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TOPIC:

ART OF TAMING OBLIGATE INVADERS THE BATTLE BETWEEN THE HOSTS AND THE DEADLY BUGS

By
PROFESSOR S. A. OMILABU

ART OF TAMING OBLIGATE INVADERS - THE BATTLE BETWEEN THE HOSTS AND THE DEADLY BUGS

An Inaugural Lecture Delivered at the University of Lagos Main Auditorium on Wednesday, 19th August, 2015.

By

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PROTOCOL

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Greatest Akokites;
My Lords, Spiritual and Temporal;
Gentlemen of the Press;
Distinguished Ladies and Gentlemen.

I give thanks and praises to the Almighty Allah, Most. Merciful and ever faithful for making this day a reality.

I wish to express my gratitude to the Vice-Chancellor for approving my choice of date for this inaugural, also for giving me the opportunity to deliver this lecture which is long overdue.

INTRODUCTION

Mr. Vice-Chancellor Sir, this lecture titled, "**Art of Taming Obligate Invaders - The Battle between the Hosts and the Deadly bugs,**" is designed to highlight the role Virologists play in the battle between the hosts (Human, Animals, Insects, Plants, etc.) and the obligate invaders/deadly bugs called Viruses.

Mr. Vice-Chancellor, Sir, it is pertinent before I proceed with this enlightenment lecture to quickly highlight the following:

What are Viruses? When did Virology start? Battles between Viruses and their Hosts and the Tools Virologists use in Taming these Obligate Invaders.

1. What are Viruses?

Viruses are small infectious agents that are unique because they can only live and multiply inside the cells of other living things called the host cell. Most viruses are approximately one hundred times smaller than an average bacterium. They can infect all types of life forms, from animals and plants to microorganisms, including bacteria and Archea and they are found in almost every ecosystem on earth. These minute life forms are the most abundant type of biological entity. While not inside an infected cell; viruses exist in the form of independent particles.

These viral particles, also known as virions, consist of two or three parts: (i) the genetic material made from either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) - long molecules that carry genetic information; (ii) a protein coat that surrounds and protects the genetic material called the Capsid made of capsomere; and in some cases (iii) a viral wrapper - an envelope of lipids

that surrounds the protein coat when they are outside a cell. The shapes of these virus particles range from simple helical and icosahedral forms for some virus species to more complex structures for others (Figure 1).

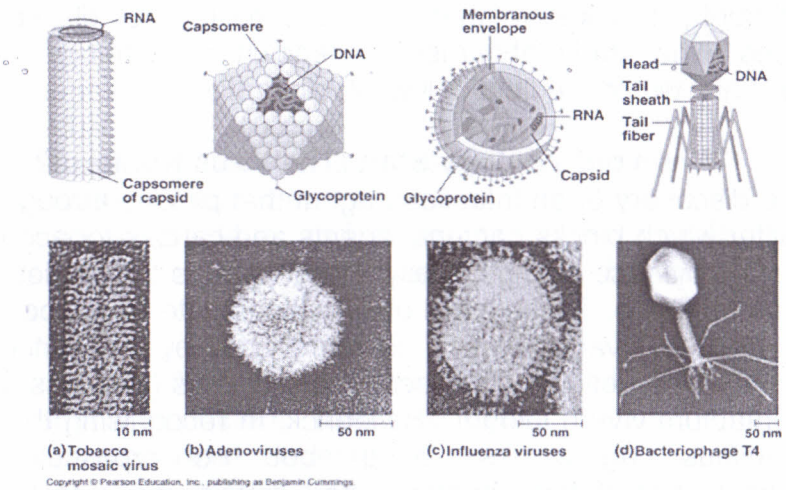


Fig. 1: Structure Composition and Shapes of Viral Particles

The common concept of viruses focus on their role as pathogen. Actually, there are vast numbers of viral entities that are beneficial to individual species as well as providing ecosystem services. For example, a class of viruses known as bacteriophages can kill a spectrum of harmful bacteria, providing protection to humans as well as other biota.

Viruses are key in the carbon cycle; their role in ocean biochemistry includes microbiological, metabolic, and decomposition processes. It is the decomposition process that stimulates massive carbon dioxide respiration of marine flora. That respiration annihilates effectively about three gigatons of carbon each year from the atmosphere. Significantly, viruses are being

developed as tools for constructive modern medicine as well as the critical field of nanotechnology.

Mr. Vice-Chancellor, Sir, approximately 5000 different viruses have been described in detail at the current time, although, it is known that there are millions of distinct types. The study of viruses is known as Virology, a specialty within the field of Microbiology.

2. When did Virology Start (The Virus Hunters)?

The discovery of an infectious agent that passes through a filter which blocks bacterial agents and causes tobacco mosaic disease was generally recognised as the earliest virus research. These initial observations date to a report in 1892 by Ivanovski and 6 years later by Beijerinck (1898), who described Tobacco Mosaic Virus (TMV) as a "contagium vivum luidum." Beijerinck, in recognising this infectious agent as living but noncorpuscular, distinguished it from bacteria, and considered it to be more complex in their organisation.

These moments in the history of virus research, and especially Beijerinck's work, are widely considered the start of virology. However, a curious paradox exists here. In 1953, the Australian Microbiologist and Immunologist; Macfarlane Burnet claimed that virology did not become an independent science until the 1950s. Scholarly activities during the 1950s certainly made it tempting to designate these years as the dawning period of virology. For instance, several journals dedicated to virology, including *ViroZogy* (1955), *Advances in Virus Research* (1953), *Voprosy Virusologii* (1956), *Acta Virologica* (1957), *Progress in Medical Virology* (1958), and *Perspectives in Virology* (1959), were started during this period. Moreover, the original edition of Salvador Luria's seminal textbook, *GeneraZ Virology,* was published early

during that decade. Critical to these conceptual developments was the widely accepted realisation that viruses replicate within host cells during a non-infectious phase, since then it had been known as the "eclipse" period.

On the other hand, a quarter century earlier, there had been a similar burst of scholarly activity, including publication in 1928 of the collection of essays, *Filterable Viruses,* edited by Thomas Rivers. During this earlier period, viruses were viewed as replicating in the same way as bacteria and other microorganisms by binary fission but differed from them by being, "filterable."

Mr. Vice-Chancellor, Sir, eventually, microbiologists realised that none of the viruses could be grown on ordinary nutrient media because they are obligate parasites that depend on host cells to replicate. An important practical breakthrough toward this realisation came from the early studies of Ernest Goodpasture; who grew fowl pox viruses on the chorioallantoic membranes of chicken embryos. Later, Macfarlane Burnet developed techniques for using other types of tissues and membranes as host cells for growing various viruses.

The seeming invisibility of viruses eventually fell prey to better microscopes and newer techniques. In the 1920s and 1930s; dark field illumination and UV microscopy enabled some of the larger viruses to be visualised, for example, Joseph Barnard in England used UV microscopes to view several of the poxviruses during this period.

Also during this era, several investigators began using newly available ultracentrifuges to study the filterable viruses. From such studies, Wendell Stanley compared

the sizes of selected viruses and those of various bacteria and proteins. On the basis of such comparisons, investigators came to understand that viruses have discrete sizes, ranging from that of the smallest bacteria to two - to threefold larger than several proteins found in serum.

On the whole, Tables 1 and 2 below gives a summary of the different eras and land mark achievements in Virology research.

Table 1: Eras in Virology

Era	Years	Description[a]
Protovirology	1796–1885	Before viruses were recognized
Auroravirology (named for the Roman goddess of dawn)	1892–1933	Dawn of virology
Meridiovirology (from Latin for midday, sequel to dawn)	1934–1955	From the demonstration that bacteriophages are composed of protein and nucleic acid and the crystallization of TMV to the in vitro assembly of infectious TMV from purified RNA and protein
Ianovirology (named for the Roman god of endings and beginnings)	1956–1975	Spans the interval between classic virology and the beginning of the era dominated by viral sequence information; encompasses the elucidation of essential features of gene structure, expression, and regulation and the development of essential techniques, including cloning and restriction sequence mapping
Neovirology	1976–present	Begins with the first complete sequencing of viral genomes and atomic resolution structures of intact viruses

[a] TMV, tobacco mosaic virus.

Table 2: Landmarks in Virology Research

Era and year	Landmark (virus or scientist)
Protovirology	
1798	Cowpox lesions used to vaccinate against smallpox (Jenner)
1882	Transmission of tobacco mosaic disease with cell-free extracts (Mayer)
1885	Development of rabies vaccine (Pasteur, Roux)
Auroravirology	
1892	Description of filterable infectious agent (TMV) (Ivanovsky)
1898	Development of concept of virus as contagious element (TMV) (Beijerinck)
	Discovery of first animal virus (FMDV) (Loeffler, Frosch)
1901	Discovery of first human virus (yellow fever virus) (Reed)
1903	Discovery of rabies virus (Remlinger, Riffat-Bay)
1908	Discovery of first leukemia-causing virus (Ellerman, Bang)
1909	Discovery of poliovirus (Landsteiner, Popper)
1911	**Discovery of first solid tumor virus (RSV) (Rous)**
	Discovery of measles virus (Goldberger, Anderson)
1913	Virus cultivation in tissue culture (VV) (Steinhardt, Lambert)
1915	Discovery of bacterial viruses (bacteriophages) (Twort, d'Hérelle)
1917	Development of the plaque assay and discovery of the particulate nature of viruses (bacteriophage) (d'Hérelle)
1931	Propagation of virus in embryonated chicken eggs (Woodruff, Goodpasture)
1932	Discovery of first mammalian tumor virus (MMTV) (Little, Bittner)
1933	Discovery of human influenza virus (Smith)
	Discovery of rabbit papillomavirus (Shope)
	First description of viral mutants (TMV) (Jensen)
Meridiovirology	
1934	Discovery that bacteriophages are composed of protein and nucleic acids (Schlesinger)
1935	**Crystallization of TMV (Stanley)**
1938	**Development of yellow fever vaccine (Theiler)**
	Use of electron microscopy for viruses (TMV) (von Borries, Ruska, Ruska)
1939	Description of one-step growth cycle (bacteriophage) (Ellis, Delbrück)
1941	Discovery of first virus-associated enzymes (influenza virus) (Hirst)
1943	**Discovery of genetic origins of mutations (bacteriophage) (Luria, Delbruck)**
1945	Development of influenza vaccine (Francis)
1946	Discovery of genetic recombination by bacteriophage (Delbruck)
	Replication of poliovirus in nonneuronal cell cultures (Enders, Weller, Robbins
	Discovery of eclipse phase of virus infection (bacteriophage) (Doermann)
1951	Discovery of bacteriophage λ (E. Lederberg)
	Discovery that lysogenic phages produce diphtheria toxin (Freeman)
1952	**Plaque assay of animal virus (poliovirus) (Dulbecco)**
	Discovery that viral genome is nucleic acid (Hershey, Chase)
	Transduction of genetic information by bacteriophage (Zinder, J. Lederberg)
1953	Discovery of host-controlled restriction and modification (Luria, Bertani, Weigle)
1954	Development of polio vaccines (Salk, Sabin)
1955	Culture of human cells (HeLa) (Gey)
	Optimization of cell growth medium (Eagle)
	Definition of a gene (*cis-trans* test) (bacteriophage) (Benzer)
	In vitro assembly of infectious virus (TMV) (Fraenkel-Conrat, Williams)
Janovirology	
1956	Discovery of mRNA in bacteriophage infection (Volkin, Astrachan, Brenner, Jacob, Meselson)
	Discovery that virus particles are composed of identical subunits (Watson, Crick)
	Discovery that RNA can carry genetic information (TMV) (Schramm, Fraenkel-Conrat, Williams)
1957	Discovery of interferon (Isaacs, Lindemann)
	Discovery of respiratory syncytial virus (Chanock)
1958	**Discovery of bacteriophage λ regulation paradigm (Pardee, Jacob, Monod, Lwoff)**
1960	Discovery of SV40 (Sweet and Hilleman)
	Demonstration of the triplet nature of the genetic code (bacteriophage) (Crick)
	Elucidation of nonsense codons (bacteriophage) (Campbell, Epstein, Bernstein)
1962	**Studies of virus structure (Klug, Caspar)**
1964	Demonstration of the colinearity of gene with polypeptide chain (bacteriophage) (Brenner)
	Discovery of first human tumor virus (EBV) (Epstein, Barr, Burkitt)
1965	Autocatalytic in vitro synthesis of bacteriophage DNA (Spiegelman)
1966	**Experimental transmission of spongiform encephalopathy to primates (kuru) (Gajdusek, Gibbs, Hadlow)**
1967	**Discovery of hepatitis B virus (Blumberg)**
	Isolation of bacteriophage λ repressor (Ptashne)
	Discovery of viroids (Diener)
	Discovery of first virion-associated polymerase (VV) (McAuslan, Kates)
1970	**Discovery of retroviral reverse transcriptase (Temin, Baltimore)**

Table 2 Continued

Era and year	Landmark (virus or scientist)
1971	Discovery of RNA polyadenylation (Darnell, Edmonds)
1972	**Development of first recombinant DNA molecules (phage λ, SV40) (Berg)**
	Proposal that reassortment of influenza virus segments is the origin of pandemic strains (Webster, Laver)
1973	**Development of first restriction map (SV40) (Nathans)**
	Discovery of major histocompatibility locus restriction of viral antigen recognition (Doherty, Zinkernagel)
	Discovery of human rotavirus (R. Bishop)
1974	Development of first transgenic mouse (SV40) (Mintz)
1975	Discovery of mRNA capping (Shatkin, Moss)
Neovirology	
1976	First RNA virus genome sequenced (bacteriophage MS2) (Fiers)
	Demonstration that retroviral oncogenes are derived from cells (J. M. Bishop, Varmus)
1977	First DNA virus genomes sequenced (ΦX174, SV40) (Sanger, Fiers, Weissman)
	Discovery of RNA splicing (adenovirus) (Roberts, Sharp)
	Discovery of tumor suppressor p53 (SV40) (Levine, Crawford)
	Description of first virus crystal structure (TBSV) (Harrison)
1978	Development of the first infectious molecular clone of an RNA virus (Qbeta, Weissmann)
1979	Declaration of smallpox eradication by World Health Organization
	First in vitro replication of eukaryotic viral DNA (adenovirus, SV40) (Kelly, Hurwitz, Stillman)
	Development of first in vitro mRNA transcription system (adenovirus) (Roeder)
	Discovery of first highly active, template-specific, RNA-dependent RNA polymerase from a eukaryotic source (BMV) (Hall)
	Discovery of tyrosine kinases (Hunter, Erikson, Eckhart)
1980	Discovery of first human retrovirus (HTLV-1) (Gallo)
1981	Development of first infectious molecular clones of an animal RNA virus (poliovirus) (Baltimore)
	Discovery of transcriptional enhancers (Chambon, Khoury, Schaffner)
	Development of hepatitis B virus vaccine
	Identification of mammalian transcription factors (MMTV, SV40) (Yamamoto, Tjian)
	Discovery of insertional activation of cellular oncogenes by retroviruses (Hayward, Astrin)
	Identification of polyadenylation signal (Shenk)
	Discovery of the Cre/lox recombination system in phage P1 (Sternberg)
1982	**Development of antiviral and other drugs (Elion, Hitchings)**
	Definition of prions (Prusiner)
1983	**High-risk human papillomaviruses identified and linked to cervical cancer (zur Hausen)**
	Discovery of AIDS virus (HIV) (Montagnier, Barre-Sinoussi, Gallo)
1984	Discovery of nuclear localization signals (Smith, Butel)
	Production of first infectious, multicomponent virus from cloned DNA (BMV) (Ahlquist)
1986	Development of first recombinant viral vaccine (hepatitis B virus)
	Generation of transgenic virus-resistant plants (TMV) (Beachy)
	Discovery of hammerhead ribozymes (TRSV, ASV) (Bruening, Symons)
1988	Discovery that DNA virus oncogene products bind cellular tumor suppressor proteins (adenovirus, SV40, HPV) (Harlow, Weinberg, Livingston, Howley)
	Development of first ribozyme with engineered specificity (Haseloff)
	Discovery of internal ribosome entry sites (poliovirus) (Wimmer, Sonenberg)
1989	Discovery of hepatitis C virus (Houghton)
1990	Development of first human gene therapy with a retrovirus vector (Anderson, Blaese)
1991	Discovery of viral antiapoptotic proteins (baculovirus) (Miller)
1995	Development of HAART treatment for AIDS
1998	**Discovery of gene silencing by double-stranded RNA, an antiviral response (Fire, Mello)**
	Use of plant virion for synthesis of nanoparticles (Young)
	Discovery that plant viruses encode suppressors of RNAi (Vance, Baulcombe)
2001	Discovery of the caveosome (SV40) (Helenius)
2002	Worldwide outbreak and containment of SARS
2005	Reconstruction and sequencing of the 1918 influenza virus genome (Palese, Garcia-Sastre, Tumpey, Taubenberger)
2006	Development of vaccine against human papillomavirus, the first vaccine designed to prevent human cancer

3. Battles between Virus and Host

According to Sun Tzu in The Art of War, "All warfare is based on deception." A virus must infect, replicate and spread for it to survive with the host attempting to thwart it at every step of the way. This ancient battle has been waged for millions of years and has spawned an innumerable number of viruses, each with their own unique ways of trying to outsmart the host. Some viruses encode proteins that directly inhibit/degrade/alter host pathways and some simply have evolved ways to hide from the host's detection system. However, the host is

also not passive in this battle. It has evolved complex pathways and redundant mechanisms to respond to these viral interlopers.

Mr. Vice-Chancellor, Sir, in the last 70 - 80 years; Scientists have used viruses to illuminate many of the secrets that the host uses to fight back against the hoard. It was a virus that taught us about an "interfering" molecule that is secreted from cells during infection and can be used to then protect other cells around it from subsequent infections. This molecule known as Interferon has led to treatment of numerous viral and inflammatory diseases such as Hepatitis C, Multiple Sclerosis and Cancer. The more we understand how viruses interact with the host the more we can modify them for good; as vectors to deliver antigens such as, vaccines, gene therapy delivery vehicles and targeted cancer destroying missiles.

I know that we must be prepared for the next MERS-CoV or Chikungunya virus possible outbreak in Nigeria. The only question is, "Can we figure out their battle plans before it's too late?"

4. Tools Used for Taming Viruses

There are several different tools/methods used to study viruses and viral diseases, as the field of virology is constantly changing with the discovery of new methodologies and technologies. I will provide a cursory overview of the most commonly used techniques in diagnostic virology and virology in research. The following methods are commonly employed;

1. Isolation of Viruses
    a. Egg Inoculation
    b. Animal Inoculation
    c. Tissue Culture

2. Physical Methods
    a. X-ray Crystallography
    b. Electron Microscopy
    c. Ultracentrifugation

3. Serological Methods
    a. Haemagglutination (HA)
    b. Haemagglutination Inhibition (HI)
    c. Virus Neutralisation
    d. Complement Fixation

4. Immunological Methods
    a. Immunofluorescence
    b. Immunogold EM
    c. Immunoprecipitation
    d. Immunoblot
    e. Enzyme Linked Immunosorbent Assay (ELISA)

5. Molecular Biology Methods to Analyse Viral Proteins
    a. SDS PAGE
    b. Western Blot
    c. Protein Sequencing
    d. X-ray Crystallography

6. Molecular Biology Methods to Analyse Viral Genome
    a. Restriction Analysis
    b. DNA Sequencing
    c. Southern Blot
    d. Northern Blot
    e. Polymerase Chain Reaction (PCR)/RT-PCR
    f. Real Time PCR

Furthermore, since 1990s; the era to study an organism's entire genome called "Genomics era" began. This was not new to the field of Virology as complete viral

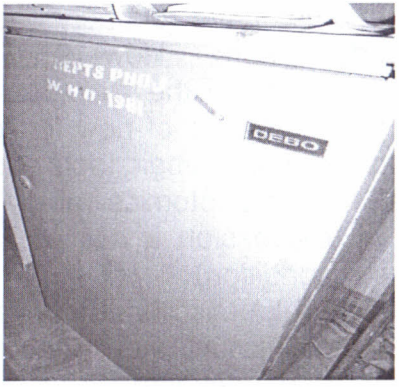
genomes have routinely been sequenced since the past thirty years. However, the genomics era has revolutionised the biological sciences and has heralded the emergence of new 'omics' methodologies which are also useful virologic tools such as;

a. Transcriptomics (study of the gene expression and expression levels of mRNAs at a given time and condition).
b. Proteomics (study of the entire protein content of a cell/tissue under various conditions, their structure and functions).
c. Metabolomics (study of the metabolite profile of different cellular processes).
d. Phosphoproteomics (a branch of proteomics that characterises proteins that are phosphorylated).
e. Interactomics/system biology (a science that unifies transcriptomics, proteomics and metabolomics to look at the organism as a whole), etc.

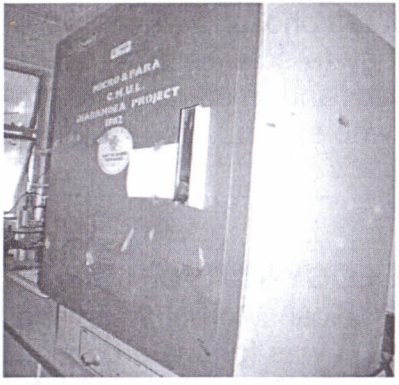
MODULE ONE

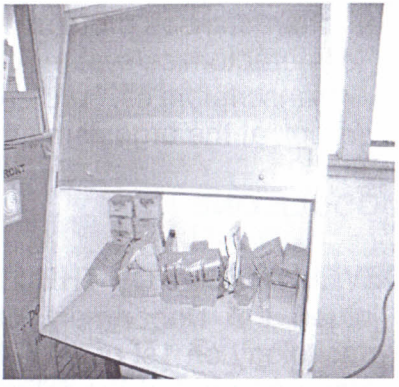
DEVELOPMENT OF THE VIROLOGY UNIT, C.M.U.L.

