016).

Much as sexual transmission of Zika virus is thought to be low, Zika virus has been known to be present in semen up to two weeks after recovery from the virus infection (UK Gov. Travel Health Pro, 2016). Sexual transmission of Zika virus through semen has been documented, therefore practicing safer sex (including the use of condoms) is recommended throughout pregnancy to protect the fetus (ECDC, 2016). Also, the British Medical Association (BMA) recommended that male partner arriving from Zika affected area should be advised to use a condom if their female partner is at risk of getting pregnant, or is already pregnant; for the following durations:

- For 28 days after his return from a Zika virus affected area if he has not had any symptoms compatible with Zika virus infection. The 28 days represents an estimated 14 days incubation period plus an estimated 14 days period of viremia
- For six months following recovery if a clinical illness is compatible with Zika virus infection or laboratory-confirmed Zika virus infection was reported (BMA, 2016).

Until the obvious association between Zika virus infection and microcephaly is either established or disproved, the above primary precaution must be taken. Also, an effective approach to surveillance of infection among pregnant women, at least in current endemic regions, should be initiated (Petersen, et al., 2016). Health care professionals should be vigilant for any increase of neurological and autoimmune syndromes in both women and children or congenital malformations in new born infants (Icheke, 2016).

As noted earlier, people infected with Zika virus will have no symptoms or fall ill; one in five of the people infected with the disease become symptomatic. Thus, the performance of RT-PCR (test) is required on serum specimens collected within the first week of suspected case of Zika virus infection as a precautionary measure. After the onset of the virus infection, Immunoglobulin M and neutralizing antibody testing should be performed on specimens collected ≥ 4 days. However, the Zika virus IgM antibody assays can be positive due to antibodies against associated flavivirus such as

dengue and yellow fever viruses. A virus-specific neutralization testing provides added specificity but might not discriminate between cross-reacting antibodies in people who have been previously infected with or vaccinated against the associated Flavivirus (CDC, 2016, Icheku, 2016).

Lastly, the issue of Zika virus transmission through blood transfusion should be considered as part of the primary intervention measures. CDC (2017) postulated that the current blood donor screening by a questionnaire, without a laboratory test, is insufficient for identifying Zika-infected donors in areas with the active mosquito-borne transmission of Zika virus due to the high rate of asymptomatic infection. One of the most important aspects of blood safety is making sure that donated blood does not cause harm to the recipient. Thus, Marano, et al., (2015), recommended a stringent safety policy for managing blood and blood products in addition to an effective implementation measures that must also be established and practiced. CDC (2016) plays an important role in keeping the blood supply safe by developing an Investigation Toolkit: *Transfusion-Transmitted Infections (TTI)* to assisting state and local health departments and hospitals to ensure that donated blood are safe for transfusion. The World Health Organisation should encourage member states to promote the use of such Toolkit in their fight against the public health threat posed by Zika virus.

Secondary preventive interventions

There is no cure, no vaccine treatment as yet for Zika virus. Thus, World Health Organization in its Handbook proposed Integrated Vector Management (IVM), which was originally advocated as a method of combating *Aedes aegypti* mosquito transmission of dengue but would also, be an appropriate strategy for Zika virus (WHO, 2012). The European Centre for Disease Prevention and Control (ECDC) endorsed integrated management approach that is aimed at reducing mosquito vector density in a sustainable manner as of paramount importance (ECDC, 2016). Integrated Vector Management has been described as a deliberate, rational decision-making process aimed at the optimal use of resources for vector control. The implementation of integrated management approach requires evidence-based selection and delivery of different interventions or combinations of different interventions that are informed by, and thereby tailored to, local settings (WHO, 2012).

ECDC (2016) stated that intersectoral collaboration and efficient public communication strategies that ensure community participation are required for sustainable vector control programs. The program activities aimed at supporting the reduction of mosquito breeding sites in outdoor and indoor areas should include:

- draining or discarding sources of standing water at the community levels
- removal of all open containers with stagnant water in surrounding environment on a regular basis e.g. flower plates and pots, used tires, tree holes, and rock pools), or, if that is not possible, treatment with larvicides,
- tight coverage of water containers, barrels, wells and water storage tanks, and the wide use of physical barriers that reduce the risk of exposure to mosquitos bites (ECDC, 2016).