I joined the Department of Medical Microbiology and Parasitology on 1st of July, 1991. I was fortunate enough to have on ground the retinue of moribund and obsolete facilities for virological work. These facilities had been abandoned for over a decade. Thanks to the efforts of the two eminent Professors namely; Dosunmu Ogunbi and Njoku Obi (all of blessed memory) who pioneered the Virology Unit. The unit became abandoned following the exit of Prof. Njoku Obi in 1967 as a result of the Civil War and retirement of Prof. Ogunbi in the early 1980s. Some pictures of what I met are shown below.



Picture Plate 1a: Inverted Microscopes and Research Refrigerator Initially Present





Picture Plate 1b: Microbiological Incubator and Wooden Hood Initially Present

The task of reviving the Unit fell on me so I took the challenge very squarely. I started the cleaning of the two laboratories (Serology and Tissue Culture). I fumigated the Tissue Culture Room severally and I had to go to Ibadan to meet and discuss with my teachers and senior colleagues on how to make Lagos Virology Laboratory more functional. I got their support materially and spiritually. I also got the support from Prof. Abdul Salam Nasidi (The Head of the Federal Vaccine Production

Laboratories, Yaba). My first set of masters students in 1992 were taken to the laboratory in Yaba for their exposure to Tissue Culture. I cleverly designed their project work in Tissue Culture related areas.

Serological work was re-established in Idi-Araba in January, 1992. We started with ELISA kits for CMV and HSV 1 and 2; I added Neutralisation Assays using Tissue Culture Techniques. Both the M.Sc. and Diploma students in my unit were taken through this. I further added Compliment Fixation test to the serological work as student population increased in the unit. For the CFT to be functional I had to establish the Guinea Pig colony in our animal house. This was made possible by a student whose parents were raring Guinea Pigs. I successfully re-established the Tissue Culture Laboratory at Idi-Araba, in 1994. We were now maintaining the cells in our laboratory using it for students' projects and diagnostic requests.

The arduous tasks of reviving and establishing the virology laboratory components were shouldered by me and the pioneering students. A greater part of my salary and contributions from the students went into this; Virology Laboratory is quite expensive to maintain. The area is highly evolving, hence, the need for training and retraining of virologists. One important facility in virology laboratory is freezing equipment as viruses are better preserved frozen. When I joined the department in 1991, there was no functional freezer (even -20°C). We had to refurbish some abandoned carcasses. One of my students then (Bola Oyefolu) used his experience in refrigeration training to build a (-35°C) freezer in the laboratory. This freezer served us for more than three years and at a point in time, we had four refurbished deep freezers in our unit.

The Virology Unit in the Department of Medical Microbiology and Parasitology was now gaining recognition and reference. We were able to generate data especially on live viral vaccines used in Lagos State. We also provided diagnostic services to some Consultants at the Lagos University Teaching Hospital especially in the departments of Obstetrics and Gynaecology, Paediatrics and Medicine.

In 1996, we were fortunate enough to receive a team of virologists from Luxembourg; they were interested in Measles virus surveillance. Our laboratory started collaboration with the group; headed by Prof. C.P. Muller of the Institute of Immunology, National Public Health Laboratory, Luxembourg. Grants were secured after a year of our collaboration. This collaboration brought the much expected changes to our laboratory in terms of facilities and scope of laboratory diagnostics. Our Tissue Culture unit was now also well catered for. Facilities for respiratory tract viruses were developed and the laboratory was now able to involve students in more advanced diagnostic techniques in virology.

We started generating publications on the average of 2 papers in either International or National journals since 1996. My student (Dr. Bola Oyefolu) was the first to win the National Universities Commission (NUC), Best Ph.D Thesis prize in the Medical category for the University of Lagos in the year 2002. The NUC also awarded me the best Ph.D. Supervisor in Nigeria for the feat of being the first Virologist to locate our local wild measles virus strains in Nigeria which Dr. Bola Oyefolu obtained his Ph.D. on. Unfortunately, the University administration then did not recognise this as a feat for the student nor the supervisor. Thank goodness! The story has changed today, especially with the present university

administration's policy towards academic achievements by both the students and their supervisors.

Without being in-modest; my laboratory was the first to establish molecular diagnostics for notable viruses of public health importance in Nigeria. This was achieved in 2003 upon the award of Equipments Grant by the Alexander von Humboldt Foundation in Germany. These set of equipments actually revolutionised our laboratory in addition to other Grants jointly awarded by the Volkswagen Foundation and the German Research Foundation some years after. These sets of equipment also put my laboratory in a very good advantage to set our priorities aright as seen in the picture plate 2 below.

In terms of training and exposures; my students are well trained locally and they also get internal exposures. Our laboratory is always available for diagnostic services using molecular biology tools. The very recent one was the 2014 Ebola Virus Disease that sneaked into our country.

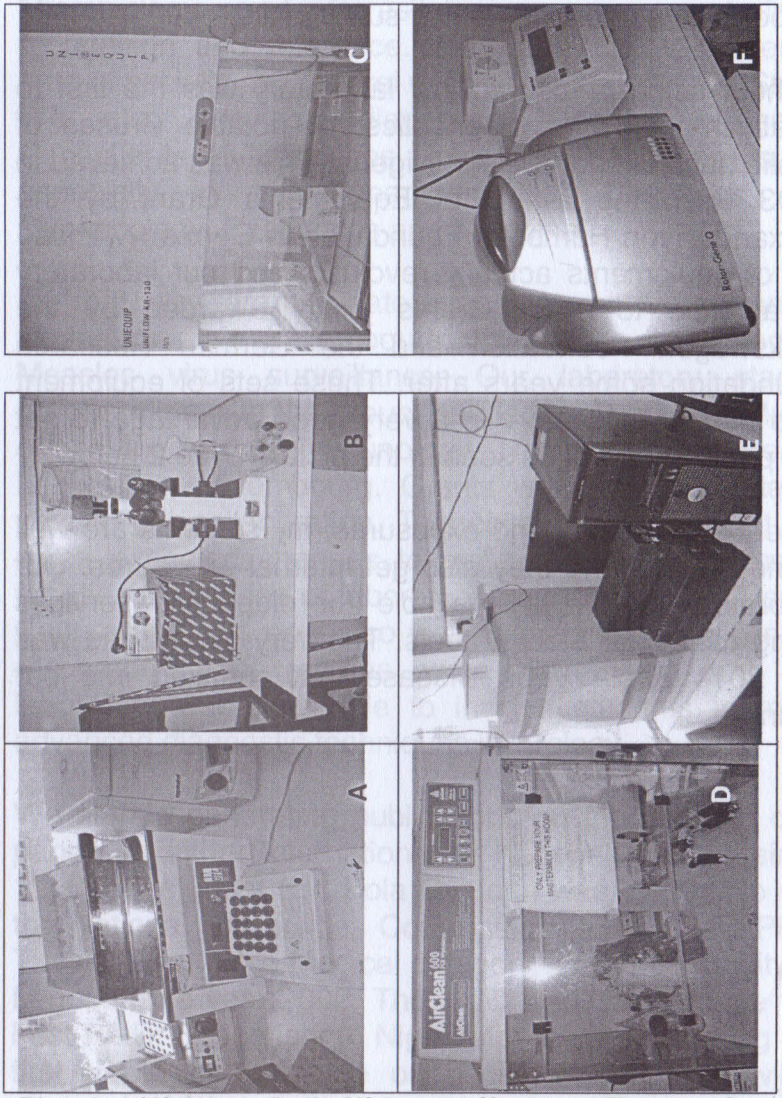
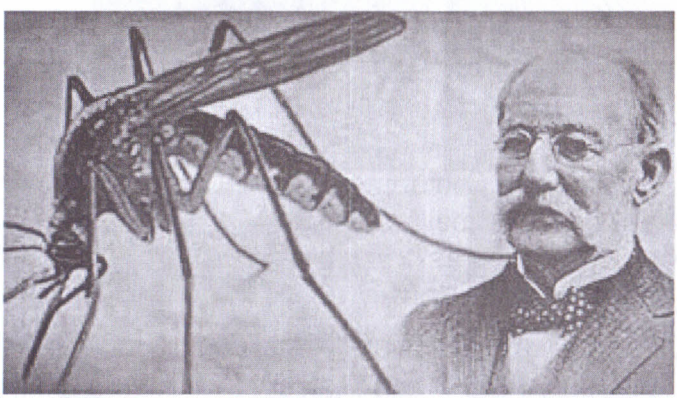


Plate 2: (A) Water Bath, Microcentrifuge and Thermomixers,
(B) Inverted Microscope and Tissue Culture Flasks,
(C) Class II Biosafety Cabinet for Sample Preparation,
(D) PCR Workstation for ReagentPreparation,
(E) ABI 7300 Real Time Machine,
(F) Qiagen Rotor-Gene Q Real Time Machine for VHFs.

Catching the Arthropod-borne Viruses (ARBOVIRUSES)

Arboviral (arthropod-borne) infections are caused by any number of viruses transmitted by arthropods such as mosquitoes and ticks. These infections generally occur during warm weather months, when mosquitoes and ticks are active. The connection of arthropods and disease was described when the Cuban doctor and scientist Carlos Finlay proposed that Yellow Fever may be transmitted by mosquitoes instead of human contact (Chaves-Carballo, 2005).

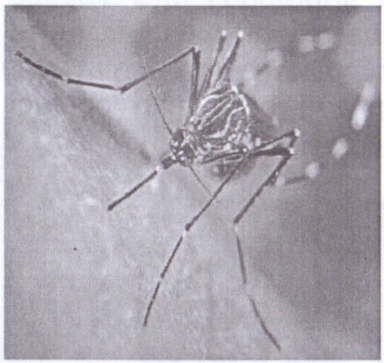


Carlos Finlay (1833-1915)
Pioneer Researcher in Yellow Fever

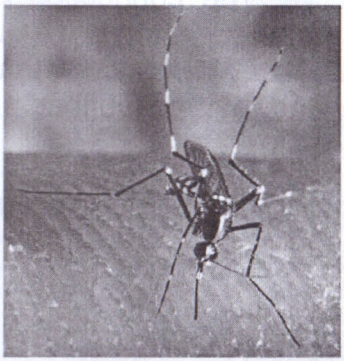
The primary vector, *Aedes aegypti*, had spread globally from the 15th to the 19th centuries as a result of globalisation and the slave trade (Simmons *et al.*, 2012). This geographic spreading caused Dengue fever epidemics throughout the 18th and 19th centuries, and later, in 1906, transmission by the *Aedes* mosquitoes was confirmed, making Yellow fever and Dengue fever the first two diseases known to be caused by viruses

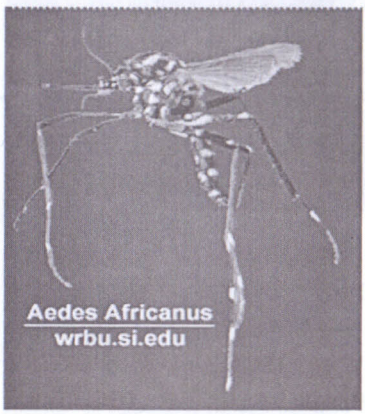
(Henchal and Putnak, 1990). The discovery of the West Nile virus came in 1937, and has since been found in Culex populations causing epidemics throughout Africa, the Middle East, and Europe. Humans are exposed to arboviruses when they invade rural environments or when sylvatic vectors bring viruses into peridomestic environments (Weaver and Reisen, 2010).

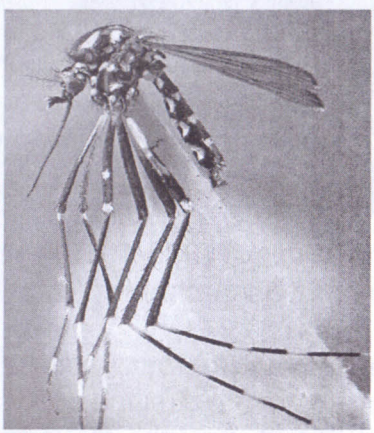
Aedes aegypti



Aedes albopictus







Aedes stegomyia

The arboviruses include a wide variety of alpha viruses (*Togaviridae*); the flaviviruses; Bunyaviruses and Orbiviruses (*Reoviridae*) as highlighted in Table 3. These

groups of RNA viruses have a variety of types of RNA genomes and replication strategies; suggesting that the arthropod-borne transmission strategy has arisen many times during the evolution of RNA viruses. The only known DNA arbovirus is the African swine fever virus (*Asfarviridae: Asfarvirus*) (Weaver and Reisen, 2010).

During the years 1964 to 1970, 171 arboviruses of 15 different types were isolated from humans in Nigeria. Isolation rates were highest in 1969 and lowest in 1965 and 1967. Monthly arbovirus activity was highest in the rainy season months of June, July and August and lowest in the dry months of January and February.

Viruses were isolated from all age groups, with the majority from children; one to four years old. The viruses isolated in largest numbers were *chikungunya* and yellow fever, which caused epidemics in 1969, and dengue types 1 and 2 and *Tataguine*, which are endemic in Ibadan. *Bwamba* virus was isolated in 1964 and 1969, and *Bunyamwera* group viruses were encountered for the first time in 1969. Other viruses recovered less frequently were Zika, Igbo-Ora (an agent related to o'nyong-nyong), two viruses related to the Uganda mosquito virus Ug MP 359, Dugbe, Thogoto, Lebombo and Shuni. Several of these are new agents and have not previously been isolated from man (Moore *et al.*, 1975). Thereafter, several works by Professors Fabiyi, David-West, Fagbami, Tomori, Olaleye, my humble self, Baba and many more have continued in the surveillance and taming of these highly pathogenic agents.

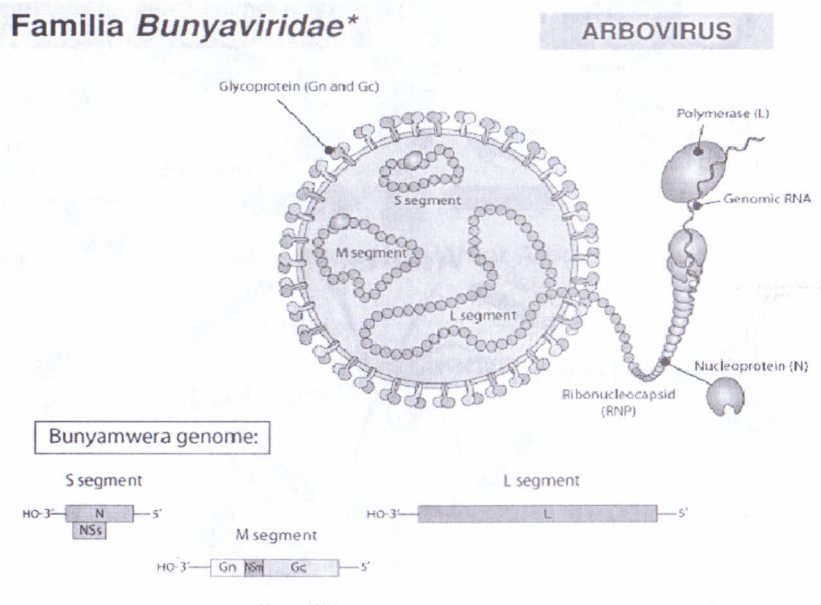
Table 3: Classification of Arboviruses

Family: Bunyaviridae	Family: Flaviviridae	Family: Reoviridae	Family: Togaviridae
Genus: Nairovirus Crimean Congo Haemorrhagic fever virus Dugbe virus Genus: Orthobunya virus Bunyamwera virus California encephalitis virus La crosse encephalitis virus Genus: Phlebovirus Rift Valley fever virus Toscana Virus Heartland virus	Genus: Flavivirus Tick-borne viruses Mosquito borne viruses Dengue Viruses I-IV Japanese encephalitis virus group Japanese encephalitis virus (JEV) Murray Valley encephalitis virus (MVEV) St Louis encephalitis virus (SLEV) West Nile virus (WNV) Yellow Fever virus group Yellow fever virus Wesselsbron virus Potiskum virus	Genus: Orbivirus African Horse Sickness virus Bluetongue disease virus (BTV) Equine Encephalosis virus (EEV) Genus: Seadornavirus Banna virus (BAV) Genus: Coltivirus Colorado tick fever virus (CTFV)	Genus: Alphavirus Eastern equine encephalitis virus (EEE) Ross River virus (RRV) Venezuelan equine encephalitis virus (VEE) Western equine encephalitis virus (WEE) Chikungunya virus (CHIKV) Igbo-Ora virus

Mr Vice-Chancellor, Sir, kindly permit me to briefly discuss some those arboviruses that have plagued Nigeria in the past.

BUNYAVIRIDAE

In Nigeria, many bunyaviruses have been isolated from man, animals, insects such as ticks and mosquitoes in which sero-surveillance studies have confirmed their presence in humans. They are negative sense single-stranded RNA viruses with three segments. Their nucleic acid is encapsulated by medium-sized, helical nucleocapsid surrounded by an envelope diameter of 80-



120 nm (Figure 2).

Figure 2: Structural and Genomic Structure of Bunyaviridae

Crimean-Congo Haemorrhagic Fever Virus

One of the members of the Bunyaviridae family is the Crimean-Congo haemorrhagic fever virus (CCHFV). It

was first discovered in 1944 in the Crimea region of Ukraine and it belongs to the genus *nairovirus*. Its mode of transmission is presented in Figure 3. Many isolates of the virus have been obtained from domestic animals, arthropods, and wildlife in Nigeria and antibody has been found in human sera. Its clinical symptoms begin after 7 days of incubation beginning with fever, chills, headache, sore throat, vomiting, photophobia, abdominal pain, muscular pain, and diarrhea.

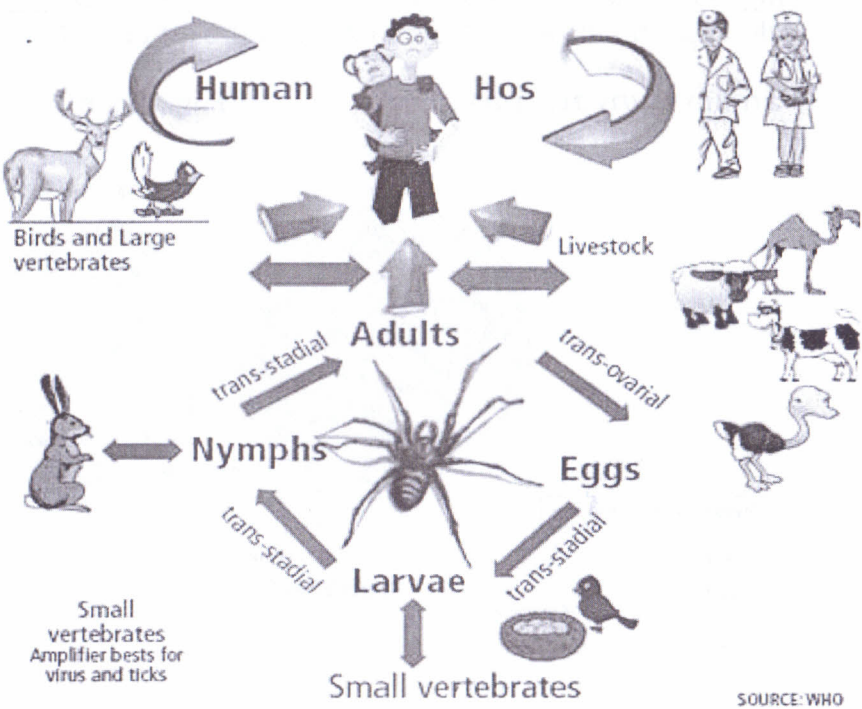


Figure 3: Transmission Modes of Cremea-Congo Haemorrhagic Fever virus

Dugbe Virus

Another member of the genus *nairovirus* is the Dugbe virus isolated from the *Amblyomma* ticks by Prof. David-West of the Virology Department of the University College, Ibadan-Nigeria in 1967. The virus was also isolated from *Ixodes* ticks and *Culicoides* (Figure 4). It has similar clinical symptoms with other members of the Bunyaviridae arboviral agents.

Figure 4: Common Ticks known to Harbor Arboviral Agents.

Rift Valley Fever Virus

Another member of the Bunyaviridae family of arboviruses is the Rift Valley fever virus (RVFV) which has also been isolated from Culicoides (biting midges) and mosquitoes in Nigeria. Several sero-surveillance studies have been conducted in Nigeria in both humans and animals showing that the virus is significantly circulating amongst livestock workers and wildlife rangers than other categories of people in our environment (Olaleye *et al.*, 1996).

The possibility of horses serving as a focus for infection for abattoir workers and other related occupational groups was investigated in a study I conducted in conjunction with Professors Olaleye, Oladosu, Baba and

Fagbami on the Complement Fixing Antibodies in Horses at Lagos, Nigeria. It was observed in this study that 10 percent of 51 horse sera tested showed Complement Fixing (CF) antibody to the virus.

FLAVIVIRIDAE

Flaviviruses comprise more than 70 different viruses, many of which are arthropod-borne and transmitted by either mosquitoes or ticks. Taxonomically, they form a genus in the family *Flaviviridae* which in addition includes the genera hepacivirus and pestivirus (Heinz and Stiasny, 2012). Medically important viruses in Africa are Dengue, Yellow Fever, West Nile, Wesselsbron, Uganda S, Zika, Usutu, Banzi, and Hepatitis C virus.

Structurally they are small size diameter (40 nm) positive sense single-stranded RNA viruses with a capsid surrounded by an envelope (Figure 5). They have glycoprotein projections such as haemaglutinins on the virus surface (Chambers and Monath, 2003).

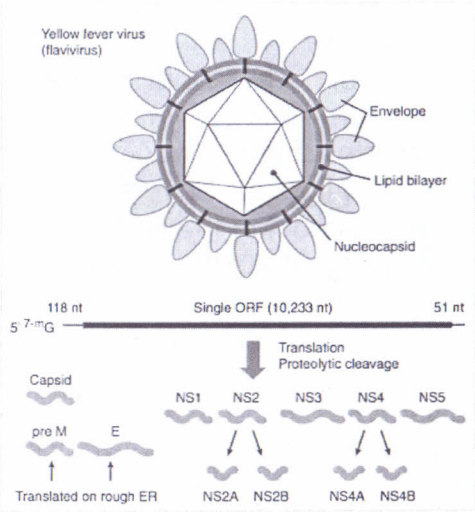


Figure 5: Depiction of Flavivirus Structure

Dengue Fever Virus

Dengue virus is the causative agent of dengue or "break bone fever," a disease first described by Benjamin Rush in the 18th Century. It is an acute febrile disease consisting of four serotypes (DENV 1 to 4) (Westaway *et al.*, 1985). Transmission of Dengue virus infection is by bite of *Aedes aegypti or A. albopictus* mosquitoes.