As there is no specific prophylactic treatment, differential clinical diagnostic should be considered as well as co-infection with other mosquito-borne diseases such as dengue fever, chikungunya, and malaria. As noted earlier, the current treatment is symptomatic and mainly based on a good hydration, pain relief, and anti-histamines for the pruritic rash. Treatment with acetylsalicylic acid and no-steroidal anti-inflammatory drugs should be discouraged if the diagnosis of dengue is not excluded because of a potential increased risk of haemorrhagic syndrome. Acetylsalicylic acid should also discourage because of the risk of Reye's syndrome after viral infection in children and teenagers (ECDC, 2016).

Lastly, CDC (2017) citing WHO (2017) recommended low technology intervention that focuses on vector control such as insecticide spraying, limit mosquito breeding and providing protection from mosquito bites as the best measures in the fight against Zika virus infection. Some scholars stated that such measures are short-term interventions aimed at the management of the Zika virus epidemic in the Americas. The scholars added that any intervention for prevention of a global pandemic must include effective vaccine development (Gyawali, et al., 2016). Thus, as an effective vaccine is crucial in the fight against the Zika virus infection, the next section in this chapter will examine current Zika virus vaccines development.

Current Zika virus vaccines development

This book has successfully documented global transmission and distribution of Zika virus and its association with increased rates microcephaly leading to birth defects and Guillain-Barre Syndrome in adults. The public health implications highlighted by the increasing cases of microcephaly and Guillain-Barre Syndrome has created an urgent need for Zika virus vaccines development. This section aims to examine the scope of current research to develop vaccines for the future treatment of the Zika virus.

The battle to develop a vaccine against Zika began in 2016, the year Zika virus emerged as a global public health threat of international concern (WHO, 2016). An article published in the British Medical Journal stated the race to develop a vaccine against Zika began in February 2016, when the unusual clustering of cases of microcephaly and other neurological disorders associated with Zika virus infection led to the declaration of a public health emergency of international concern. As shown in figure 6.10, 14 active vaccine projects were announced when the World Health Organization held its first consultation in March 2016 (Hombach, et al., 2016). Subsequently, WHO established pipeline tracker that attracted about 30 active projects, pursued by developers from endemic and non-endemic countries, private and public sector. In addition, institutions such as CureVac, Geovax, GlaxoSmithKline, Institut Pasteur, Johnson & Johnson, Merck, Oxford University, PaxVax, Pfizer, Profectus Biosciences, Protein Sciences, Semantics, Sinergium, Takeda have communicated their active consideration of the field or have committed planning/discovery stage activities to the World Health Organisation (2016).

Figure 6.10: Active Zika virus vaccines' projects

Institution	Technology	Status & timelines	Collaboration
Bharat	Inactivated purified virus as priority project; VLP with pRME protein	Preclinical work is ongoing, GMP lots 3Q2016	
Bio-Manguinhos / Fiocruz	Inactivated purified; YF17DD chimeric; VLP; DNA	Work initiated	Under consideration
Butantan	Live dengue recombinant; inactivated purified	Work initiated	Collaboration with US NIH
US CDC	DNA plasmid expressing VLP; live recombinant adenovirus	Work initiated	
Hawaii Biotech	Insect cell line produced recombinant proteins plus Alhydrogel or proprietary adjuvant for collaborator	Work initiated. GMP lots 4Q2016	Under discussion
InOvivo/GeneOne	DNA – electroporation; work initiated	Preclinical work initiated	
Institut Pasteur	Lentivirus-vectored, measles	Work initiated	Measles vectored

	vectored		work in collaboration with Themis
New Link	Purified Inactivated virus	Work initiated, clinical evaluation 2018	
US NIH	Zika targeted mutation live attenuated (longer-term), DNA, live VSV recombinant	Work initiated	Various
Novavax	E protein – nanoparticles	Preclinical work initiated	
Replikins	Synthetic reply link peptides	Preclinical work initiated	
Sanofi	ChimeriVax (YF17D); other undisclosed technologies	Work initiated	Under consideration
Themis Bioscience	Measles vaccine virus vector (live)	Work initiated	Institut Pasteur
Valneva	Purified inactivated vaccine	Work initiated	