After an incubation period of 3 to 15 days, classical Dengue Fever (DF) begins with an abrupt onset of high fever. During the febrile phase, dehydration may cause neurological disturbances and febrile seizures in young children. The condition is self-limiting through debilitating illness with headache, retro-orbital pain, myalgia, arthralgia, petechiae rash and leucopenia. A maculopapular recovery rash appears 3 to 5 days after the onset of fever, and it usually starts on the trunk before spreading peripherally (Back and Lundkvist, 2013).

Early symptoms of Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF) are indistinguishable, but DHF is associated with haemorrhagic manifestations, plasma leakage and thrombocytopenia (Back and Lundkvist, 2013).

Dengue Shock Syndrome (DSS) is distinguished from DHF by the presence of cardiovascular compromise, which occurs when plasma leakage into the interstitial spaces result in shock. DSS is a fatal condition with mortality rates as high as 20% but can be less than 1% in places with sufficient resources and clinical experience (Back and Lundkvist, 2013).

The 1964 - 1968 DENV-2 activity among humans in Ibadan is epidemiologically interesting. Only 3 of the 10 DENV-2 strains collected in 1966 were identified as sylvatic strains and isolation from febrile patients suggest the first documented outbreak of sylvatic DENV-2 in humans (Vasilakis *et al.*, 2008). Since the isolation of Dengue 2 virus, several sero-surveillance by Prof. Fagbami had been on.

Mr. Vice-Chancellor, Sir, my laboratory in recent past helped clear the air on several cases of children with Pyrexia of unknown origin. Laboratory investigations using Polymerase Chain Reaction (PCR) identified Dengue virus as the causative agent (Figure 6).

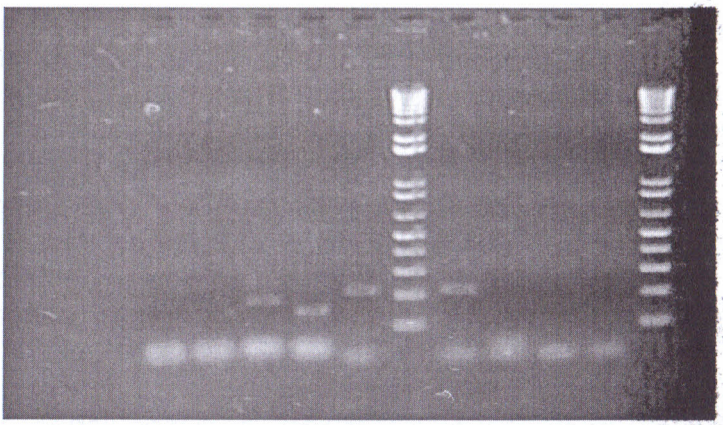


Figure 6: Agarose Gel Image Showing Polymerase Chain Reaction (PCR) of Viral RNA Isolated from Children with Pyrexia of Unknown Origin in Lagos

West Nile Virus

West Nile virus is another member of the Flaviviridae which was originally isolated from Uganda. The first Nigerian isolate (Ib-AN 4067) was isolated in 1965 from sentinel mouse in Ibadan. It is widely distributed in Africa

where it is transmitted by several species of mosquitoes including the *Culex spp.* Wild birds are the main reservoirs and humans are the dead-end hosts of the virus.

Mr. Vice-Chancellor, Sir, part of my quest in search and taming of arboviruses led to the sero-epidemiololgy of West Nile virus in human populations of Ibadan and Oshogbo. Investigation was further spread over domestic animals using Complement Fixation Test (CFT) on sera collected from Maiduguri **(Omilabu** *et al.*, 1990). One hundred and seventy human sera (75 and 95 from Ibadan and Ogbomoso respectively) and 52 animal sera were tested for West Nile CF antibody.

One hundred and eleven (62%) were positive, (53%) from Ibadan and 71/95 (75%) from Ogbomoso. Age distribution of complement fixing antibody to West Nile in both communities is shown in Table 4.

Table 4: Age Distribution of Complement Fixing Antibody to West Nile in both Communities

Age	IBADAN		OGBOMOSO		TOTAL	
	No. Tested	No. (%) +ve	No. Tested	No. (%) +ve	No. Tested	No. (%) +ve
0-9	39	12(31)	0	0	39	12(31)
10-14	4	2(50)	0	0	4	2(50)
15-19	4	3(75)	1	1(100)	5	4(80)
20-29	18	15(84)	49	37(76)	67	52(78)

30-39	5	4(81)	22	18(82)	27	22(82)
40+	5	4(80)	23	15(65)	28	19(68)
TOTAL	75	40(53)	95	71(75)	170	111(65)

It was observed that the highest prevalence of West Nile complement fixing antibody was in persons aged 20-29 years in Ibadan and 30 - 39 years in Ogbomoso. Out of the 52 animal sera tested for complement fixing antibody, 17 (33%) were positive. The highest prevalence of West Nile CF antibody (62%) was found in camels followed by cattle (4%). The only goat serum tested was negative.

Another survey in collaboration with Olaleye *et al.* (1990) also investigated West Nile virus haemagglutination inhibiting antibody in humans and domestic animals. Blood samples were obtained from 304 voluntary human donors attending Catholic Mission Hospital, the University College Hospital and Jericho Health Centre all in Ibadan, Nigeria. Sucrose acetone antigens were prepared with West Nile (Ib-AN4069) - Yellow fever (17D) and Potiskum (Ib-AN 10069) viruses according to the method of Clarke and Casals (1958). Sera were first screened against West Nile and all HI positive sera tested against Yellow fever and Potiskum viruses.

Out of the 304 human sera from Ibadan, 123 (40%) were positive. Age distribution of positive sera showed that the prevalence of WNV antibody increases with age as shown in Table 5.

Table 5: Age Distribution of West Nile Virus HI Antibody in Residents of Ibadan, Nigeria

Age (Years)	No. of Sera Tested	No. (%) Positive
0-4	51	10 (20)
5-9	10	2 (20)
10-14	18	7 (39)
15-19	31	9 (29)
20-29	93	40 (43)
30-39	57	32 (56)
40+	44	23 (52)
Total	304	123 (40)

Moreso, results of tests for other flaviviruses HI antibodies in the 123 WNV positive sera showed that 104 (85%) had yellow fever antibody and 78 (75%) had Potiskum antibody (Table 6).

Table 6: Results of Tests for other Flaviviruses HI Antibody in West Nile Virus Positive Sera

Age (years)	No. WNV HI Positive Sera Tested	No. (%) HI Positive	
		Yellow fever	Potiskum
0-4	10	4(40)	3(30)
5-9	2	1(50)	1(50)
10-14	7	5(71)	2(29)
15-19	9	9(100)	8(88)
20-29	40	34(85)	24(71)
30-39	32	29(90)	20(69)
40+	23	22(5)	20(90)
Total	123	104(85)	78(75)

Further investigations in 200 animal sera showed the percentage of WNV HI antibody positive sera in the animals as follows: cattle 6%, sheep 20%, goat 18% and camel 26% (Table 7). A high percentage of WNV positive animal sera also contained HI antibodies to Yellow fever and Potiskum viruses (Table 7).

Table 7: Results of Tests for West Nile HI Antibody in Animal Sera

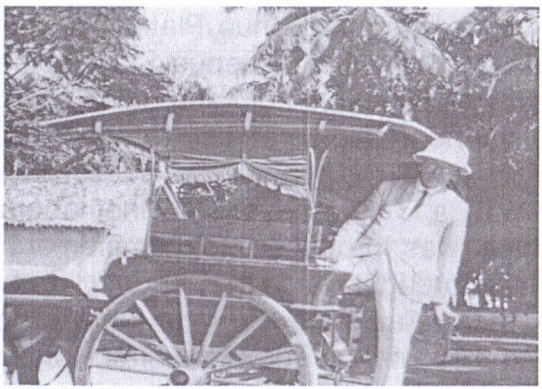
Species	No. of Sera Tested	No. (%) Positive
Cattle	49	3(6)
Sheep	51	10(20)
Goat	50	9(18)
Camel	50	13(26)
Total	200	35(18)

Mr Vice-Chancellor, Sir, these data are proofs that West Nile Fever virus is active in our environment. There are several unreported cases of the viral infection after laboratory diagnosis in patients with pyrexia of unknown origin in Nigeria. Test on animal sera revealed the presence of WNV HI antibody in all the species tested indicating that domestic animals are being infected by the virus.

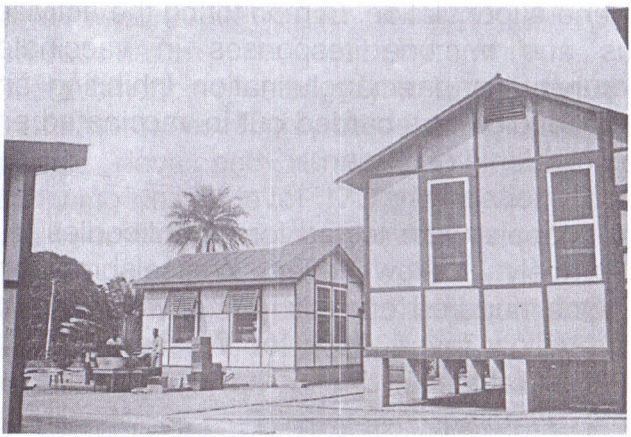
Yellow Fever Virus

Yellow fever virus causes a disease characterised by variable symptoms ranging from mild or non-descript febrile illness to severe disease with haemorrhage and death. The first epidemic of the disease was recognised in Barbados in 1647, but the virus was first isolated from the blood of a Ghanaian patient called Asibi in 1927 by the United States Rockefeller Institute Research Group in

the Virus Research Laboratory, Yaba, now Nigerian Institute of Medical Research. An image of one of the then researchers who developed the methods for growing the virus in monkeys is shown below.



Dr. Wilbur A. Sawyer
From Hookworm to Yellow Fever: Rockefeller Foundation



The Animal House of the Yellow Fever Laboratory, Yaba, Lagos Nigeria January 20 1933 - Dr. Wilbur A. Sawyer

Several epidemics of yellow fever have occurred over the past decades in Nigeria and have been well documented by various workers. These includes the 1913 Ogbomoso epidemic, the 1925 Lagos epidemic, the Ogbomoso epidemic of 1946, the 1969 Jos epidemic, the 1970 epidemic of Okwoga district of Benue Plateau State, the 1973 Mabudi epidemic, the Oju in Benue State epidemic of the second half of 1986 which did spread to 15 out of 19 States in Nigeria then. This spread till 1992.

In Yaba, there was a Yellow fever vaccine laboratory where the vaccine was produced to complement the imported vaccines brought into the country but the vaccine laboratories are all gone now and there are very few genotyping studies on the virus strains from Nigeria.

All of these epidemics were characterised by high morbidity and mortality. Surveys for yellow fever immunity carried out in Nigeria showed that there was marked variation in the levels of immunity to yellow fever virus in the general population. In monitoring the activities of the virus and immune responses in vaccinated persons; a survey for haemagglutination inhibiting and neutralising antibodies was carried out in vaccinated and unvaccinated residents of Ibadan.

A total of 207 people were tested for HI antibodies to 3 flaviviruses namely; Yellow fever, Wesselsbron and Uganda S., One hundred and six (51%) were positive with 26% for yellow fever, 18% for Wesselsbron and Uganda S (33%) (Table 8).

Table 8: Results of Tests for Flavivirus HI and Yellow Fever Neutralizing Antibodies in Human Sera from Ibadan.

Age	No. Tested	No. (%) Positive			Total Flavivirus	No. (%) YF N Positive
		YF	WSL	UGS		
0-9	3	1(33)	1(33)	1(33)	1(33)	0
10-19	50	8(16)	2(4)	14(28)	20(40)	2(4)
20-39	105	32(30)	18(17)	30(29)	54(51)	24(23)
40	26	10(38)	11(42)	17(65)	22(85)	11(42)
Unknown	23	3(13)	5(22)	7(30)	9(39)	0
Total	207	54(26)	37(18)	69(33)	106(51)	37(18)

Of the 207 samples, 37 (18%) had neutralising (N) antibody to yellow fever virus; 2 of 52 (4%) children and adolescents aged 0 - 19 years and 35/131 (27%) adults. The prevalence of Neutralising antibody is significantly higher in adults than in children ($P<0.01$). Eighteen of 37 yellow fever immune sera were available for further testing. Seventeen were positive to yellow fever only and Uganda S viruses. Twenty one (10%) of post-vaccinated sera was available for testing. Ten (48%) had no prevaccination HI antibody while 7 (33%) had prevaccination HI antibody to one flavivirus and 4(19%) to 2 flaviviruses. Eighty percent and 90% of sero negative people developed HI and N antibodies respectively, following yellow fever 17D vaccination; all vaccines with pre-vaccination flavivirus antibodies sero-converted.

Conversely, at the peak of the vaccination exercise from 8th through 15th May, 1987, an outbreak of untoward reactions occurred among the vaccinees at Shaki, Oyo State, Nigeria. Twenty-five patients presented with rapidly progressing swelling of the left arm, fever and associated constitutional symptoms at the Baptist Hospital, Shaki from 8th through 19th May, 1987.

The swelling progressively spread to the whole upper and pectoral region of the left arm within 24-48 hours of inoculation with 17D vaccine in all the patients. Five of the patients were clinically in shock at the time of admission into the hospital and died within 40 hours of admission. All the five patients who died were vaccinated at illegal clinics. Three of them were vaccinated by one person. Investigation about position of each patient on the inoculation queue showed that the five patients who died were either at the middle or at the end of the line while four of the others were reported to have been in front of the queue.

Further evaluation of the vaccination procedure showed that 2 out of 6 (40%) people vaccinated at the authorised centre and 8 of 19 (42.1%) vaccinated at the illegal clinics had the inoculation sites properly cleaned with alcohol swabs before they were injected with the vaccine. None of the patients could remember having seen the needles cleaned between individuals inoculated either at government centres or in the illegal clinics (Oyelami *et al.*, 1994).

Mr. Vice-Chancellor, Sir, I would like to briefly highlight that I and other colleagues reported the human and animal infections with Wesselsbron virus for the first time in Nigeria. In one of our studies, the virus was isolated and studied in West African Dwarf goats (Baba *et al.*, 1989; Baba *et al.*, 1995). Wesselsbron virus infection causes a big economic loss in sheep and goat rearing and it is characterised by fever, severe leucopenia, abortion in pregnant ewes and high mortality in lambs and kids. Also, we reported the first evidence of wide spread human infection with Igbo-Ora virus in Nigeria. In 1966 two serologically related viruses, named Igbo-Ora

virus, were isolated from human blood, one in Ibadan (Ib-H10964) and one in Igbo-Ora (Ib-H12628). Subsequently, these isolates were shown to be alphaviruses, antigenically closely related to Chikungunya and O'nyong-nyong.

In 1967, Igbo-Ora virus was isolated from the Central African Republic (Pasteur Institute, Darkar, 1986) (Olaleye *et al.*, 1988). We further studied the growth characteristics of Igbo-Ora virus in Cell cultures such as Vero cells, MRC5, MDCK, and MA014 in order to provide the best system for virus detection (Olaleye *et al.*, 1990).

Potiskum Virus

In May 1966, virus surveillance was carried out in the northern part of Nigeria. At Fika, a town in Potiskum district of Borno State (now Fika Local Government Council), eighteen giant rats (*Cricetomys gambianus*) were trapped and their tissue were processed for virus isolation.

Cricetomys gambianus

A virus isolate, Ib-AN 10069, was obtained from the liver suspension of one of the animals. One of the six baby

mice infected fell sick on day 7 post infection. A second passage from the sick baby mouse made five other baby mice sick with the incubation period shortened from 7 to 3 days. The isolate was tentatively named POTISKUM (POT) virus. Preliminary investigations on Ib-AN 10069 revealed its close relatedness to Uganda S. and more broadly related to Flaviviruses including yellow fever, Wesselsbron, Dengue, West Nile, etc.

Apart from the preliminary tests, information on the characteristics of the virus and its sero-epidemiological pattern were scanty until a study was carried out to use some aspects of biochemical and biophysical tests to elucidate its relationship to other flaviviruses; determine the host range of the virus using laboratory and domestic animals as well as arthropods, determine the cell cultures susceptibility of the virus, and carry out sero-epidemiological studies and roles played by other flaviviruses in the actual epidemiology of Potiskum virus.

The Physical and Chemical characteristics of the virus revealed that there was no loss of infectivity when filtered through the average pore diameter (APD) of 0.45 and 0.22 µm. However, significant loss of infectivity of greater than 4.0 logs was obtained when the virus was passed through Hemmings filter. It was observed that the virus was inactivated by ether, chloroform and thermal inactivation (**Omilabu,** 1994). This study also demonstrated the susceptibility of laboratory animals to the virus as shown in Table 9.

Tissue culture susceptibility studies showed that the cell lines used in this study were adapted to the Potiskum virus (Figure 7).

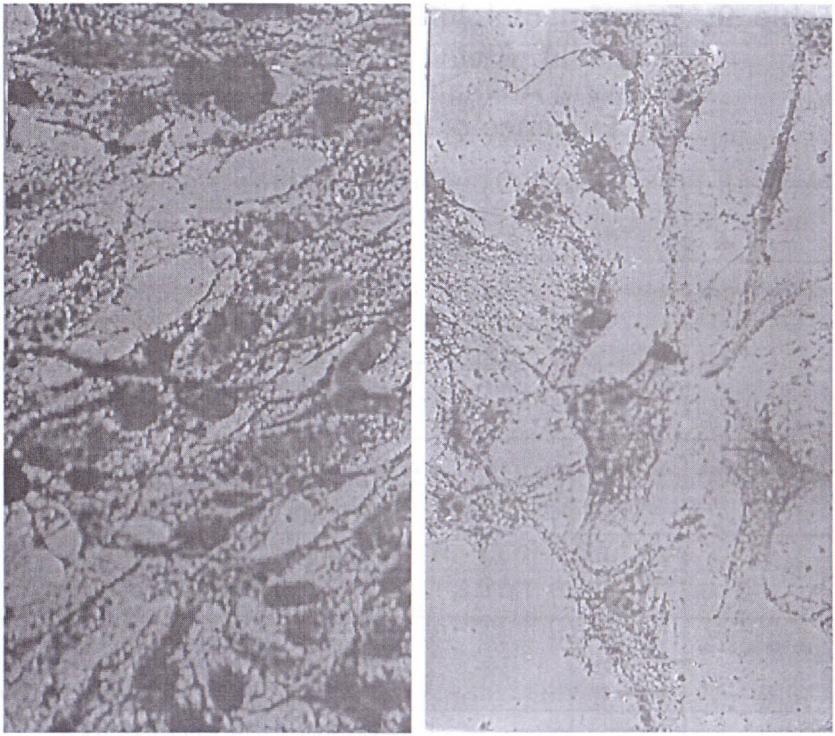


Figure 7: Uninfected (A) and POT Virus Infected (B) BHK-21 Cells

Table 9: Experimental Infection of Laboratory and Domestic Animals with Potiskum Virus-Showing Animals, Age, route of Inoculation and Evidence of Infection.

ANIMAL	AGE RANGE	ROUTE OF INOCULATION	EVIDENCE OF INFECTION	
			SICKNESS/DEATH	VIREMIA/ANTIBODY
Suckling mice	2-4 days	i.c. i.p. s.c. oral	Paralysis and death " " " " " " NIL survived	Viremia developed till death
	5-12 days	i.c. i.p.	Paralysis and death " " "	Viremia detected and persisted till death
Weanling mice	3-4 weeks	i.p. i.c.	Dehydration, rough fur, Hindlimb paralysis and death	Viremia was detected
Adult mice	6 weeks and above	s.c. i.p.	No sign was noticed death from high dose	Viremia detected early in the experime
White albino	8 weeks and above	s.c. i.p.	No sign was noticed	No viremia detected No neutralising antibody detected
Chicks	4-5 days 7-25 days	oral (per os) s.c.	Ruffled feathers weakness of the limbs, body pains and death	Viremia developed from day 1 post infection
Rabbits	Adults	s.c.	No sign was noticed	No viremia, Neutralising, CF and HI antibodies were detected early in the experiment
West African Dwarf Goat	2-3 months	s.c.	Fever, occulo-nasal discharges, watery diarrhoea and general debility	Viremia developed early

How can Arboviral Infections be Prevented?

The following recommendations are suggested to prevent arboviral infections. It is advised that we should minimise exposing our skin outdoors in mosquito-or tick-infested areas. Consider wearing long sleeves and tucking pants into socks and shirt into pants when in tick habitat or

outdoors at dusk or dawn; the time of day when mosquitoes are most active. Furthermore, wear light-colored clothes to spot ticks easily.

Furthermore, to reduce the mosquito population around our homes and properties; reduce or eliminate all standing water:

- Dispose of tin cans, plastic containers, ceramic pots or similar water-holding containers.
- Remove and recycle all discarded tires on your property. Used tires are a significant mosquito-breeding site.
- Drill holes in the bottoms of recycling containers that are kept outdoors.
- Remove leaf debris from yards and gardens.
- Clean vegetation and debris from edges of ponds.
- Clean and chlorinate swimming pools, outdoor saunas and hot tubs.
- Use landscaping to eliminate standing water that collects on your property.
- Make sure window and door screens fit properly and are in good condition.

MODULE 3

VIRUSES PLAGUING CHILDREN

I also began to have interest in the viruses plaguing children as a result of the high morbidity and mortality in this part of the world; most especially in children less than 5 years old. Viruses can easily spread when children have close contact with each other, such as in childcare centres, kindergarten or school by tiny droplets from the nose (sneezing or runny nose) and mouth (saliva or cough), vomit or faeces (especially if someone has diarrhoea).

There is usually a delay between when a child is exposed to the virus and when they develop an illness. This generally happens within a few days but for some viruses, it may be up to two to three weeks later. It is common for children to have between six and 10 viral illnesses a year in the first few years of life. It is also common for children to get sick from one virus shortly after getting better from a different one, seeming to parents like they are sick all the time. As children get older, the frequency of viral illnesses usually reduces.