Source: WHO (2016) Current Zika Product Pipeline, 3 March 2016

<http://www.who.int/csr/research-and-development/zika-rd-pipeline.pdf?ua=1>

WHO/UNICEF (2017) state in a recent that although, the epidemiology of Zika virus infection in the aftermath of large epidemics such as has occurred in Latin America is currently unknown, there are likely to continue to be outbreaks in the coming years in populations with low immunity. WHO/UNICEF (2017) warned that such outbreaks could occur in Latin America or other parts of the world, such as Asia and Africa and will continue put susceptible populations at risk. Thus, in collaboration with UNICEF and a working group of independent subject matter experts developed a Zika virus vaccine target product profile (TPP) for use in an emergency, or in a future outbreak. The primary public health objective of the TPP is to prevent prenatal Zika virus infection, associated microcephaly, other nervous system malformations and pregnancy-related complications. Other populations, in particular men, may be included in emergency vaccination campaigns, if vaccine supply permits. The TPP was revised in February 2017 taking into consideration new data that emerged since the original document was published in mid-2016 (WHO/UNICEF, 2017).

A recent study found that research is urgently required to address the severe clinical complications associated with the disease infection, including microcephaly and Guillain-Barre Syndrome. The key to this effort is the development of well-characterized animal models that recapitulate human disease (Smith et al., 2017). A new study published in PLoS Pathogens found that neonatal mice strain is susceptible to the Zika virus infection and develop neurological symptoms 12 days post infection. The mice eventually recover from the disease and thus the model provides an opportunity to study the virus' long-term effects as well as an additional means for early exploration of experimental Zika virus vaccines (Manangeeswaran, et al. 2016). However, some scholars pointed out that the major limitation with Zika virus mouse models is that they utilize immunodeficient mice, which lack a key component of antiviral immunity which impairs comprehensive evaluation of medical counter measures (Smith et al., 2017). Dawes, et al., (2016) maintained that more studies are required before conclusions can be made on potential Zika virus mouse models.

Live attenuated vaccines (LAVs) provide some hope for Zika virus vaccine given that it offers protective immunity after one or a few doses because of multiplication of the vaccine in the host, which stimulates T and B cells (Dawes, et al., 2016). However, LAV's effectiveness is limited safety issues; there is always a risk of reversion to virulence (Ulmer, et al., 2006). This limitation may have

prompted Dawes, et al., (2016) to express their doubt over the likelihood of LAV becoming an effective Zika virus vaccine. DNA vaccines seem to offer more hope for Zika virus vaccine as it provides a platform that induces robust cellular and humoral immune responses in small animals and non-human primates but yet to show promising results in limited clinical studies (Dawes, et al., (2016).

The development of a Zika virus vaccine started well, but all players need to keep up the momentum if a vaccine is to become a reality within the next three to five years (Hombach, et al., 2016). With most of the research institutes and companies that are involved in the production of the Zika virus vaccine working at the nonclinical level, the development Zika virus vaccine is still a long way ahead (Maurice, 2016). Some scholars argued that even if nonclinical studies are addressed leading to the production of the Zika virus vaccine; the implementation of clinical trials may be logistically difficult because of the sporadic nature of arboviral outbreaks. The scholars also express concern over the use of Zika virus vaccine to protect pregnant women due to the association of Zika virus infection with fetal neurological defects such as microcephaly. They maintained that pregnant women are a special population, and therefore any Zika virus vaccine will need to undergo appropriate nonclinical and clinical safety testing before undergoing trials with pregnant women (Dawes, et al., 2016).