A cock tail of viruses' plagues children and I will be discussing majorly on Respiratory and Gastroenteric viruses in Children.

Respiratory Viruses in Children

The aetiology and epidemiology of acute respiratory infections have been intensively studied in the temperate areas of the world. Information from tropical regions is scantier, but what evidence there is that the viruses responsible for respiratory disease in the tropics are no different from those found in temperate zones. However, the severity of illness and its sequelae, as well as their seasonality, may be markedly different from those in the developing world.

Common viral respiratory diseases are illnesses caused by a variety of viruses that have similar traits and affect the respiratory tracts. The disease burden from respiratory infection is greater than that of any other cause of disease. Acute respiratory infections are estimated to cause approximately 1.9 million childhood deaths annually, 70% of them in Africa and South-east Asia. The contribution of acute respiratory infections to overall childhood mortality ranges from <5% in the

developed countries to 25% in some developing countries (Malik *et al.*, 2008).

The respiratory tract can be divided into upper and lower parts, with the boundary at the lower end of the larynx. Viral implicated in the upper respiratory tract infection (URTI) are rarely life-threatening, with the exception of croup. They can be uncomfortable but do not usually call the individual's future into question. The viruses involved may be the respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), influenza viruses (IFVs), enteroviruses (EVs), adenoviruses (ADVs), human rhinoviruses (HRVs), human metapneumovirus (hMPV), and human coronaviruses (HCoVs).

Respiratory Syncytial Virus (RSV)

Human respiratory syncytial virus (RSV) is a ubiquitous virus of worldwide distribution and is the leading cause of infant morbidity from respiratory infections. By the age of two, nearly all children have been infected and can cause severe bronchiolitis and pneumonia in this age group (Al Johani and Akhter 2013). The World Health Organization (WHO) estimates that RSV is responsible for 64 million infections worldwide and 160,000 deaths per annum.

Respiratory syncytial virus (RSV) is negatively sensed single stranded RNA virus, a member of the order *Mononegavirales*, family *Paramyxoviridae*, subfamily *Pneumovirinae*, and genus *Pneumovirus*. The incubation period of RSV respiratory disease is estimated to be three to five days. RSV is closely related to several other RNA viruses, including measles, mumps, and parainfluenza type 1, 2, and 3. Respiratory syncytial virus is a medium-sized (120-200nm) enveloped virus that contains a lipoprotein coat and a linear minus-sense RNA

genome. The entire genome of RSV is composed of approximately 15,000 nucleotides long.

Variability between RSV strains contributes to the ability of the virus to infect people repeatedly and cause annual outbreaks. Consistent shifts in RSV group dominance have been reported worldwide in which RSV group A viruses are more frequently detected. Large epidemics occur annually in the same season, but the seasonality of RSV epidemics may vary in different geographical regions. The starting date and extent of the epidemic may vary but the annual epidemic occurs reliably. For diagnostic purposes there is only one serotype, but two subtypes (A and B) have been described and they may co-circulate, with one usually predominating in any given year. No obvious differences in disease severity or pathogenesis have been documented. RSV causes a substantial but variable lower respiratory tract disease burden in tropical countries.

Parainfluenza Virus

Parainfluenza viruses have pleomorphic, spherical virions that range in average diameter from 150 to 200 nm. Parainfluenza viruses are also of worldwide distribution and are important agent of acute respiratory tract disease (ARD) of Children in Africa and elsewhere. There are four serotypes of parainfluenza, with type 4 possessing two subtypes: 4a and 4b. Type 1 and 2 typically cause croup, a high-pitched barking cough in children which is profoundly irritating to their parents. Type 3 can cause bronchiolitis or pneumonia and, less often, croup. In temperate countries, types 1 and 2 (together with RSV) are more prevalent in the winter months, whereas type 3 is unusual (among respiratory viruses) occurring more often in spring and early summer. This dissociation

between the peaks of activity of parainfluenza type 3 and RSV has also been observed in tropical regions.

Influenza A and B Virus

Influenza virus belongs to the genus *Orthomyxovirus* in the family *Orthomyxoviridae* which consists of influenza A, B and C viruses and has an envelope, single-stranded, negatively sensed RNA, eight separate segments and pleomorphic appearance with an average diameter of 120 nm.

Antigenically, these are the most variable of the respiratory viruses. Both exhibit antigenic 'drift,' in which the surface antigens of the virus change gradually in the face of immunological pressure from the host species, with one or two variants predominating at a given time. In showing this progressive and 'directional' antigenic change, they are unique among respiratory viruses.

In addition, influenza A, but *not* influenza B, shows occasional major antigenic changes in the surface antigenic structures (haemagglutinin and/or neuraminidase) (Figure 8), called 'antigenic shift,' which may lead to a pandemic. Such pandemic influenza viruses are derived from avian influenza viruses through genetic re-assortment with animal or human strains. This results in the incorporation of new viral surface antigens to which the human population is immunologically naïve. The timing, extent and direction of either 'drift' or 'shift' have so far been completely unpredictable. However, when viruses with antigenic shift appear in the human population, a worldwide pandemic of influenza A becomes possible; memorable examples occurred in 1918 ('Spanish flu'), 1957 ('Asian flu') and 1968 ('Hong Kong flu') (Malik *et al.*, 2008). With no animal reservoirs

to provide such new antigens; shift does not occur in influenza B.

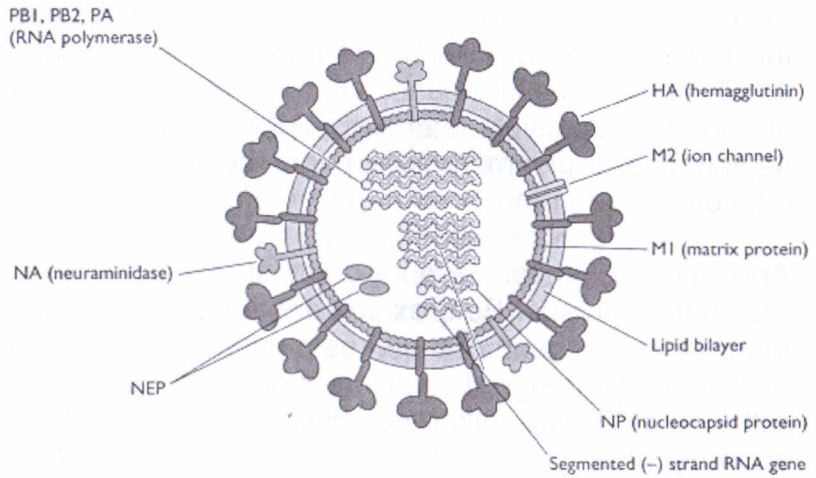


Figure 8: Structure of Influenza Virus.

Adenovirus

There are 51 different serotypes but the majority of respiratory infections involve type 1 - 7 with figure 9 showing a representative structure of Adenoviruses. Type 1, 2, 5 and 6 are usually associated with endemic disease in temperate regions, while type 3, 4 and 7 are associated with epidemics. The higher-numbered serotypes appear in the respiratory tract from time to time but the majority of them have been found only in the gut.

Adenoviruses are unusual, in that prolonged carriage (up to 2 years in some cases) may occur in the tonsils of children, often with no continuing illness. The clinical significance of adenoviruses isolated from the throats of children must therefore be interpreted cautiously, especially if the strain has not been typed. However, they may cause a primary and severe pneumonia in

debilitated children, in whom it may be rapidly fatal, and in some immune-compromised patients.

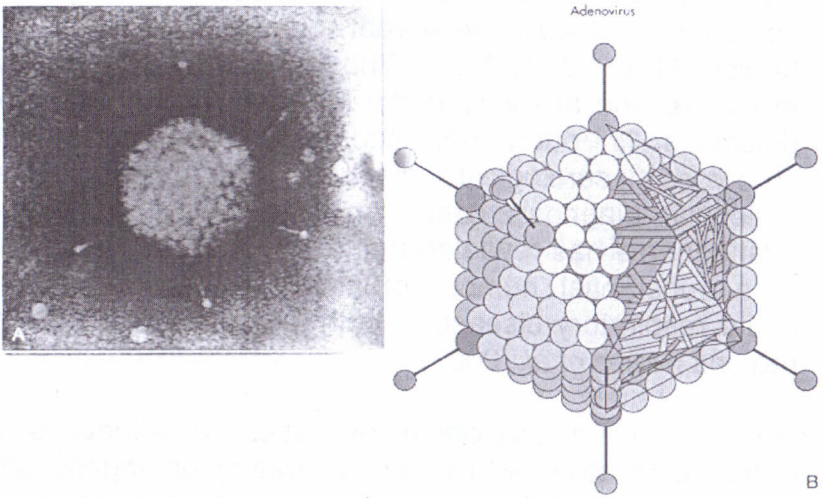


Figure 9: Structure of Adenovirus.

Human Metapneumovirus

This virus, which resembles respiratory syncytial virus (RSV), was discovered in 2001 by van den Hoogen and colleagues in The Netherlands (van den Hoogen *et al.*, 2003). It is now recognised to be a separate virus in its own right, although, the disease it causes, its worldwide distribution and seasonality are similar to those of RSV (Banerjee *et al.*, 2007). It, too, may cause infections in the elderly as well as in babies under 1 year old, and its discovery has accounted for some of the diseases in these age-groups for which no cause had been found hitherto.

Retrospective serology, though, has shown that this is not a new pathogen, even for man, but it has been around for a long time (Malik *et al.*, 2008).

Rhinoviruses

These are frequent causes of the 'common cold,' itself; a frequent winter and summer illness in temperate countries but they have a year-round seasonality in the tropics (Miller *et al.*, 2007). They can be difficult to grow in culture and are very under-reported, mainly because diagnosis is often not attempted. With over 100 serotypes, serological diagnosis is impracticable. Molecular diagnosis based on conserved parts of the viral genome has revealed that rhinoviruses are detected in a substantial number of children hospitalised with acute respiratory disease in both temperate and tropical regions (Miller *et al.*, 2007).

However, in a proportion of cases, a rhinovirus is detected together with other respiratory pathogens and the relative contribution of rhinovirus to the illness is unclear. A better understanding of the epidemiology of rhinoviruses in apparently asymptomatic children (and adults) is needed. Rhinoviruses are now also recognised to be a significant precipitating factor in exacerbations of asthma and chronic obstructive airways disease in both children and adults. They have also occasionally been the sole pathogens present in the lungs of immune-compromised patients dying with respiratory signs and symptoms (Malik *et al.*, 2008).

Coronaviruses

Human coronavirus (HCoV) strains 229E and OC43 have been long recognised as the second main cause of the common cold. More recently, three other coronaviruses have been detected in humans, SARS CoV, HCoV-NL63 and HCoV-HKU1.The HCoV 229E, OC43, NL63 and HKU1 viruses are ubiquitous and are regularly detected in respiratory specimens of a small proportion (1–10%) of

children hospitalised with acute respiratory disease and in many parts of the world. Infection with these human coronaviruses presents as an upper respiratory tract infection, asthma exacerbation, acute bronchiolitis, pneumonia, febrile seizures and also as croup (especially NL63). HKU1 can be associated with URTI, LRTI (especially in those with underlying diseases of the respiratory tract) and with febrile seizures in children. 17 HCoV are not readily cultivable and require molecular methods (such as reverse transcription polymerase chain reaction, RT-PCR) for detection.

SARS-coronavirus

In 2003, a coronavirus causing a severe and often fatal pneumonia emerged in southern China. Within weeks of its spread to Hong Kong, the disease had also spread worldwide to affect over 30 countries across five continents (Peiris *et al.*, 2003). This was a dramatic illustration of how rapidly a newly emerging respiratory disease can spread. It is unusual in that it caused severe disease, which can also readily be transmitted to those caring for the patients. Unlike many other respiratory viral infections; viral load in the upper respiratory tract will not peak until the second week of illness and, consequently, transmission is rare within the first 5 days from onset of illness. This allowed public health measures of early case recognition and isolation to interrupt transmission within the community.

SARS was a disseminated infection and not one confined to the respiratory tract. Virus was detectable in the faeces and urine and these may also contribute to transmission under some circumstances. The virus originated as a zoonosis. The precursor virus is present in bats (*Rhinolophus* spp) (Lau *et al.*, 2005). While the

transmission of the human-adapted virus that caused the global outbreak in 2003 has been interrupted, it is possible that the disease may reappear, either through the escape of the human-adapted SARS CoV from a laboratory or by the re-adaptation of the animal virus to efficient human transmission.

Measles

Measles is often not recognised as a major cause of LRTI morbidity or mortality, and there are a number of factors that may account for this under assessment. Children with measles may not always be admitted to a hospital and the aetiology may be attributed to a super infecting pathogen rather than to measles. Some patients with measles (especially when immunocompromised as a result of malnutrition, cytotoxic drug treatment or for other reasons) will fail to develop the typical rash. In patients who do not manifest typical clinical features, both clinical and laboratory diagnosis of measles is difficult, even in the developed world. Measles is found to be a major cause of LRTI, accounting for 6 - 21% of morbidity and 8–50% of the mortality attributed to LRTI. The effects of the virus on the respiratory tract can be direct (giant cell pneumonitis) or indirect. The latter includes the depressive effects of the virus on the host immune system, stores of vitamin A and overall nutritional status. All of these can lead to an increased risk of super-infection with other viral or secondary bacterial pathogens.

Contributions of My Research Works in the Area of Respiratory Viruses Plaguing Children

Mr Vice-Chancellor, Sir, I began my journey in elucidating viruses plaguing children since 1985 at the University College Hospital in Ibadan with respect to Influenza virus

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Tables 10

Results of tests for influenza virus serological conversion in children with respiratory diseases at the University College Hospital, Ibadan, Nigeria

Age (months)	Sex	Interval between 1st and 2nd specimens (weeks)	HI antibody titre		Sero-conversion	
			1st specimen	2nd specimen	Virus type	Virus strain
24	M	5	10	40	A	H3N2(M)*
24	M	5	10	80	A	H1N1(T)
96	M	4	—	40	B	Arbor
36	F	2	10	160	A	H3N2(L)
144	F	3	40	160	A	H3N2(M)
15	M	2	20	80	A	H3N2(M)
15	F	2	10	80	A	H1N1(C)
			10	40	A	H3N2(L)
24	M	5	10	80	A	H1N1(C)
48	M	3	80	2560	A	H3N2(L)
30	F	8	20	320	A	H3N2(M)
12	M	6	20	80	A	H3N2(M)
60	M	3	10	80	A	H3N2(L)
25	F	3	20	80	A	H3N2(M)
			10	640	A	H1N1(T)
24	M	3	10	40	A	H3N2(M)
14	F	12	10	80	A	H3N2(M)

*(M) = Mississippi 1/85; (L) = Leningrad 360/86; (C) = Chile 1/83; (T) = Taiwan 1/86.

Table 11

Monthly distribution of influenza A subtypes infections in children with respiratory symptoms at the University College Hospital, Ibadan (1985–1987)

Months of the year	Total number tested	Number showing seroconversion to influenza A subtypes		Total number of cases
		H3N2	H1N1	
January	2	1	0	1
February	0	0	0	0
March	1	0	0	0
April	2	2	1	3
May	9	2	1	3
June	2	0	0	0
July	4	1	0	1
August	2	0	0	0
September	6	1	1	2
October	2	0	0	0
November	9	3	1	4
December	3	1	0	1
Number of cases	42	11	4	15

Due to the inherent importance of Influenza in medical care particularly in children and the scarcity of information on the epidemiology of Influenza viruses in Nigeria, I continued in my quest in providing useful information on epidemiology of these viruses in Nigeria by further testing using Haemagglutination Inhibition (HI) test of human sera in the collection of our laboratory in 1991 for the presence of antibodies to Influenza viruses. In conjunction with other colleagues, we presented some data on the distribution of antibody to Influenza viruses in the population in five ecological (Vegetational) zones of Nigeria as shown in **Table 12:** the swamp forest, rainforest, derived savannah, guinea savannah and sudan savannah zones.

The results also indicated considerable activity of Influenza A and B in various Nigerian population groups and in all the vegetational zones as highlighted in **Table 13**. Monotypic reactions to different influenza types and subtypes further strengthened evidence for co-circulation of the viruses in all vegetational zones of the country and suggests the endemicity of Influenza in Nigeria (Olaleye *et al.*, 1991).

Table 12: Source, Date of Collection and Number of Human Sera for Influenza Virus HI Antibodies in Nigeria.

Vegetational Zone	Locality	Date of Collection	Number of sera
Swamp forest	Lagos	April 1987	125
Rain forest	Ijebu-Ode	March 1988	88
	Ibadan	February 1987	125
	Sabongida-Ora	April 1987	78
Derived Savannah	Ogbomoso	April 1987	135
Guinea Savannah	New Bussa	March 1986	136
	Abuja	March 1986	55
	Oju	October 1986	44
Sudan Savannah	Maiduguri	December 1986	56
	Sokoto	October 1987	180
Total			1,022

Table 13: Summary of Influenza Virus Reactivities in Different Locations in Nigeria.

Location		No. Tested	No. (%) Positive	No. (%) Negative
Swamp Forest: Lagos		125	118 (94.4)	7 (5.6)
Rainforest:				
Ijebu-ode		88	49 (55.7)	39 (44.3)
Ibadan		125	91 (72.8)	34 (38.6)
Sabongida		78	46 (58.9)	32 (41.1)
	Subtotal	291	186(63.9)	105 (36.1)
Derived Savannah: Ogbomoso		135	42 (31.1)	93 (68.9)
Guinea Savannah:				
New		136	129 (94.9)	7 (5.1)

Bussa				
Abuja		55	49 (89.1)	6 (10.9)
Oju		44	24 (54.5)	20 (45.5)
	Subtotal	235	202 (86.0)	33 (14.0)
Sudan Savannah:				
Maiduguri		56	48 (85.7)	8 (14.3)
Sokoto		180	136 (75.6)	44 (24.4)
	Subtotal	236	184 (78.0)	52 (22.0)
Total		1022	732 (71.6)	290 (28.4)

Consequently, periodic surveillance for Influenza viruses was recommended to be incorporated into the National health programme for proper preventive and control measures. This was birthed in the country during outbreak of Avian flu in 2006 – 2007 in Nigeria with the establishment of a surveillance system for flu.

Also, there is a possibility of genetic re-assortment of avian influenza viruses with animal or human strains; by the incorporation of new viral surface antigens to which the human population is immunologically naïve. There are two qualities of influenza virus that account for much of its spread. First is the ability to emerge and circulate in avian or porcine reservoirs by either genetic re-assortment or direct transmission and subsequently spread to human at regular intervals.

Second, is the fast and unpredictable antigenic change of important immune target once the virus is established in humans. Based on these, I ventured in my research work, looking at the possibility of tracking Influenza virus in Pigs in 2012. This research work is the first documented detection of influenza A virus in pigs in Lagos, Nigeria. It further demonstrates the need for a sustainable surveillance mechanism of swine and other

influenza viruses to be able to prevent influenza epidemic in the environment (Anjorin *et al.*, 2012).

My journey in unraveling viruses plaguing children continued with research works on Measles virus since 1993 in an attempt to give laboratory back up service to vaccines administered in Nigeria by determining the potency status of some live-attenuated viral vaccines administered in some selected immunisation centres (**Omilabu** *et al.*, 1998) and in 2007 with the Evaluation of vaccine cold chains in Lagos, Nigeria (Oyefolu *et al.*, 2007).

Four channels of vaccine distribution have been identified: the national cold store (L1), state cold store (L2), local government cold store (L3) and vaccination centres (L4), in descending order. It was observed that despite that all criteria of the National Programme on Immunisation (NPI) accreditation checklist for the L1 to L3 facilities were met in accordance with WHO recommendation as highlighted in **Table 14**; the status of vaccine potency deteriorates as the distribution channel go down the ladder, i.e. from the national cold store level (L1) to the vaccination center level (L4) as shown in **figure 10**.

In an attempt to find the factors associated with the problems of loss of potency at different channels of vaccine distribution, four essential elements (equipment, manpower, transportation and vaccines) were identified. These essential elements were found to be available and adequate both at the national and state cold store levels while they were virtually absent and/or non-functional if available at the local government level and vaccination centres.

Table 14: NPI Accreditation Criteria met by L1 to L3 Cold Stores in Lagos, Nigeria

Storage Level	1 Adequacy of fridge for vaccine storage	2 Normal fridge t°	3 Diluent in fridge	4 Freezer for ice-packs only	5 Daily am & pm t°	6 Functioning standby generator	7 Adequacy of freezer for vaccine storage	8 Normal freezer t°	9 Normal vaccine spacing in fridge/ freezer	10 Vaccine within expiry date	Total score (%)
L1	YES	YES	NA	YES	YES	YES	YES	YES	YES	YES	100
L2	YES	YES	NA	YES	YES	YES	YES	YES	YES	YES	100
L3 (IKR)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	100
L3 (KSF)	NO	NO	NO	YES	YES	YES	YES	YES	YES	YES	81
L3 (AJE)	YES	YES	NO	NO	NO	NO	YES	YES	YES	NO	69
L3 (ETI)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	100
L3 (ALI)	NO	NO	NO	YES	YES	NO	YES	YES	YES	YES	75
Total (%)	71	71	40	86	86	71	100	100	100	92	

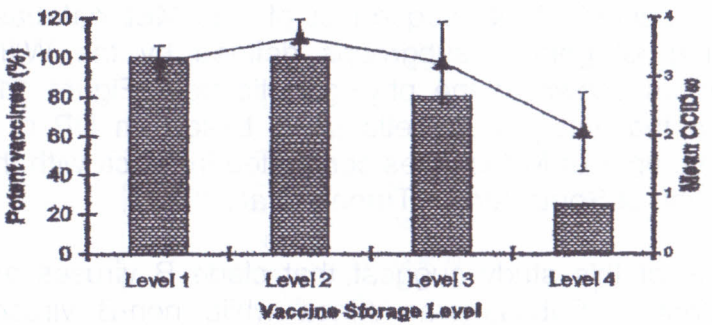


Figure 10: Potency of Vaccines across Storage Level in Lagos, Nigeria.

Mr. Vice-Chancellor, Sir, since Sub-Saharan Africa is one of the regions of the globe with the highest measles-related morbidity and mortality. Yet only seven virus isolates from this vast region have been phylogenetically characterised on the basis of their nucleoprotein, the last one was in 1991. There was no field isolates from the vast region of West Africa, including Nigeria, the most

populous African nation, to have ever been studied, thus my further interest with my collaborators in Luxembourg to characterise the prevalent wild-type measles virus isolates and to understand their circulation pattern in 1999 and to further study the diversity of Measles viruses in Nigeria in 2010.

The measles virus isolates described in the year 1999 were the first from this major region of West Africa (Nigeria) to be incriminated with the staggering mortality rates among Nigerian infants and children (Hanses *et al.*, 1999). The complete protein encoding region of the NP genes were sequenced to further elucidate the epidemiology of this virus in Nigeria. The sequences of five isolates from Lagos and 36 from Ibadan (both Nigeria) were compared to a consensus sequence based on 34 selected MV NP sequences of the EMBL database covering all genetic subgroups defined by the WHO (1998) as shown in the phylogenetic tree (Figure 11). This is the first phylogenetic study based on NP of a large number of MV isolates conducted in Africa with the exception of South Africa (Truong *et al.*, 1999).

Results of this study suggest that clade B viruses are prevalent in Sub-Saharan Africa while non-B viruses seem to dominate the south of Africa as seen from the patterns of clustering in Figure 11.

In 2010, the genetic diversity of measles virus (MV) in Nigeria (2004 - 2005) as compared with our earlier study revealed that two genetic clusters of genotype B3, both of which were most closely related to 1 clade variant from 1998, were identified as shown in figure 12. Longitudinal analysis of MV strain diversity in Nigeria suggested that only a few of the previously described 1997–1998

variants reported in 1999 had continued to circulate (Kremer *et al.*, 2010), but this finding was concomitant with a rapid restoration of genetic diversity, probably caused by low vaccination coverage and high birth rates.

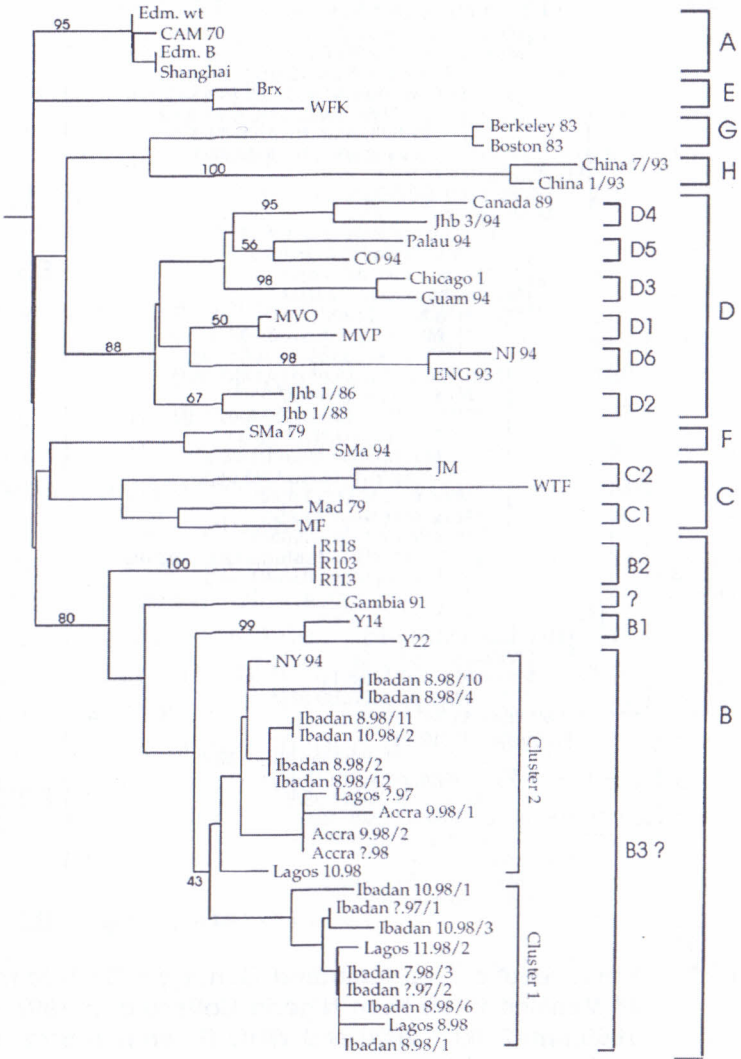


Figure 11: Phylogenetic Comparism of Nigerian Isolates with Previously Described Isolates

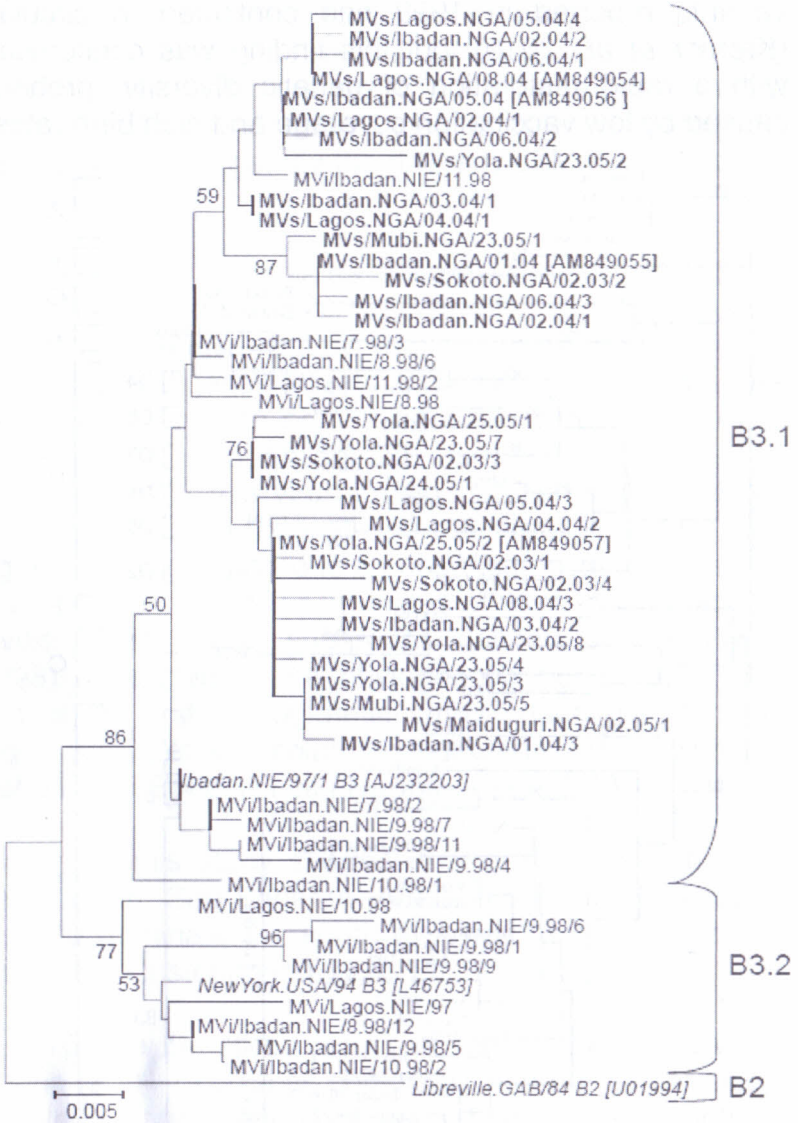


Figure 12: Phylogenetic Tree Including Genotype B3 Strains of Measles Virus from Nigeria Collected in 1997 – 1998 and 2003 – 2005 and WHO Reference Strains of Genotype B3

Gastroenteric Viruses in Children

Since Kapakian first identified a virus in the stool of a patient with diarrhoea in 1972, many viruses have been described that cause diarrhoea directly or indirectly. It is now appreciated that viruses are the most common cause of diarrhoeal illness worldwide (Clark and McKendrick 2004). Viral gastroenteritis is the inflammation of the lining of the stomach, small intestine, and large intestine. Several different viruses can cause viral gastroenteritis, which is highly contagious and extremely common. Viral gastroenteritis causes millions of cases of diarrhoea each year.

Rotavirus remains the leading cause of diarrhoeal disease, with the newly designated calicivirus family causing the most outbreaks in the industrialised nations. As diagnostic techniques improve, however, the importance of astrovirus and other previously under-reported pathogens is becoming more apparent and the number of viruses associated with gastroenteritis continues to increase. Diarrhoeal diseases remain a leading cause of morbidity and mortality worldwide. Conservative estimates put the death toll at 4 - 6 million deaths per year, placing diarrhoeal diseases amongst the top five causes of death worldwide, with most occurring in young children in non industrialised countries. Four types of viruses cause most cases of viral gastroenteritis, and these will be the basis of my discussion in this lecture.

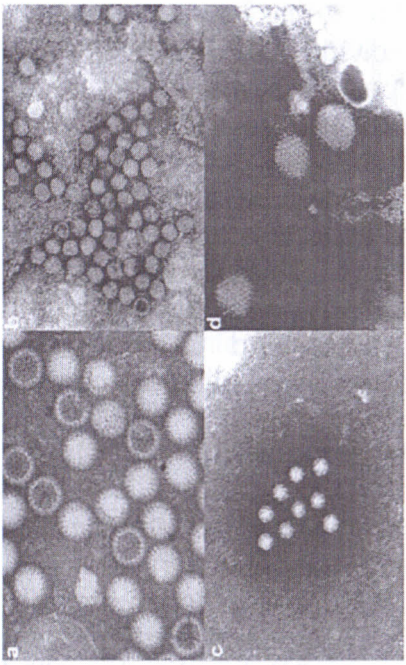
Rotavirus

The wheel-like (Latin, rota = wheel) particles of rotavirus were first described as a human pathogen in 1973 (Bishop *et al.*, 1973), and are now classified as a genus within the family Reoviridae. The particles are 70 nm, non

enveloped icosahedral structures (Figure 13a). An inner and outer capsid gives a double layer, surrounding a core containing the viral genome. The double-stranded RNA consists of 11 segments, which encode six viral capsid proteins (VP1, 2, 3, 4, 6 and 7) and six non structural proteins (NSP1–6). The outer capsid is mainly composed of two proteins, VP4 and VP7. VP4 is involved in attachment to cells and gives the spoke-like appearance of the rotavirus 'wheel,' whereas VP7 gives the virus its smooth surface (Clark and McKendrick, 2004).

Rotaviruses are classified into seven serogroups (A - G) based upon the antigenic properties of VP6, an inner capsid protein, of which groups A, B, and C are human pathogens. Within the groups, viruses are classified into serotypes on the basis of differing outer capsid antigens.

The vast majority of these infections are caused by group A rotavirus, however, group B rotavirus is also responsible for significant outbreaks and may cause endemic disease in certain regions, for example, China and Bangladesh. Group C rotavirus is known to cause sporadic disease and since its first description in the United States in 1995 it has been described in other countries. Of the rotavirus group A serotypes, at least 10 G serotypes and eight P genotypes cause human infections. G1 - 4 are the most common G types found worldwide, and P[4] and P[8] are the most common P types found in association with them. G1P[8], G2P[4], G3P[8], and G4P[8] are the most common combinations globally (Kostouros *et al.*, 2003).



Caliciviruses

Kapikian *et al.* first described the 'prototype' calicivirus in 1972 during an outbreak of gastroenteritis in a school in Norwalk, Ohio. Due to an inability to culture the virus; further classification and epidemiological study faltered until recently, when sensitive molecular techniques became available. Four genera are now described, each sharing features under electron microscopy (Figure 13b). These include noroviruses, previously denoted as 'small round structured viruses' or 'Norwalk-like viruses,' and sapoviruses, previously denoted as sapporo-like viruses. Noroviruses are a genetically diverse group of single stranded RNA viruses. There are four genogroups: genogroup I, II, and IV (GI, GII, and GIV) infect humans, and genotype III (GIII) only affect cattle.

Astroviruses

The Astroviridae family is divided into two genera: Mamastrovirus, which encompasses human astroviruses and animal astroviruses; and Avastrovirus, the avian astroviruses. Astroviruses were initially described as 28–35nm diameter, non-enveloped particles, appearing as a five or six-pointed star (Latin, astron= star; Figure 13c). The astrovirus genome is a single-stranded positive sense RNA molecule containing three open reading frames (ORFs): ORF1a, ORF1b, and ORF2. ORF2 encodes the capsid precursor protein used to classify astroviruses.

Enteric Adenoviruses

At least 51 adenovirus serotypes (Ad1–51) in six subgenera (A–F) have been described in humans. Although diarrhoea may be a feature of infection by other adenoviruses, for example Ad3 and Ad7, most adenovirus gastroenteritis is caused by the so-called enteric adenoviruses, Ad40 and Ad41, which are members of subgenus F (Figure 13d). Adenoviruses cause infection throughout the year, predominantly in young children. The incubation period of 8–10 days is longer than in other enteric viruses, as is the duration of diarrhoea.

Contributions of My Research Works in the Area of Gastroenteric Viruses Plaguing Children

Mr Vice-Chancellor, Sir, I also began my research work on gastroenteric viruses (Rotavirus, Adenovirus and Astrovirus) plaguing children since 2000 as diarrhoea remains the leading cause of illness and death among children in developing countries, Nigeria inclusive with a background study of these viruses to determine their

prevalence in Children under 5 years with diarhoea in Ilorin, Kwara State (Audu *et al.*, 2001).

Laboratory analysis of the stool samples collected revealed that infections in Ilorin were due to single infection of these viruses with a prevalence of 16.2%, 8.1% and 2.2% for Rotavirus, Adenovirus and Astrovirus respectively (Table 15). This finding suggests that rotavirus is the most important viral pathogen associated with gastroenteritis. Next to it was adenovirus and then Astrovirus in Ilorin, Nigeria.

Table 15: Prevalence of Gastroenteric Virus from Stools of Children in Ilorin, Nigeria.

Virus Detected	No. of Screened	No. Positive	%
Rotavirus	74	12	16.2
Adenovirus	74	6	8.1
Astrovirus	45	1	2.2

My further interest concerning these viruses was spurred by reports of field trials on candidate rotavirus vaccines around the world which suggests the need to study the epidemiology of rotavirus strains to formulate an effective rotavirus vaccine, because the immunity induced by candidate rotavirus vaccines is serotype-specific. Also, in Nigeria, serotype epidemiology of rotavirus infection has been reported in limited studies.

I and my team moved swiftly to study the Diversity of Human Rotavirus VP6, VP7, and VP4 in Lagos State, Nigeria (Audu *et al.*, 2002). This study aimed at extending the knowledge of VP7 serotype epidemiology for Lagos, Nigeria. The purpose was to know whether the currently-licensed vaccines and those on clinical trials

could protect our children, since they may protect less against unusual strains circulating in any country.

Analysis of the samples tested for VP6 subgroup epitope, subgroup II was predominant (51%) with only a few subgroup I strains (4%), while many could not be typed at all (45%). For theVP7 serotypes, G1 was the most prevalent strain (45%), followed by G3 strains (5%) as shown in Figure 16. Neither G2 nor G4 strains were found, although mixed G1/G2 has been reported for the first time in Nigeria. Of strains that were non-reactive to ELISA, 29 (34%) could not be typed by PCR for G type. A subset of 23 samples was selected on the basis of RNA electropherotype, VP7 serotype, and included nine strains of VP7 that were non-reactive to ELISA. VP4 genotype of this subset was determined by PCR, and the most prevalent genotype was P[6] (30%), followed by P[8] (26%). Only one P[4] strain was identified (Figure 17).

This suggests that there is a diversity of prevalence of strains in different parts of Nigeria and has shown the diversity of rotavirus strains circulating in West Africa.

Table 16: Relative Frequency of Rotavirus VP7 Types in Stools from Children with Acute Gastroenteritis in Lagos

VP7 serotype	No. (%) detected by mab ELISA (n=84)	No. detected by RT-PCR* (n=40)	No. (%) detected by both methods (n=84)
G1	30 (35.7)	8	38 (45.2)
G2	0	0	0
G3	3 (3.6)	1	4 (4.8)
G4	0	0	0
Mixed specificity			
G1 and G2	2 (2.4)		2 (2.4)
G1 and G3	4 (4.8)	2	6 (7.1)
All four G types	5 (6.0)		5 (6.0)
Not typed	40 (47.6)	29	29 (34.5)

* Only 40 specimens non-reactive to ELISA were analyzed by RT-PCR

Table 17: Combinations of Rotavirus G and P Types in Children from Lagos

Type	G1 (n=6)	G3 (n=2)	G1+2 (n=2)	G1+3 (n=4)	Not typed (n=9)	Total (n=23)
P[6]	3	0	1	1	2	7
P[8]	2	1	1	1	1	6
P[4]	0	0	0	0	1	1
P[6+8]	0	0	0	2	5	7
Not typed	1	1	0	0	0	2

Mr Vice-Chancellor, Sir, in my continued effort in generating more data and information of these Gastroenteric Viruses in Nigeria, a follow up research work was conducted in 2008 to further study the Prevalence of Rotavirus-induced Diarrhoea among Children under 5 Years in Ilorin, Nigeria (Odimayo *et al.*, 2008) to determine the prevalence of rotavirus induced diarrhoea in children <5 years of age using **electropherotyping**.

In our previous study in 2001; conducted in this environment, Rotavirus was found to be the most prevalent viral agent in paediatric diarrhoea based on findings using ELISA detection technique. However, ELISA can only detect 'group A' rotavirus. Electropherotyping is a technique used to analyse rotavirus based on the arrangement and motility of the nucleic acid segments under the influence of an electric field. This method can detect all types of rotavirus and also used in identification of type-specific strains, hence, its advantage in tracing nosocomial infection, and in vaccine development.

In this study, the prevalence of rotavirus-induced diarrhoea was 55.9% (Table 18) which was higher than the earlier prevalence seen in Ilorin. The reason for lower

prevalence in the other study may be accounted for by the limitations of ELISA (which was used) which can only detect group A rotaviruses in contrast to electropherotyping which can detect all groups of human rotaviruses.

Also, the study revealed that prevalence of rotavirus in the first 24 months of life was significantly higher than those between 24 and 60 months, showing that the ages commonly associated with diarrhoea are also commonly associated with rotavirus infection (Figure 14).We concluded that rotavirus is still the most important cause of diarrhoea among children <5 years in Ilorin, Nigeria and the prevalence of diarrhoea induced by rotavirus is highest in the first 2 years of life.

Table 18: Results of Stool Analysis

Results	Subjects	Controls
Negative	132	240
Positive	167	0
Total no.	299	240
Positivity (%)	55.9	0

$\chi^2 = 194.22$.
p-value $= 0.00000$.

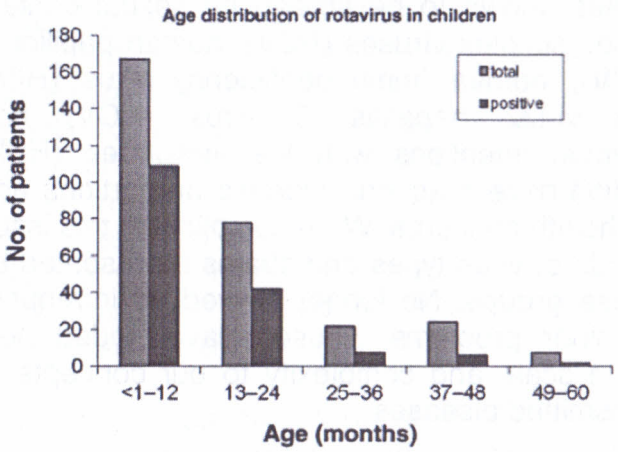


Figure 14: Age Distribution of Rotavirus Positive Children.

MODULE 4

SEXUALLY TRANSMITTED VIRUSES

The introduction of antibiotics effectively dealt with the classic venereal diseases gonorrhoea and syphilis. The number of new cases of these diseases fell rapidly, and many experts were lured into a false sense of security, going so far as to predict their elimination. With more liberal attitudes and increased sexual freedom, coinciding with the availability of birth control pills and antimicrobial therapy, the greatest fears of sexual intimacy, pregnancy and venereal disease, were significantly reduced. In this climate, there was a resurgence of sexually transmitted diseases, which included the traditional venereal diseases as well as those of viral etiology. Epidemics of known sexually transmitted viral agents originally restricted to herpes simplex virus (HSV) type 2 and less frequently, type 1.

Human viruses known to be spread by sexual contact include herpes simplex viruses (HSV), human papilloma viruses (HPV), human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus (HCV) and cytomegalovirus. Infections with the first three (HSV, HPV, and HIV) have reached epidemic proportions and pose global health concerns. What complicates this issue is the multitude of virus types and strains represented by some of these groups. No longer viewed as infrequent and often minor problems; viruses have added new dimensions in scale and complexity to our concepts of sexually transmitted diseases.

Herpes Simplex Viruses (HSV)

Herpes Simplex Virus (HSV) is a member of the *Herpesviridae* family and *Alphaherpesvirinae* subfamily of enveloped, double-stranded DNA viruses with relatively large complex genomes. HSV are neurotropic (infect nervous system) and have a short reproductive cycle (~18 hr.) with efficient cell destruction and variable host range.

Typically, HSV-1 is acquired in childhood and causes orolabial ulcers, while HSV-2 is sexually transmitted and causes ulcers of the anal and genital regions. This classical trend now varies, because both oral infections with HSV-2 and genital infection with HSV-1 are increasingly documented, probably as a result of oral-genital sexual practices (Baeten and Celum, 2006; Oke *et al.*, 2014). Herpes simplex virus-2 (HSV-2) is a worldwide common human viral infectious agent and is one of the most prevalent sexually transmitted infections. Most of the human race eventually is infected with Herpes Simplex Virus (HSV) type 1 (HSV-1), type 2 (HSV-2), or both (Jennings *et al.*, 2008). The viruses are

spread by close personal contact with someone shedding virus during social or sexual activities, although a limited number of infections can be attributed to medical or dental procedures and fomites. It has been said that HSV-1 and HSV-2 are almost perfect parasites. These viruses are able to infect exogenously, auto-infect (virus from a lesion in one area produces a lesion in another area), or super-infect (exogenous virus produces lesions in a previously infected host) almost everyone, rarely killing their human host (Agabi *et al.*, 2010).