Lastly, in support of Gyawali, et al., (2016), this book recommends research strategies for prevention of a global Zika virus pandemic but argues that effective vaccines development is crucial in the fight against the Zika virus infection. The important questions readers of this section may ask are: what happens if a future Zika virus vaccine is produced? Is it going to be used only during outbreaks to protect women of childbearing age and their babies, or should it be incorporated in routine vaccination programs? Answers to these questions will not be available for more detailed information on the evolving epidemiology of the Zika virus, the risk and scale of neurological outcomes and the level of herd immunity induced by the first wave of infection are known (Dawes, et al., 2016).

Summary and conclusion

In summary, this book has shown that Zika virus was first isolated from a monkey in East Africa in the late 1940s. The disease was reported in countries in Africa and some parts of Asia between 1952 and 1981. In 2007 the first epidemic outside of Africa and Asia was reported in the Yap islands of Micronesia. Between 2013 and 2014, there was a large outbreak of Zika virus, which occurred concomitantly with a dengue epidemic in French Polynesia. The *Aedes* mosquito-borne Zika virus infection cases were reported on Easter Island in 2014 and caught global attention due to its rapid spread in Brazil and subsequently to other American countries and territories in 2015. The Zika virus outbreak in the Americas has been associated with a significant increase in microcephaly, in which babies are born with abnormal small head and often has brain damage. The rapid increases in cases of microcephaly were quickly linked to the Zika virus and had been declared a 'Global Emergency by the World Health Organization (Petersen, 2016).

The WHO (2016) recent reported cases of Zika virus related microcephaly in African for the first time is a major concern and raises the question if Zika virus is the definitive culprit in the cases of microcephaly, why are there no similar epidemics in Africa where the virus was discovered in 1947? This book argues that Zika virus may not be, per se, the only etiological agent responsible for microcephaly and proffer the following three possible explanations for the absence of Zika virus related microcephaly in Africa:

- The chemical, Pyriproxyfen, used in a State-controlled program aimed at eradicating disease-carrying mosquitoes. Pyriproxyfen is a growth inhibitor of mosquito larvae, which alters the development process from larva to pupa to adult mosquito, thus generating malformations

in developing mosquitoes. It is an endocrine disruptor and is teratogenic that causes birth defects and may explain increasing malformations detected in thousands of babies from pregnant women living in areas where the Brazilian state was adding Pyriproxyfen to drinking water (Bowater, 2016, Science Daily, 2016).

- The existence of inequalities in the low-income countries in Americas and Africa. Health experts in both Brazilian and Argentine argued that poverty and other social and economic factors are key issues that are ignored in Zika virus related microcephaly narrative and accused their respective governments of deliberately concealing the social and economic factors in the microcephaly's narrative (Robinson, 2016).
- The likelihood that herd immunity occurred in Africa may also explain why the Zika virus has been in Africa for almost seven decades without any documented link to microcephaly. Herd immunity may have provided protection against the Zika virus in Africa when a significant percentage of the population has become immune to the disease, thereby providing a measure of protection for individuals who are not immune and thus decreasing the number of new infections (Geard, et al., 2016).

In conclusion, as an immediate response to the global health security threat posed by Zika virus, this book recommended primary preventive policy interventions such as the promotion of travel avoidance to countries where Zika virus is prevalent especially pregnant women or those planning to get pregnant; use of mosquitoes repellent; practicing safe sex, etc. As there is no cure, no vaccine or prophylactic treatment as yet for Zika virus, the book also recommended secondary interventions such IVM, reduction of mosquito breeding sites in outdoor and indoor and symptomatic treatment based on a good hydration, pain relief, and anti-histamines for the pruritic rash. Treatment with acetylsalicylic acid and no-steroidal anti-inflammatory drugs is not encouraged by this book if the diagnosis of dengue is not excluded because of a potential increased risk of haemorrhagic syndrome. Acetylsalicylic acid is also discouraged because of the risk of Reye's syndrome after viral infection in children and teenagers. Finally, as public health is the science of improving the health of a population through health promotion, research and control of diseases (CDF, 2016), this book recommended in addition to the above interventions, research inform public health policies and public health research to examine the clinical complications associated with the Zika virus infections (especially microcephaly and Guillain-Barré Syndrome).

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