The Herpes Simplex Viruses exhibit a structural and functional organisation unlike those of other viruses infecting eukaryotic cells. The genome is a linear double-stranded DNA molecule composed of two unique nucleotide sequences flanked by inverted repeated sequences, which can invert to produce four different isomers. Their icosahedral nucleocapsid contains the DNA which is surrounded by a lipid bilayer envelope containing five or six viral glycoproteins that mediate attachment and penetration into the host cell (Figure 15). There is significant homology between the HSV-1 and HSV-2 genomes, and a number of the polypeptides specified by one type are antigenically related to the other type.

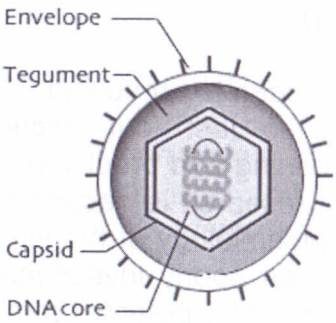


Figure 15: Structure of Herpesvirus.

Human Papillomavirus (HPV)

Human Papilloma Viruses (HPVs) are a family of small double-stranded DNA viruses that have a tropism for the epithelia of the genital and upper respiratory tracts and for the skin. Approximately 150 HPV types have been discovered so far, which are classified into several genera based on their DNA sequence. Approximately 15 high-risk mucosal HPV types are clearly associated with cervical cancer; HPV16 and HPV18 are the most carcinogenic since they are responsible for approximately 50% and 20% of all cervical cancers worldwide, respectively.

It is now also clear that these viruses are linked to a subset of other genital cancers, as well as head and neck cancers. Due to their high level of carcinogenic activity, HPV16 and HPV18 are the most studied HPV types so far. Biological studies have highlighted the key roles in cellular transformation of the products of two viral early genes, E6 and E7 (Tommasino, 2014). Many of the mechanisms of E6 and E7 in subverting the regulation of fundamental cellular events have been fully characterised, contributing not only to our knowledge of how the oncogenic viruses promote cancer development but also to our understanding of basic cell biology (Tommasino, 2014).

Despite HPV research resulting in extraordinary achievements in the last four decades; significantly improving the screening and prophylaxis of HPV-induced lesions, additional research is necessary to characterise the biology and epidemiology of the vast number of HPV types that have been poorly investigated so far, with a final aim of clarifying their potential roles in other human diseases

Hepatitis B Virus

Hepatitis B virus (HBV), a DNA virus of the family hepadnaviridae (with the smallest genome of all replication competent animal DNA viruses) is the causative agent of hepatitis B infection (Pungpapong *et al.*, 2007). HBV is an enveloped virus containing a partial or incomplete double-stranded circular DNA genome. It belongs to the family *hepadnaviridae*. It is 42 nm long and composed of 27 nm nucleocapsid core surrounded by an outer lipoprotein coat containing the Hepatitis B surface antigen (HBsAg).

Hepatitis B virus (HBV) is the leading cause of viral hepatitis in humans worldwide. Over two billion people have evidence of previous HBV infection and 350 million have become chronic carriers of the virus with 60 million of them residing in Africa. There seem to be differing risks for hepatocellular carcinoma (HCC) by geographical location, with higher risk recorded in countries in Sub-Saharan Africa and Asia compared to Europe (Willey *et al.*, 2008). It is 50 - 100 times more infectious than HIV and 10 times more infectious than Hepatitis C virus (HCV) with many carriers not realising they are infected with the virus, thus referred to as a "silent killer,"(Samuel *et al.*, 2004).

The minimum infectious dose is so low that such practices like sharing a tooth brush or a razor blade can transmit infection (Chang, 2008).The virus has been detected in peripheral mononuclear cells, tissues of pancreas, spleen, kidney and skin, and fluids like saliva, semen, sweat, breast milk, tears, urine and vaginal secretion (Chen *et al.*, 2009).

Hepatitis C Virus

Hepatitis C virus (HCV) is an RNA virus of the *flaviviridae* family and appears to have humans and chimpanzees as the only species susceptible to its infection. It was first identified in 1989 (Polyak, 2006). About 170 million people are infected with HCV worldwide (Liu and Hou, 2006; Sahakian *et al.*, 2007). Hepatitis C virus (HCV) is one of several viruses that cause hepatitis; an acute or chronic inflammation of the liver. Hepatitis C can lead to liver damage and possibly cancer. HCV is majorly transmitted by blood and blood products and it has also been detected in semen (Cavalliero *et al.*, 2008) and saliva (Chen *et al.*, 2009). The risk of vertical transmission is 6 and 25% in mothers who are only HCV positive and in those who are HCV/HIV positive respectively (Watannabe *et al.*, 2003).

The genome of HCV is highly mutable because HCV is an RNA virus and lacks efficient proofreading ability as it replicates, infecting humans undergoing evolution with time, giving rise to the notion that HCV persists as a collection of virus quasi species. By constant mutation, HCV may be able to escape host immunologic detection and elimination. HCV is highly heterogeneous and eleven HCV genotypes with several distinct subtypes have been identified throughout the world. These diversities have distinct consequences: although different strains have not been shown to differ dramatically in their virulence or pathogenicity, different genotypes vary in their responsiveness to antiviral therapy. Moreover, such heterogeneity hinders the development of vaccines.

Symptoms may appear 2 weeks to 6 months after exposure to the virus, but 75% of people have no signs of illness. Of those with symptoms, the most common is

chronic fatigue, but may also include lack of appetite, nausea, vomiting, itchiness, jaundice (yellowing of the skin and eyes), joint and muscle aches. Complications of Hepatitis C include chronic liver disease such as cirrhosis, liver cancer and liver failure.

Human Immunodeficiency Virus (HIV)

Human immunodeficiency Virus (HIV) is the only causative agent for acquired immune deficiency syndrome (AIDS) and is a member of Family *Retroviridae* and sub-family *Lentivirinae.* Since HIV/AIDS was first recognised in 1981 (Levy and Fieldsteel, 1982; Lal *et al.*, 2005), it has spread beyond all boundaries (social, political, regional, religious, and ethnical), therefore becoming a global concern (UNAIDS/WHO, 2008).

Human Immunodeficiency Virus (HIV) is a spherical, enveloped RNA virus composed of two major parts; an outer envelope and an inner core and is approximately 80 – 100 nm in size (Figure 16). There are two types of HIV, namely HIV-1 and HIV-2. HIV is subdivided into groups, subtypes, sub-subtypes, circulating recombinant forms (CRF) and unique recombinant forms (URFs) (Robertson *et al.*, 2000). Genomic characterisation of HIV-1 strains has revealed the existence of 4 phylogenetically distinct groups: M, O, N and P (Plantier *et al.*, 2009). In Nigeria, surveillance for HIV/AIDS started over two decade ago (Olaleye *et al.*, 1995; Agwale *et al.*, 2002; Lar*et al.*, 2007).

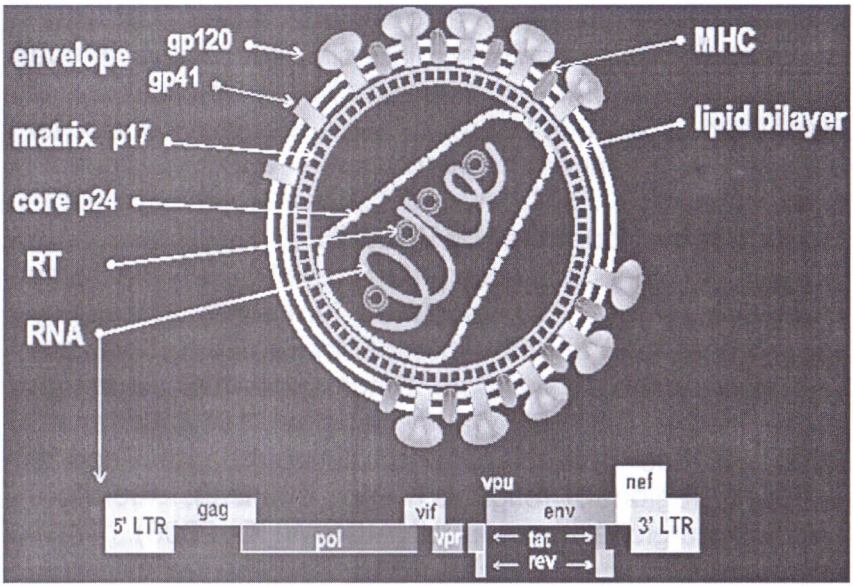


Figure 16: Structure of HIV

Contributions of My Research Works in the Area of Sexually Transmitted Viruses

My Vice-Chancellor, Sir, I began my research work on sexually transmitted viruses since 1985 with the Human immunodeficiency Virus (HIV) in Ibadan before I joined the services of the University of Lagos with the prevalence of human immunodeficiency virus types 1 and 2 infections in Nigeria (Olaleye *et al*, 1993), since the virus was first recognised in 1981 and was spreading across all boundaries.

Finding from this study revealed that from 3854 serum samples collected at 21 locations from 1985 to 1990; Seventy-eight samples (2.0%) were reactive for HIV-1 and 49 (1.3%) for HIV-2 antibodies, 5 samples were reactive for both viruses. The prevalence of HIV-1 and -2 infections, respectively, was highest among 60 female prostitutes, with 10% and 6.7% positive. For other

groups, the respective rates of positivity were 4.1% and 3.4% in 610 patients with sexually transmitted diseases, 3.6% and 1.4% in 140 tuberculosis patients, 1.6% and 0.6% of 1253 other medical patients, and 1.2% and 0.9% of 1640 volunteer blood donors. Of 153 health care workers, 1.3% were positive for HIV-1 only. The age group from 20 to 29 years had the highest prevalence of HIV-1 (3.3%) and -2 (2.2%). It was concluded from this study that in Nigeria, antibody prevalence for both viruses appears to have increased > 10-fold between 1986 and 1990.

Since HIV was an evolving pandemic and disease of enormous significance as at that time; Nigeria is yet to have a broad based surveillance report. A further study was undertaken to determine the seroprevalence of HIV-1 and 2 antibodies in Lagos, Nigeria over a 10-year period (1991 - 2000). An average prevalence of 17.79% (n = 12,315) was recorded between 1991 and 2000 with a steady increase from 1.1% in 1991 to 28.56% in 2000. This brought to light that HIV/AIDS prevalence was on the increase in Nigeria, most especially in large capital cities like Lagos. These results affirm the rising trend in infection and implications on the productive age group, thus, the situation calls for mass campaigns. (Badaru *et al.*, 2011).

Also, as access to antiretroviral drugs (ARVs) in the developing world particularly Nigeria was increasing rapidly and the changing genetic variability of HIV, development of resistance to ARVs treatment were ever increasing concern in the management of HIV positive individuals. Genetic differences among HIV-1 variants can influence the virus biological properties, susceptibility to existing and candidate antiretroviral drugs, and

evolution of antiretroviral drug resistance. It was imperative to provide information on the genetic variability of HIV-1 strains circulating in Lagos by molecular typing and phylogenetic analysis to help guide in the decision making regarding diagnostic and monitoring assays used in these treatment programmes.

In the phylogenetic sequence analysis of the protease and reverse transcriptase (RT) sequences, 6 different Circulating Recombinant Forms (CRFs) and 1 subtype of HIV-1 variants were observed circulating in this environment as shown in this study (Table 19). Further analysis of the genetic sequences generated by constructing a NJ, bootstrapped phylogenetic tree showed the relationships of the HIV-1 CRFs and subtypes sequenced in this study to reference sequences. The different 6 CRFs and 1 subtype of the HIV-1 strains are as shown in figure 17. Findings from this study confirm the presence of diverse circulating recombinants not previously reported in Nigeria.

Table 19: Subtypes and Circulating Recombinant Forms (CRFs) of HIV-1 Infected Patients in Lagos, Nigeria

S/No	FREQUENCIES (%)	SUBTYPES/CRFs	SUBTYPES/CRFs COMBINATION
1.	15 (39.5)	CRF02_AG	A,G
2.	12 (31.6)	CRF43_02G	CRF02, G
3.	6 (15.8)	CRF09_cpx	A, G, U
4.	2 (5.3)	CRF06_cpx	A, G, J, K
5.	1 (2.6)	G	G
6.	1 (2.6)	CRF19_cpx	A1, D, G
7	1 (2.6)	CRF07_BC	B^1, C

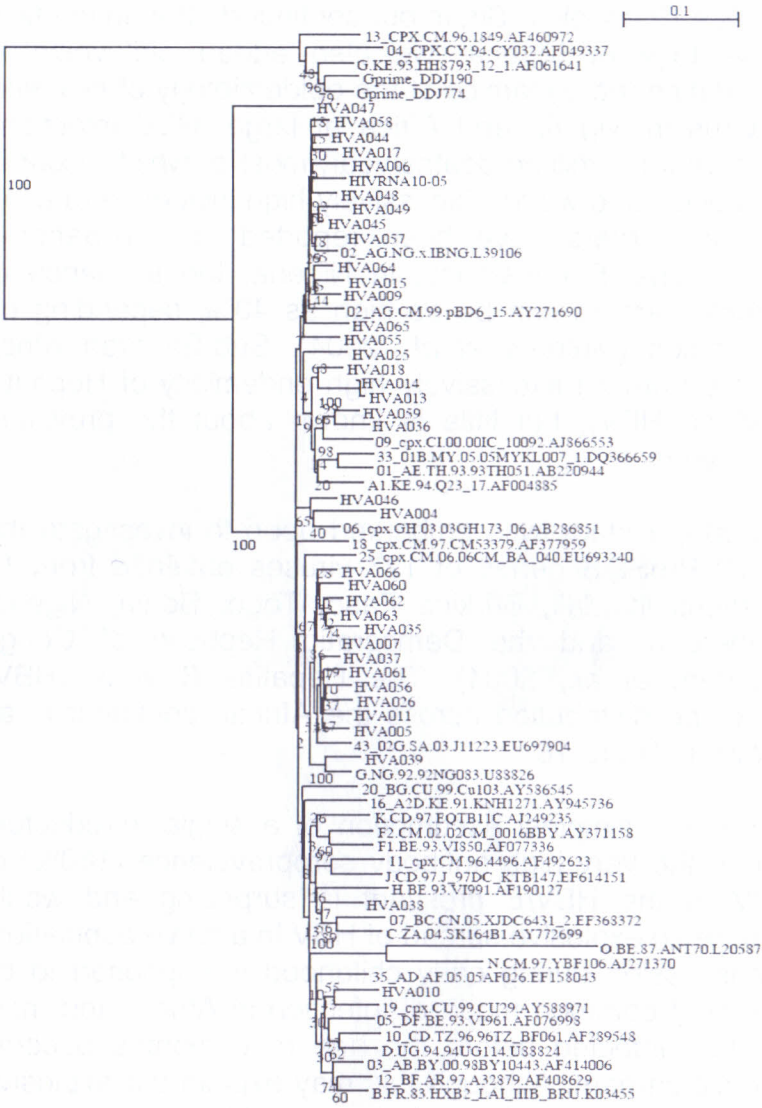


Figure 17: Phylogenetic Tree of Genotypic Sequences with Reference Sequences of Different Subtypes and Circulating Recombinant Forms Note: Lagos strains are labeled as HVAs.

Mr Vice-Chancellor, Sir, in our continued effort in the field of virology in Nigeria, we also added our voice in elucidating the dynamics of the epidemiology of Hepatitis B Virus in Nigeria and Africa at large. HBV infections account for 1 million deaths/year, most of which occur in the developing world. Excessively high incidence rates of chronic carriers have been reported in Sub-Saharan populations. For instance, in Nigeria, the incidence of chronic carriers can be as high as 40%, depending on the region (Mulders *et al.*, 2004). Sub-Saharan Africa suffers from an excessively high endemicity of Hepatitis B virus (HBV), but little is known about the prevalent genotypes.

In 2004, a study was embarked upon to investigate the PreS1/PreS2/S genes of 127 viruses obtained from 12 locations in Mali, Burkina Faso, Togo, Benin, Nigeria, Cameroon, and the Democratic Republic of Congo (Mulders *et al.*, 2004). The Hepatitis B virus (HBV) genotype distribution across the African continent is as shown in figure 18.

Under the simplest assumption of a single introductory event; the very high antibody seroprevalence (180%) of HBV in the HBV/E crescent is surprising and would require an explosive spread of HBV in a naive population. Transmission during early childhood is supposed to be the most common mode of infection in Africa, and most children infected before the age of 6 months become chronic carriers. Although this may explain the explosive spread of virtually identical viruses within a community, it is critical to understand whether it explains also the similarity of viruses across the vast expanses of the HBV/E crescent.

Infection during infancy is mostly associated with chronic carrier status, and this combination can account for the explosive spread of virtually identical viruses within a community, but whether other routes of long-range transmissions must be considered becomes an important question.

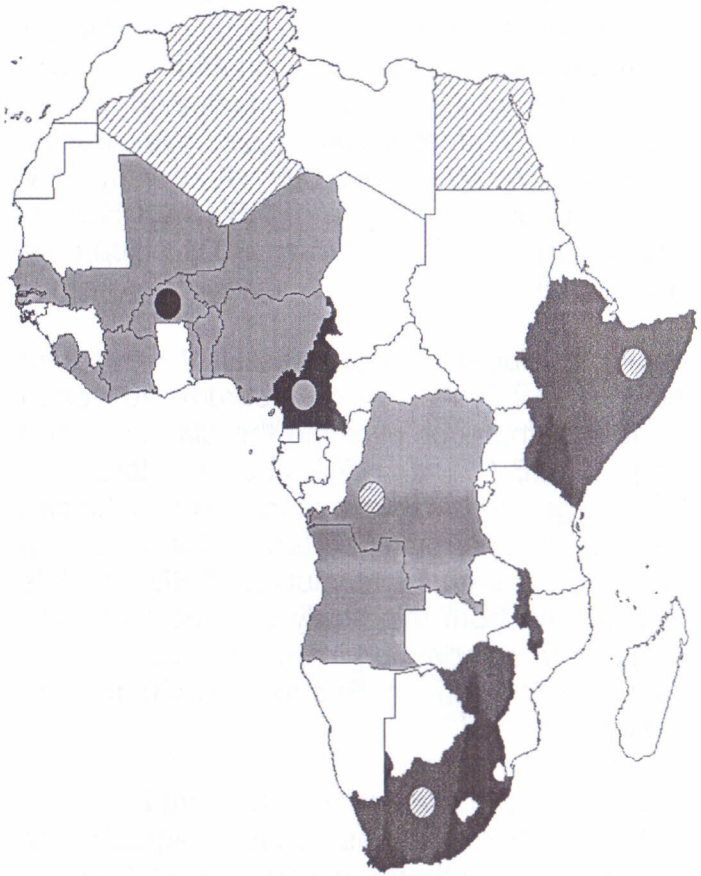


Figure 18: Hepatitis B Virus (HBV) Genotype Distribution across the African Continent. HBV Genotype A, Black; HBV Genotype D, Stripes; and HBVGenotype E, Gray

Note: Incidental Genotypes are Shown as Inserted circles.

Our research work also continued with Hepatitis D Virus (HDV), a satellite of hepatitis B virus (HBV) and infection with this virus aggravates acute and chronic liver disease. While HBV sero-prevalence is very high across Sub-Saharan Africa, much less is known about HDV in the region. Hepatitis D virus (HDV), a negative-strand RNA virus of 1.7 kb in size, is always associated with Hepatitis B Virus (HBV) infection, which it requires for proliferation. About one-fourth of the estimated 65 million chronic HBV carriers in Africa are suspected to be co-infected with HDV. Co-infection with these two viruses' results in fulminant hepatitis more often than with HBV infection alone, and super-infection of HBV with HDV is associated with chronic HDV in up to 80% of carriers (Andernach *et al.*, 2014).

Furthermore, HDV infection suppresses HBV replication and reduces HBV DNA in the serum to often undetectable levels, thus complicating the diagnosis and co-genotyping of HBV and HDV strains. Here, we substantially enlarge the database of indigenous African HDV sequences, providing important information to further understand the complex evolution of HDV on this continent. Our finding from this study showed that HDV seems to be much more common in chronic liver disease patients in the Central African Republic (CAR) than in similar cohorts in Nigeria.

In a large nested mother-child cohort in Burkina Faso, the prevalence of HDV antibodies was 10 times higher in the children than in their mothers, despite similar HBsAg prevalence, excluding vertical transmission as an important route of infection. The genotyping of 16 full-length and 8 partial HDV strains revealed clade 1 (17/24) in three of the four countries, while clades 5 (5/24) and 6

(2/24) were, at least in this study, confined to Central Nigeria (Table 20).

On the amino acid level, almost all our clade 1 strains exhibited a serine at position 202 in the Hepatitis D antigen; supporting the hypothesis of an ancient African HDV-1 subgroup. Further studies are required to understand the public health significance of the highly varied HDV prevalences in different cohorts and countries in Sub-Saharan Africa. Our study revealed high prevalences of both HBV and HDV in multiple countries and cohorts from Sub-Saharan Africa. For instance, conspicuous differences in HDV prevalence were found in cohorts with severe chronic hepatitis from Nigeria and CAR and in mother-child pairs from Burkina Faso.

Table 20: Prevalences of Hepatitis B Surface Antigen, Hepatitis D Antibodies, and Hepatitis D RNA in Cohorts from Different Western and Central African countries

Country	Sampling location (yr)	Cohort type	Cohort size (*n*)	HBV/HDV prevalence (no. of positive patients/total no. of patients [%])				HDV clade present (no. of that clade)
				HBsAg	HDV Ab[a]	HDV RNA[b]	HDV RNA/HBsAg	
Burkina Faso	Bobo-Dioulasso (2001)	Mothers	370	60/370 (16.2)	1/40 (2.5)	0/1 (0)	0/40 (0)	
	Bobo-Dioulasso (2001)	Children	424	52/424 (12.2)	9/44 (20.5)	0/9 (0)	0/44 (0)	
	Bobo-Dioulasso, Houndé (2007)	Pregnant women	337	49/337 (14.5)	0/49 (0)		0/49 (0)	
Nigeria	Ibadan (1998)	HIV$^+$ patients	106	11/69 (15.9)	3/11 (27.3)	0/3 (0)	0/11 (0)	
	Lagos (2004)	HIV$^+$ patients	319	45/308 (14.6)	3/45 (6.7)	2/3 (66.7)	2/45 (4.4)	1 (1); 6 (1)
	Ibadan (2003)	Liver patients	93	44/70 (62.9)	3/44 (6.8)	0/3 (0)	0/44 (0)	
	Ibadan (2006)	Liver patients	126	103/126 (81.7)	1/78 (1.3)	1/1 (100)	1/78 (1.3)	1 (1)
	Abuja, Nasarawa state (2006)	HBsAg$^+$	330	330/330 (100)	40/326 (12.3)	15/40 (37.5)	15/326 (4.6)	1 (6); 5 (5); 6 (1
Chad	Military camp (2007)	Military personnel	50	14/50 (28)[c]		3/14 (21.4)[c]	3/14 (21.4)[c]	1 (3)
Central African Republic	Bangui (2007)	Children	81	35/79 (44.3)	1/35 (2.9)	0/1 (0)	0/35 (0)	
	Bangui (2009)	Liver patients	37	14/29 (48.3)	7/14 (50)	5/7 (71.4)	5/14 (35.7)	1 (6)[d]

[a] Prevalence among HBsAg-positive samples, exclading equivocal samples.
[b] Prevalence among HBsAg-positive HDV Ab-positive samples.
[c] Prevalence calculations based on HBV and HDV TaqMan PCR. Samples positive for at least one assay were considered HBV positive.
[d] Includes one sample that was not tested for HBsAg and therefore not included in the previous columns.

Further research works were also done on Human Papilloma Viruses (HPV), Herpes Simplex Virus (HSV) and *Chlamydia trachomatis*. For the HPV; the study was carried out to determine the prevalence and distribution

of oncogenic HPV infection among women seen at the cytology clinic of a tertiary hospital in Lagos South-west Nigeria (**Adegbesan-Omilabu** *et al.*, 2014). Eligible women were selected by consecutive sampling method for the study. The endocervical swab samples were screened for HPV types 16, 16A, 31, 33 and 35 by the multiplex Polymerase Chain Reaction (PCR) using the specific primers for the HPV types. Twenty-four (30.4%) of the 79 tested swab samples were positive for viral DNA of high risk HPV 16.

There was a statistically significant difference in the mean ages of participants with positive cervical HPV and those without the infection respectively (34.8 ± 9.9 vs. 46.2 ± 10.1 years; P = 0.028). However, there were no significant differences found between the women with HPV positivity and those without, with respect to marital status (P = 0.074), tribe (P = 1.009), religion (P = 0.681) and educational status (P = 0.552) (Table 21).

Other identified risk factors that showed statistically significant differences for oncogenic HPV infection were age at sexual debut (P = 0.009), parity(P = 0.003), number of lifetime sexual partner(s) (P = 0.000), use of combined oral contraceptives (P = 0.044), HIV seropositivity (P = 0.000) and smoking (P = 0.033).

Summarily, cumulative high risk HPV infection is high in Lagos, Nigeria. These findings thus support the need for routine and early screening of all identified high risk sexually active women for HPV infection in Nigeria, as well as emphasising further the importance of sex education for the girl child in school and increased awareness for parents towards HPV vaccination for their generally healthy adolescent girls.

Findings from the study on HSV aimed to determine the seroprevalence of HSV-2 among attendees of an HIV counselling and testing Centre (HCT), at a large HIV treatment centre in Lagos, Nigeria (Oke *et al.*, 2014), was a cross sectional study among clients presenting for voluntary HCT, who were counselled and screened for HIV and HSV-2.Two hundred and fifty eight participants enrolled for the study with 60% of participants being female.

The most prominent age group was 24 - 29 years (22.6%) for female and 30-35 years for male (25.2%). The prevalence of HIV and HSV-2 among the participants was 29.8% and 9.7% respectively. In addition, 7.8% tested positive to both HSV and HIV, with HSV-2 prevalence among the participants that tested positive to HIV significantly higher than participants that tested negative to HIV ($P < 0.001$). The strength of the association by partial correlation demonstrated a medium correlation for HIV and HSV-2 and a weak correlation for age group and HSV-2 (0.359 and 0.187 respectively). The association between HSV-2 and HIV infection is attested to by this study showing a high prevalence of HSV infection among HIV positive participants.

Finally on this note, our study on Chlamydia was aimed to determine the prevalence of Chlamydia trachomatis and the association between its infection and cervical intra-epithelial lesion (**Adegbesan-Omilabu** *et al.*, 2014). It was a cross-sectional case control study carried out at the Lagos University Teaching Hospital (LUTH) with the study participants selected into 2 groups: the case group (women with abnormal smears) and the control group (women with normal Pap smear).

Relevant information was obtained using a structured interviewer-administered questionnaire. Endocervical swab samples were collected and analysed by Polymerase Chain Reaction (PCR) test. Results from the study showed that the overall prevalence of *C. trachomatis* was 27.7% with a decreasing trend noted with age ($P < 0.05$) (Table 22). The majority of women with *C. trachomatis* were in the reproductive age group of 25-45 years. 50% of women with abnormal smears were positive for *C. trachomatis*, compared to only 16.7% of the controls ($X2 = 10.95$; $P = 0.001$). There was no statistically significant association between prevalence of *C. trachomatis* and cervical cytological types ($X2 = 1.892$; $P = 0.595$).

The study also revealed an association between *Chlamydia trachomatis* and precancerous lesions of the cervix. Therefore, routine screening and treatment of sexually active adolescents and women in the reproductive age group is recommended as an indirect measure to reducing the incidence of cervical cancer in Nigeria.

Table 21: Socio-demographic Characteristics of the Study Population (n=79)

	HPV positive N (%)	HPV negative N (%)	*P value
Age of respondents			
<25	0 (0.0)	2 (100.0)	0.028
25-34	11 (30.6)	25 (69.4)	
35-44	7 (26.9)	19 (73.1)	
45-54	4 (33.3)	8 (66.7)	
≥55	2 (66.7)	1 (33.7)	
Mean ± SD	34.8 ± 9.9	46.2 ± 10.1	
Marital Status			
Single	5 (26.3)	14 (73.7)	0.074
Married	15 (31.9)	32 (68.1)	
Divorced/separated	3 (37.5)	5 (62.5)	
Widowed	1 (20.0)	4 (80.0)	
Tribe			
Yoruba	10 (29.4)	24 (70.6)	1.009
Hausa	5 (26.3)	14 (73.7)	
Ibo	7 (43.8)	9 (56.2)	
Others	2 (20.0)	8 (80.0)	
Religion			
Christianity	15 (31.9)	32 (68.1)	0.681
Islam	9 (30.0)	21 (70.0)	
Others	0 (0.0)	2 (100.0)	
Educational status			
None	1 (100.0)	0 (0.0)	0.552
Primary	5 (29.4)	12 (70.6)	
Secondary	11 (33.3)	22 (66.7)	
Tertiary	6 (24.0)	19 (76.0)	
Postgraduate	1 (33.3)	2 (66.7)	
Total	24 (30.4)	55 (69.6)	

Table 22: Prevalence of *Chlamydia trachomatis* in Women with Normal and Abnormal Smears

Age (years)	Chlamydia positives N (%)	Chlamydia negatives N (%)
25-30	3 (75.0)	1 (25.0)
31-35	5 (21.0)	19 (79.0)
36-40	10 (32.3)	21 (67.7)
41-45	6 (60.0)	4 (40.0)
46-50	1 (14.3)	6 (85.1)
>50	0 (0.0)	14 (100.0)
Total	25 (27.7)	65 (62.3)

Viral Haemorrhagic Fevers

Viral Haemorrhagic Fevers (VHFs) refer to a group of illnesses that are caused by several distinct families of viruses. In general, the term "Viral Haemorrhagic Fever" is used to describe a severe multisystem syndrome (multisystem in that multiple organ systems in the body are affected). Characteristically, the overall vascular system is damaged, and the body's ability to regulate itself is impaired. These symptoms are often accompanied by haemorrhage (bleeding); however, the bleeding is itself rarely life-threatening. While some types of haemorrhagic fever viruses can cause relatively mild illnesses, many of these viruses cause severe, life-threatening diseases.

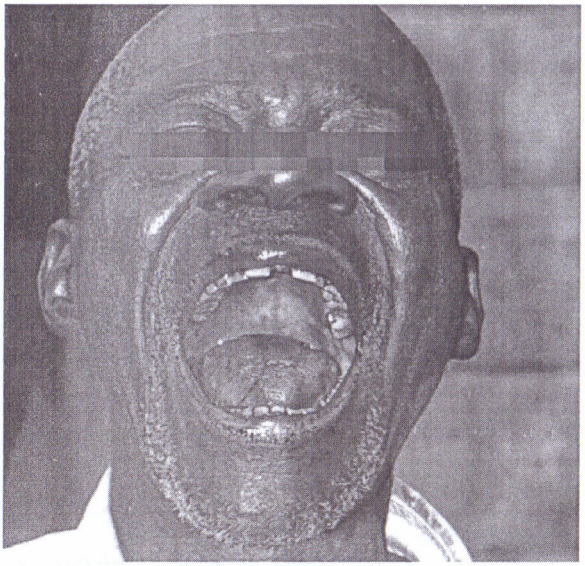


Figure 19: Bleeding in the Gum as Seen in a Lassa Infected Patient

VHFs are caused by viruses of four distinct families: arenaviruses, filoviruses, bunyaviruses, and flaviviruses (Table 23).

Table 23: Viral Hemorrhagic Fever Family Viruses

Arenaviridae	Bunyaviridae	Filoviridae	Flaviviridae
Junin	Crimean- Congo H.F.	Ebola	Kyasanur Forest Disease
Machupo	Hantavirus	Marburg	Omsk H.F.
Sabia	Rift Valley fever		Yellow Fever
Guanarito			Dengue
Lassa			

Some of the members of the Bunyaviridae (Crimean Congo Haemorrhagic Fever Virus (CCHF) and Rift Valley virus) and Flavivirdae (Yellow Fever and Dengue Haemorrhagic Fever Viruses) have been discussed in Module 2 of this lecture. However, I shall focus on two viruses (Lassa Fever Virus and Ebola Virus) that have greatly plagued our society in recent times. Clinically, they are characterised by severe multisystem syndrome, damage to overall vascular system accompanied by conjunctivitis, petechia, and echymosis.

ARENAVIRIDAE

Arenaviruses are rodent-borne viruses, some of which are aetiological agents of severe haemorrhagic disease in Africa and America. Seven arenaviruses cause human disease: Lymphatic Choriomeningitis, Lassa Fever, Machupo, Junin, Guanarito, Sabia, and Lujo viruses. Lassa virus has been known to cause human diseases in Nigeria and some parts of West Africa while Lujo was identified in South Africa.

Survival of the virus is dependent on an animal or insect host, for the natural reservoir. Virus transmission and amplification occurs in rodents and shed virus through urine, feaces, and other excreta. Contact with contaminated materials or infected persons causes infections in humans.

Figure 20: *Mastomys natalensis* - A major Reservoir Host of Lassa Virus

- Arenaviruses associated with human disease

Virus	Origin of Name	Year	Distribution
Lassa	Town, Nigeria	1969	West Africa
Junin	Town, Argentina	1957	South America
Machupo	River, Bolivia	1962	South America
Guanarito	Area, Venezuela	1989	South America
Sabia	Town, Brazil	1990	South America
LCMV	Clinical disease	1933	Worldwide
Lujo	Sigla	2008	Southern Africa

Lassa Fever Virus

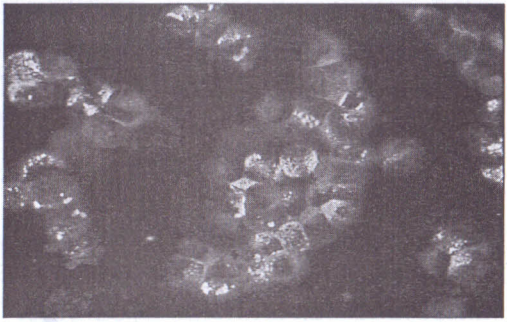
Lassa fever was first noticed early in 1969 in three missionary nurses in Brethen Mission House, Lassa village, Adamawa State. The disease later affected two laboratory workers at the Yale Arbovirus Research Unit (YARU) in New Haven. Two of the nurses and one of the Laboratory worker died. Dr. Janette Troup who also described the clinical and pathological findings on the virus also died in 1970 (Figure 21). She described Lassa fever, a hitherto unknown viral disease from Nigeria. Onset is gradual with fever, weakness, myositis, and ulcerative pharyngitis, progressing to symptoms of myocarditis, pneumonitis, and pleuritis, encephalopathy and evidences of haemorrhagic diathesis. It is characterised in the early stages by moderate leucopenia, with increase of immature neutrophilic elements. It can be transmitted directly from person to person; the incubation period is about a week.

After this outbreak, there was no news on Lassa virus until in the early 90s when a Nigerian-American visited Nigeria for his grandmother's funeral in Ekpoma, Edo State and lost his life when he got back to America after showing clinical symptoms of Viral Haemorrhagic Fever.

This prompted the CDC to conduct an epidemiological studies on the virus and hence, began a new research page on the virus in Nigeria. The virus was found to be transmitted by Rodents such as *Mastomys natalensis*, *M. huberti*, and *M. erytholecus*. Till date Lassa fever virus has continued to plague Nigeria and the West African Sub-region.

Figure 21: Some of the Nurses and Researchers who got Involved with Lassa Fever Virus

Mr. Vice-Chancellor, Sir, may I humbly inform you, Sir, that my laboratory was the first to indigenously diagnose Lassa fever virus using Immunofluorescent microscopy (Figure 22) and the first to carry out Molecular epidemiology using the PCR platform in 2003 (Figure 23).



Lassa viral antigens seen as granules/dots within the cytoplasm

Figure 22: Immnofluorescent Detection of Lassa Fever

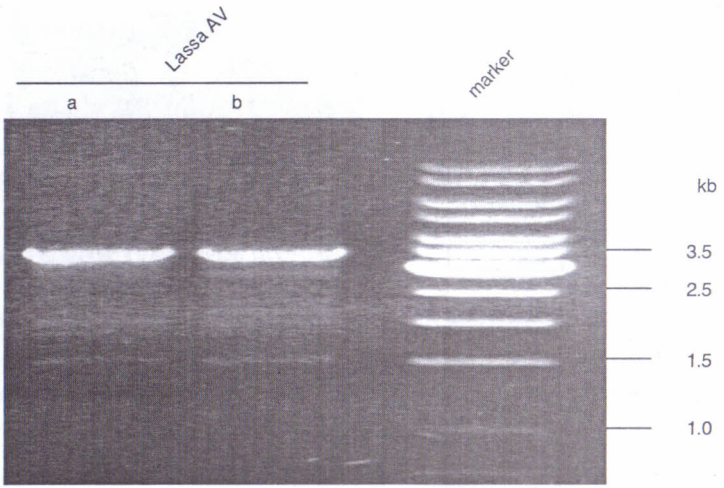


Figure 23: Agarose Gel Image showing PCR Amplicon Bands of Lassa Fever Virus

A collaboration with the Benard Nocht Institute, Germany led to the award of grants from the Volkswagen Foundation, Germany; this provided the expansion of the research capacity of my laboratory in terms of Molecular diagnosis. Out of the grants provided for my laboratory, we also did set-up the Lassa fever laboratory in Irrua, Edo State.

My laboratory has published several works on the Epidemiology of Lassa fever virus and the development of new PCR primers that have serve as detection platforms for other laboratories in the world. I also trained postgraduate students and produced a Ph.D (Dr. Ehichioya Deborah) from the work (**Omilabu** *et al.*, 2005; Olschlager *et al.*, 2010; Ehichioya *et al.*, 2010). Some laboratory data generated during the course of our work are presented thus:

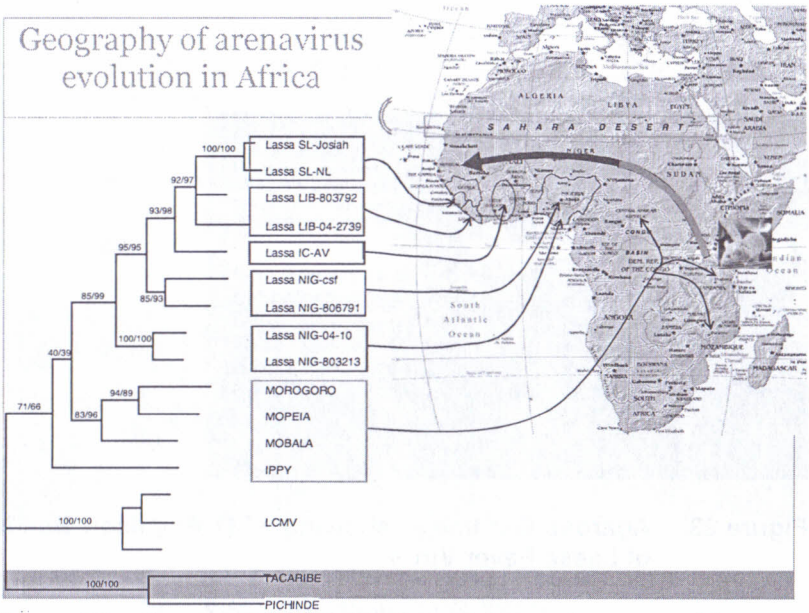


Figure 24: Geographical Evolution of Arenaviruses and Lassa

Table. Lassa virus–specific findings in 60 serum samples from Irrua Specialist Teachin Hospital, Edo, Nigeria*

Patient	RT-PCR†	IgM titer‡	IgG titer‡
Patients with fever (n = 31)			
04-10	Positive§	–	–
04-02	Positive	1:40	–
04-51	–	1:160	–
04-34	–	1:40	–
04-03	–	1:>20,480	1:20,480
03-05	–	1:320	1:20,480
03-01	–	1:160	1:10,240
04-08	–	1:80	1:20,480
04-33	–	1:20	1:640
04-52	–	1:160	1:40
04-53	–	1:40	1:40
Contact persons (n = 17)			
04-04	Positive	1:20	–
03-04	–	1:160	1:>20,480
04-11	–	–	1:80
Hospital staff (n = 12)			
04-31	–	–	1:80
04-32	–	–	1:80
04-17	–	–	1:80
04-20	–	–	1:20

*Data not shown for patients whose samples were negative in all tests. RT-PCR, reverse-transcriptase polymerase chain reaction; Ig, immunoglobulin; –, negative result.
†RT-PCR targeting the Lassa virus glycoprotein gene (4). PCR products were detected in ethidium bromide–stained gel and sequenced (GenBank accession nos. DQ010030 and DQ010031 for 04-0 and 04-10, respectively).
‡Immunofluorescence assay used cells infected with Lassa virus strain Josiah. Findings were confirmed with μ-capture and IgG enzyme-linked immunosorbent assays (data not shown).
§Lassa virus was isolated in cell culture (strain Nig04-010), and part of the L gene was sequenced (GenBank accession no. AY693637).

FILOVIRIDAE

The family *Filoviridae* contains three genuses: *Marburg*, *Ebola* and *Cuevavirus* in which Marburg and Ebola viruses have greatly plagued the African Continent and scared the world at large. They are antigenically unrelated but have similar morphology and are agents of viral haemorrhagic disease.

The *Marburg virus* was first reported in Europe in 1967 among laboratory personnel working with tissues of African green monkeys imported from Uganda to Germany and Yugoslavia. Sporadic outbreaks of this virus have been reported in South Africa (1975 and 1982), Kenya (1980 and 1987), Angola (2005) killing a lot of people.

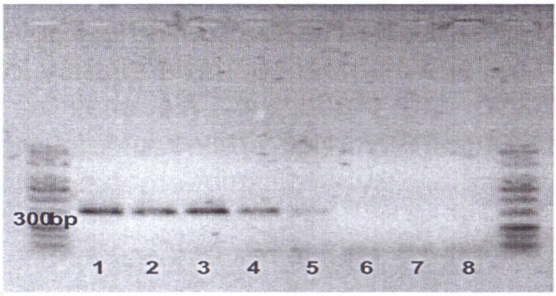
However, the largest outbreak recorded in the history of man was the last Ebola outbreak that began from a two year old child from Guekedou in Guinea in December 2013 but was undetected until there were reports of related deaths in the community. This led to the multiple transmission of the virus that caused the largest outbreak along the Makona River between Guinea, Liberia and Sierra Leone. The virus further spilled to neighboring African countries (Senegal, Mali and Nigeria) and other parts of the world such as USA, Spain, Italy and United Kingdom killing over 11,193 as at June 17, 2015.

Mr. Vice-Chancellor, Sir, my job as a hunter and tamer of viruses led to the pro-active measures taken by my laboratory to prepare for a possible entry of the Ebola virus into Nigeria as evidenced in July, 2014. Prior to the entry of index case into our country, my laboratory had developed and tested necessary molecular detection platforms. The heroic clinical work of Dr. Adadevoh

(Blessed memory) by reporting and submitting the suspected case's sample to my laboratory abated a massive outbreak that would have wiped out a lot of Nigerians. The rapid detection of the virus by my laboratory shocked some members of the World Health Organisation not believing that a laboratory in Africa could diagnose ebola virus as quickly as we did.

Mr. Vice-Chancellor, Sir, our laboratory therefore reported the first laboratory detection of Ebola virus in Nigeria using the Reverse Transcription PCR platform.
In our reports, PCR amplicons on the agarose gel (Figure 25) for Ebola virus detection were purified and products were sequenced using Filo A2.3 primer on the sanger dideoxy sequencing technology platform with an Applied Biosystems 3130xl genetic analyser. Sequence trace file was blasted against the gene bank and the RNA-dependent RNA polymerase (L) gene, partial cds sequence for EBOV/Hsap/NGA/2014/LIB-NIG 01072014 was deposited in the National Center for Biotechnology Information (NCBI) gene bank and assigned the accession number KM251803.1.

A set of 30 different Filovirus genomes were selected from NCBI's gene bank. FASTA format of the L-gene region of all the selected genomes were downloaded and aligned with KM251803.1 sequence using the MUSCLE tool of MEGA-6 software. Reliability of each node on the phylogenetic tree was tested by bootstrapping with 100 replicates (Figure 26).



1= Neat Blood
2= 1:10 Diluted Blood
3= 1:100 Diluted Blood
4= Neat Urine
5= 1:10 Diluted Urine
6= 1:100 Diluted Urine
7= Negative Sera
8= Negative PCR water

Figure 25: Agarose Gel Image Showing Bands of the Specimens and Listed in the Legend

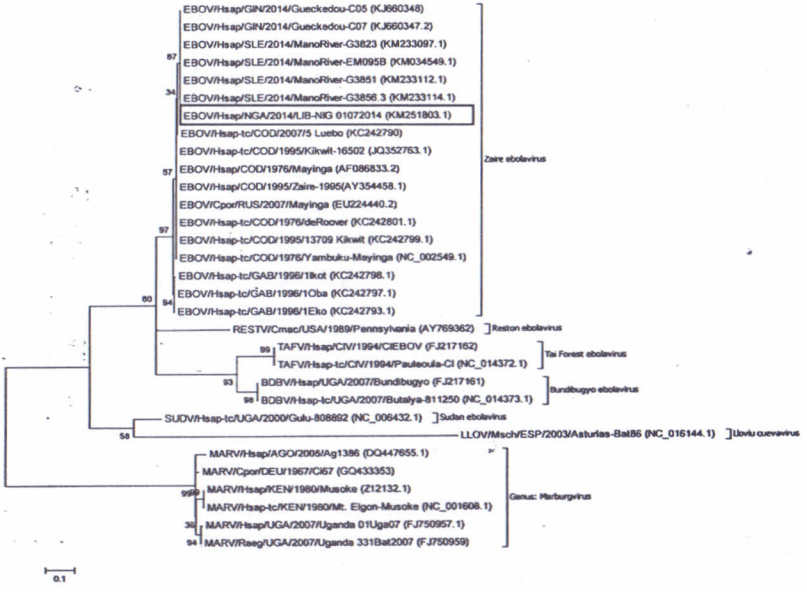


Figure 26: Molecular Phylogenetic Analysis of the L-Gene Segment of EBOV/Hsap/NGA/2014/LIB-NIG 01072014in Comparison with Selected Filoviruses Sequences by Maximum Likelihood method. Sequences are labelled using the ICTV Consensus Nomenclature for Variants of Filoviridae Family and their Corresponding Genebank Accession Numbers in parenthesis

Mr. Vice-Chancellor, Sir, lessons learnt from the Ebola outbreak has taught me and members of my laboratory to be prepared, proactive and productive. We shall not relent in our quest to tame many more viruses.

RECOMMENDATIONS

The University should give priority to Research, Development and Innovations (RD and I) through adequate funding and exposures. This will make the University to serve her role as a larger contributor to the economic and social development of the country. This will also boost the internally generated resources of our universities thus making us less dependent on the governments' inadequate funding experienced nowadays. Consequently, the Gown will be inviting the Town to come and take advantage of the RD and I for commercialisation through annual exhibitions of our research products.

The didactic form of training our students should be discouraged and replaced with modern and universal mode of training, i.e. case based and interactive delivery of lectures. Modern day equipment should replace our obsolete, inadequate and unserviceable equipment donning our university laboratories.

Our libraries should take fully the advantage of E-library enjoyed universally as this reduces cost of volumes of hard text and journals. Students and lecturers need adequate consultation of resources to prepare their notes and lectures/presentations respectively.

Our university should also ensure that both lecturers and students have adequate knowledge of how to conduct good research, research ethics, good proposal and publication writing. This will be achieved through adequate mentoring of both students and our young lecturers.

Furthermore, our various governments must invest adequately in disease monitoring and surveillance. This will make them spend less on combating the myriads of infectious diseases circulating in our environment. We should also borrow a leaf from the EBOLA VIRUS DISEASE. There are other deadly viral borne diseases that are yet to emerge or with potentials of re-emerging with its catastrophes.

Our immunisation policy should not be toyed with. As a country, we should be preparing, producing and supplying our much needed vaccines and be less dependent on importations. If well managed; vaccines can be exported to other African countries and of course serve as a huge source of revenue and employer of labour. Our immunisation programmes also are over dependent on donors; we should desist from this and look inwardly into local manufacturing of our vaccines.

ACKNOWLEDGEMENTS

I praise Allah, the Creator of the Heavens and Earths and all that dwells in it. The One that taught PEN the art of writing. I cannot thank HIM enough for what He made out of me. I thank Him for the opportunity to have come, and be part of existence in the last two centuries. I thank HIM for what He has done in my life; what is doing right now and what He will continue to do in my live. I thank HIM also for the opportunity given me to realise my POTENTIALS.

I give praise unto Allah for evolving me through my parents; Alhaji Abdul Raheem (a retired Police Officer) from Ibadan land and my mother "Iyaniwura," nee Omotayo family of Ifaki Ekiti. I thank them for my up-bringing. I thank them for the education they gave me at the time it mattered most. Allah SWT will continue to keep you for me. I know the two of you are full of praises to God, Almighty for His Kindness towards you. I also extend my gratitude to my uncles, nieces, cousins, and my siblings, especially the Omilabus, the Omotayos, the Onis, the Fashoyins, Ajagbes and the Adegbenros.

I acknowledge with thanks my in-laws from Oke-Odan; the Lawals and Yunus family of Iga Balogun and the Adegbesan Ruling family of Ise. I remain indebted to HRM, Oba Abdul Ganiyu Adegbesan, the Onise of Ise, Chairman Council of Traditional Rulers and Chiefs in Ibeju Lekki LCDA, the Olori Adegbesan and the entire Adegbesan family.

To my other extended parents, especially, my teachers in my formative ages (my primary school teachers at Ipetu

Ijesha and Oshogbo), my tutors at the secondary school, I say a big thank you.

I thank specially Chief D.B. Oni (B.A. Hons. Camb.) - our principal at Adekile Goodwill Grammar School, Ibadan. I always remember your efforts in Oral English, that you made compulsory at all levels but as students we felt indifferent.

I thank immensely all my lecturers at the University of Ife where I had my first degree. I will mention my supervisor Professor Deboye Kolawole and Professor (Mrs.) Kolawole for their interest in me. The foundation of my sojourn into research world was laid in Papa Kolawole's laboratory. The mentoring he gave me opened my intellect. May God Almighty continue to bless and keep you for us - Amen. I remember also some of my classmates 1981/82 set - especially Barrister Niran Ajilore, Eniola Awolaru and Rilwan Adebayo.I also remember my late cousin Eng. Lateef Olabode. He encouraged and devoted his time to teach me Chemistry and Physcis. May Allah grant him eternal rest amen. I gratefully acknowledge the various supports received from my childhood friends Engr. M. Odegbekun and A. Owoye.

I remember my NYSC days at Nigeria Institute of Medical Research in the laboratories of Professors Tekena Harry and Abdul Salam Nasidi. I owe to them my specialising in Virology; I will remain grateful. I owe a lot of indebtedness also to my Professors during my Postgraduate training at the College of Medicine University of Ibadan and all my teachers, then, who were all Professors - Tam David-West, Oyewale Tomori and Ademola Fagbami. I learnt a lot from these serving

Professors. I place also on record the academic and research training received from Professors Fagbami who directly supervised my projects and Oyewale Tomori whose laboratory I learnt the serological techniques I later exported to the College of Medicine, Idi-Araba.

I remember late Professor Akinyele Fabiyi for his advice on some aspect of my development. I place on record the adequate supervision received from Professor Clement Ojeh who co-supervised my work at a time. I also place on record the support received from Professors O.D. Olaleye, S.S. Baba, F. Adu and Dr. J. Adeniji.

I will remain indebted to the University of Lagos and College of Medicine, Idi-Araba managements at various times for giving me the opportunity to revive the Virology Unit to the present status. I thank the management for the approvals granted for my overseas trainings; more importantly for recognising my humble contributions to knowledge through promotions at various times in my stay at the University.

I specially thank Mr Vice-Chancellor, Professor Rahamon A. BELLO, my Provost, Professor Folasade OGUNSOLA and my Dean, Faculty of Basic Medical Sciences, Professor Olufunmilayo ADEYEMI for their gesture. I cannot but mention the Chief Medical Director (CMD) and the management of the L.U.T.H for the support given to my laboratory especially in recent years.

I place on record the recognition and support received from the Federal Ministry of Health through appointments at various times to serve on Emergency Preparedness as well as Taskforce Committees on the control of Lassa Fever, Yellow Fever and Avian Flu in Nigeria. I

acknowledge the confidence reposed in me by the immediate past Honourable Minister of Health; who appointed me to chair National Task Force Committee on the control of Viral Haemorrhagic Fevers in Nigeria throughout his tenure. I also appreciate Professor Oyekanmi Nash of NABDA for a lot of our collaborations on avian flu and VHFs.

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I would like to express my gratitude to all my seniors and other colleagues in the Department of Medical Microbiology and Parasitology, CMUL (both living and deceased) for their support and tolerance. I remember late Professors J.P.O. Oyerinde and A. F. Fagbenro-Beyioku today and always. They received me very warmly into their midst in 1991. May God continue to grant their souls' eternal rest, Amen. I thank Professors

A. O. Coker, F.O. Ogunshola, Drs, W. Oyibo, O. Oduyebo, A. Adenusi and A.O. Oladele. I profusely express my gratitude to Professor (Chief) Tolu Odugbemi, FAS, MNIOM and his wife Mama Odugbemi for their love and special interest in me. Professor Odugbemi took over the job of mentoring from my teachers in Ibadan; he supported my laboratory to the fullest. 'Aburo,' will continue to remain grateful for your generous support and belief in his competence. May God Almighty continue to shower His blessings and abundant life on the Odugbemis - Amen.

I remember my students whom God used as pillars to support my efforts and yearnings towards establishing a vibrant virology laboratory in CMUL. To God be the Glory; I had the rare opportunity of moulding 5 vibrant Virologists (Ph.Ds), co-supervised 5 Ph.Ds in other areas of microbiology and biochemistry and over 50 MSc. graduates. They are all making their waves in several establishments. Some of these are Drs. Mrs Rosemary Audu, Akeeb Bola Oyefolu, Olanrewaju Badaru, Deborah Ehichioya, Olumuyiwa Salu, Ayorinde James to mention just a few.

To my immediate family, I acknowledge the unflinching support of my wives and children for bearing with my usual excuses and absence from home and for tolerating my virological nuisance of sleeping in the laboratory ceaselessly. Are you not proud of yourselves today, being part of history? I thank you immensely for the steadfastness and understanding.

Mr. Vice-Chancellor, Sir, on a very sad note, while we were preparing the materials for this Inaugural Lecture, the cold hands of death snatched away my beloved wife

and partner; Late Dr (Mrs.) Maymunah Adeshola, Adegbesan-Omilabu, who until her death, was a Senior Lecturer and Consultant in the Department of Obstetrics and Gynaecology, CMUL. I pray fervently that Allah grant her Al-Jana Fridaus, Allahumo Aamin.

To all my invited guests and well wishers, great students of the UNILAG, I thank you all for your physical, moral and spiritual supports. May Allah Bountifully reward and Grant you all Journey Mercy back to your various destinations. I remain ever grateful. 'Shukran'

REFERENCES

Agabi, Y. A. *et al.*, (2010). Seroprevalence of Herpes Simplex Virus Type-2 among Patients Attending the Sexually Transmitted Infections Clinic in Jos, Nigeria. J Infect Dev Countries, 4(9): p. 572-5.

Agwale S. M., Zeh, C., Robbins, K. E, Odama, L., Saekhou, A., Edubio A., Njoku M., Sani-Gwarzo, N., Gboun, M. S., Gao, F., Reitz, M., Hone, D., Pieniazek, D., Wambebe, C. and Kalish M. L., (2002). Molecular Surveillance of HIV-1 Field Strains in Nigeria in Preparation for Vaccine Trials. Vaccine; 15; 20(16):2131-2139.

Baba, S. S., Fagbami, A. H. and **Omilabu, S. A.,** (1989). Wesselsbron Virus Infection in West African Dwarf Goats (Fouta djallon); Virological and Immunological Studies. Acta Virologica. 33: 81-86.

Baba, S. S., Fagbami, A. H., Ojeh, C. K., Olaleye, O. D., **Omilabu, S. A.,** (1995). Wesselsbron Virus Antibody in Domestic Animals in Nigeria: Retrospective and Prospective Studies. Microbiologica. 18: 151-158.

Bäck, A. T. and Lundkvist, Å., (2013). Dengue Viruses: An Overview. Infection Ecology & Epidemiology. 3:19839-21

Baeten, J. and Celum, C., (2006). Herpes Simplex Virus and HIV-1., in HIV In Site Knowledge Base. Regents of the University of California.

Banerjee, S., Bharaj, P., Sullender, W., *et al.* (2007). Human Metapneumovirus Infections among Children with Acute Respiratory Infections Seen in a Large Referral Hospital in India. J. Clin Virol. 38:70–72.

Cavalleiro N. P., Santos A. C. O., Melo C. E., Morimitsu S. R., Barone A. A., (2008). Hepatitis C Virus

Detection in the Serum of Infected Patients. Braz. J. Infect. Dis. doi: 10.1590/1413 – 86702008000500003. 12(5):358-36.

Chang, M. H. (2008): Hepatitis B Virus Infection. Foetal, Neonatal Medicine. 12: 160-167.

Chaves-Carballo, E., (2005). Carlos Finlay and Yellow Fever: Triumph over Adversity. Military medicine. 170 (10): 881–885.

Chen, L., Liu, F., Fan, X., Gao, J., Chen, N., Wong, T., Wu, J., Wen, S.W., (2009): Detection of Hepatitis B Surface Antigen, hepatitis B Core Antigen and Hepatitis B Virus DNA in Parotid Tissues. Int. J. Infect. Dis. 13: 20-23.

Clarke, D. H. and Casals, J., (1958). Technique for Haemagglutination-inhibition with Arthropod-borne Viruses. American Journal of Tropical Medicine and Hygiene. 7: 561-573

Ehichioya, D., Hass, M., Olschlager, S., Becker-Ziaja, B., Onyebuchi-Chukwu, C. O., Coker, E. B. A, Nasidi, A., Ogogua, O. O., Gunther, S., **Omilabu, S. A.,** (2010). Lassa Fever, Nigeria, 2005-2008. Emerg. Infect. Dis. 16(6): 1040-1.

Heinz, F. X. and Stiasny, K., (2012). Flaviviruses and Flavivirus Vaccines. Vaccine,30; 4301-4306.

Henchal, E. A., Putnak, J. R., (1990). "The Dengue Viruses." Clinical Microbiology Reviews. 3 (4): 376–396.

Jennings, J. M., *et al.*, (2008). Geographic Prevalence and Multilevel Determination of Community-level Factors Associated with Herpes Simplex Virus Type 2 Infection in Chennai, India. American Journal of Epidemiology, 167(12): p. 1495-1503.

Lal, R.B., Chakrabarti, S. and Yang, C., (2005). Impact of Genetic Diversity of HIV-1 on Diagnosis,

Antiretroviral Therapy & Vaccine Development. Indian J. of Med. Res.; 567:21-49.

Lar, P., Lar, N., Bemis, K., Jelpe, J., Enzyguirre, L., Ayuba, L., Zella, D., Kanki, P., Carr, J. K., Blattner, W. and Abimiku, A. G., (2007). HIV Subtype and Drug Resistance Patterns among Drug Naïve Persons in Jos, Nigeria. African Journal of Biotechnology. 6(16):1892-1897.

Lau, S. K., Woo, P. C., Li, K. S., *et al.*, (2005). Severe Acute Respiratory Syndrome Coronavirus Like Virus in Chinese Horseshoe Bats. Proc Natl Acad Sci USA; 102:14040–14045.

Levy, J. A. and Fieldsteel, A. H., (1982), Freeze-drying is an Effective Method for Preserving Infectious Type C Retroviruses. J. Virol. Methods, 5:165-171.

Liu, Z. and Hou, J., (2006). Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Dual Infection. Int. J. Med. Sci. 3: 57–62.

Miller, E. K., Lu, X., Erdman, D. D., *et al.*, (2007). New Vaccine Surveillance Network. Rhinovirus Associated Hospitalisations in Young Children. J. Infect Dis. 195:773–781.

Moore, D. L., Causey, O. R., Carey, D. E., Reddy, S., Cooke, A. R., Akinkugbe, F. M., David-West, T. S. and Kemp, G. E., (1975). Arthropod-borne Viral Infections of Man in Nigeria, 1964-1970. Ann Trop Med Parasitol, 69; 49-64.

Olaleye, O. D., Bernstein, L., Ekweozor, C. C., Sheng, Z., **Omilabu, S. A.,** Li, X., Sullivan-Halley, T. and Rasheed, S., (1995). Prevalence of Human Immunodeficiency Virus type 1 & Type 2 Infections in Nigeria. J. Infect. Dis; 167(3):710-714.

Olaleye, O. D., Tomori, O. and Schmitz, H., (1996). Rift Valley Fever in Nigeria: Infections in Domestic Animals. Rev Sci Tech, 15; 937-46.

Olaleye, O. D., Tomori, O., Ladipo, M. A. and Schmitz, H., (1996). Rift Valley Fever in Nigeria: Infections in Humans. Rev Sci Tech, 15; 923-35.

Olaleye., O. D. **Omilabu, S. A.** and Fagbami, A. H., (1988). Igbo-Ora Virus (An Alpha-virus Isolated in Nigeria): A Serological Survey for Haemagglutination Inhibiting Antibody in Humans and Domestic Animals. Transactions of the Royal Society of tropical Medicine and Hygiene82: 905-906.

Olaleye, O. D., **Omilabu, S. A.** and Baba, S. S., (1990). Growth of Igbo-Ora Virus in some Tissue Cultures. Acta Virologica34: 367-371.

Olschlager, S., Lelke, M., Emmerich, P., Panning, M., Drosten, M., Hass, M., Asogun, N. Ehichioya, D., **Omilabu, S.,** Gunther, S., (2010). Improved Detection of Lassa Virus by Reverse Transcription PCR Targeting the 5' Region of S-RNA. Journal of Clinical Microbiology. 48(6): 2009-2013.

Peiris, J. S., Yuen, K. Y., Osterhaus A. D., *et al.*, (2003). The Severe Acute Respiratory Syndrome. N Engl J Med; 349:2431–2441.

Plantier, J. C., Leoz, M., Dickerson, J. E., De Oliveira, F., Cordonnier, F., Lemée, V., Damond, F., Robertson, D. L. and Simon, F., (2009). A New Human Immunodeficiency Virus Derived from Gorillas. Nat Med.; 15(8):871-872.

Polyak, P., (2006). Innate Intracellular Defence against HIV and its Modulation by HCV Gene Product. Postgraduate Course, Vienna. pp. 30-33.

Pungpapong, S., Kim, W. R., Poterucha, J. J., (2007). Natural History of Hepatitis B Virus Infection: An Update for Clinicians. Mayo Clinical Procedures. 82: 967-975

Robertson, D. L., Anderson, J. P., Bradac, J. A., Carr, J. K., Foley, B., Funkhouser, R. K. *et al.*, (2000). HIV-1 Nomenclature Proposal. Science; 288:55-56.

Badaru S. O. S., *et al.*, (2011). Seroprevalence of Hiv-1 and 2 Antibodies in Lagos, Nigeria over a 10-year Period. Poster Exhibition: The XIV International AIDS Conference: Abstract no. MoPeC3325

Sahajian, F., Venhems, P., Bailly, F., Fabry, J., Trepo, C., Sepatjam, M., (2007). Screening Campaigns of Hepatitis C among Under Priviledged Peolpe Consulting in Health Centres of Lyon Area, France. Eur. J. Pub. Health 17: 263-271.

Samuel, D., Muller, R. and Alexande G., (2004). Educational Research, National Hepatitis B Virus Programme. Infect. Dis. 234: 221-332.

Simmons, C. P., Farrar, J. J., Nguyen, N., Wills, B., (2012). "Dengue." New England Journal of Medicine. 366 (15): 1423–1432.

Omilabu, S. A., Badaru, S. O., Peter Okokhere., Danny Asogun., Christian Drosten., Petra Emmerich., Beate Becker-Ziaja., Herbert Schmitz and Stephan Gunther., (2005) .Lassa Fever Activity in the North of Edo State, Nigeria, in 2003 and 2004. Journal of Emerging Infectious Diseases –Vol. 11(10): 1642-1644

Tommasino, M., (2014). The Human Papilloma Virus Family and its Role in Carcinogenesis. Semin Cancer Biol. Jun;26: 13-21.

UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. (2008). Epidemiological Fact Sheet on HIV and AIDS in Nigeria. http://www.who.int/hiv, http://www.unaids.org:1-25.

Van den Hoogen, B. G., van Doornum, G. J., Fockens, J. C., *et al.*, (2003). Prevalence and Clinical Symptoms

of Human Metapneumo Virus Infection in Hospitalised Patients. J Infect Dis. 188:1571–1577.

Vasilakis, N., Tesh, R. B. and Weaver, S. C., (2008). Sylvatic Dengue Virus Type 2 Activity in Humans, Nigeria, 1966. Emerging Infectious Diseases.14; 502.

Watannabe, H., Saito, T., Shinzawa, H., Okumoto, K., Hattori, E., Adachi, T., Takeda, T., Sugahara, K., (2003). Spontaneous Elimination of Serum Hepatitis C Virus RNA in Chronic HCV Carriers: A Population Based Cohort Study. J. Med. Virol. 71: 56-61.

Weaver, S. C., Reisen, W. K., (2010). Present and Future Arboviral Threats. Antiviral Research. 85(2): 328

Westaway, E., Brinton, M., Gaidamovich, S. Y., Horzinek, M., Igarashi, A., Kääriäinen, L., Lvov, D., Porterfield, J., Russell, P. and Trent, D., (1985). Flaviviridae. Intervirology, 24; 183-192.

Willey, J. M., Sherwood, L. M., Woolverton, C. J., (2008). Presscott, Harley and Kleins Microbiology (4th Edition). McGraw Hill Publishers, New York; pp. 936-972.

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