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2018 international meeting of the Global Virus Network

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A B S T R A C T

The Global Virus Network (GVN) was established in 2011 to strengthen research and responses to emerging viral causes of human disease and to prepare against new viral pandemics. There are now 45 GVN Centers of Excellence and 7 Affiliate laboratories in 29 countries. The 10th International GVN meeting was held from November 28–30, 2018 in Veyrier du Lac, France and was co-hosted by the two GVN Centers of Excellence, the Mérieux Foundation and the University of Veterinary Medicine Hannover (TiHo). The theme of this 10th International GVN meeting was “Eradication and control of (re-) emerging viruses”. This report highlights the recent accomplishments of GVN researchers in several important areas of medical virology, including strategies for the eradication of smallpox, measles, polio, SARS and vector-borne or zoonotic infections, emergence and intervention strategies for retroviruses and arboviruses, preparedness for outbreaks of Filo- and other hemophilic viruses, pathogenesis, impact and prevention of respiratory viruses, as well as, viruses affecting the central and peripheral nervous system. Also threats in crisis settings like refugee camps were presented.

1. Introduction

The Global Virus Network (www.gvn.org) is a not-for profit organization co-founded in 2011 by Robert C. Gallo, MD, of the Institute of Human Virology (IHV) at the University of Maryland School of Medicine, Baltimore, MD, USA; William Hall, MD, PhD of University College of Dublin, Ireland; and the late Reinhard Kurt, MD, PhD, of the Robert Koch Institute, Berlin, Germany. The concept of the GVN was originated in the 1980s, when Dr. Gallo realized there was a lack of global directive for researching the cause of AIDS.

The Network is comprised of 45 Centers of Excellence and 7 affiliate institutions throughout the world. The GVN Centers and Affiliates are led by expert, independent global virologists, who are the pillars of the organization. The mission of the GVN is to strengthen medical research, respond to current viral causes of human disease and prepare for new viral pandemic threats. The GVN meets its mission in three ways: research, advocacy and training. The GVN vision is to have a world better prepared to control and prevent viral epidemic threats, through the collaboration of a global network of expert virologists.

Part of the GVN's research programs includes an international scientific meeting to present and discuss current findings in medical and veterinary virology, and their application to existing and emerging viruses of global importance, explore new approaches to the prevention, treatment and cure of infectious disease, engage and inspire early career scientists to advance virology research and to promote collaborations among world expert virologists.

Past GVN International meetings have taken place in Washington DC, USA and Dublin, Ireland (2011), Naples, Italy and Baltimore, MD, USA (2012), Munich, Germany and Moscow, Russia (2013), Beijing, China (2015), Sapporo, Japan (2016), and Melbourne, Australia (2017).

The 10th International Global Virus Network (GVN) Meeting was

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held from November 28–30, 2018 in Veyrier du Lac, France and was co-hosted by the two GVN Centers of Excellence: the Mérieux Foundation (FM) and the University of Veterinary Medicine Hannover (TiHo), Germany and led by FM's Dr. Hubert Endtz, TiHo's Dr. Ab Osterhaus and GVN's Dr. Christian Bréchot.

At the « 10th International Global Virus Network (GVN) meeting: Eradication and control of (re-) emerging viruses», a major theme included emerging and reemerging viruses that are widely recognized threats to human health. This meeting was organized in seven sessions: “Eradication of Viruses”, “Retroviruses: emergence and intervention strategies”, “Arboviruses: emergence and intervention strategies”, “Filo- and other HF viruses: outbreaks & preparedness”, “Respiratory viruses”, “Viruses affecting the CNS and PNS: challenges” and, “Viral threats in crisis settings”.

This meeting addressed the challenges of eradication and control of (re-) emerging viruses in the context of climate change, urban expansion, increased risk of infectious pathogens “spilling over” from animals to humans, deforestation, increased international travel and trade, vaccination skepticism, weak public infrastructures and biosafety measures, among other factors.

2. The 2018 Robert C. Gallo award for scientific excellence and leadership

Criteria for the selection of this award include:

1. The candidate has published important scientific information on virology in the areas of interest to the GVN, including but not limited to: basic science, clinical aspects, pathogenesis, epidemiology, diagnostics, antivirals, and vaccine development.
2. The candidate has made a consequential and meaningful contribution to the GVN and has furthered the mission of the GVN, including but not limited to; development of the network of Centers of Excellence, participation in training programs, contributions to meetings and other GVN activities, and contributions to advocacy and public communication activities.

The 2018 awardees were Erica Ollmann Saphire, PhD and Michael B.A. Oldstone, MD, from The Scripps Research Institute, La Jolla, CA, USA.

3. Scientific presentations

3.1. Eradication of viruses

Mariano Esteban (National Center of Biotechnology, Madrid, Spain) reviewed the history of smallpox, its eradication through vaccination and the current availability of vaccines, diagnostics and antivirals for smallpox and related orthopoxviruses. Smallpox is a highly virulent human virus with mortality of up to 90% in children and 60% in adults resulting in an estimated 300–500 million deaths. WHO mounted a worldwide vaccination campaign and the disease was declared eradicated in 1980. However, the virus is maintained in Russia and the United States for research purposes and in 2019 the World Health Assembly will again determine whether those stocks should be destroyed. Because the virus could be reconstructed from available sequence information, there is a need to have vaccines, diagnostics and antivirals available in case of an outbreak. New vaccines include MVA and 3rd generation pox vectors. New monoclonal antibodies are improving diagnosis. ®TPOXX is a poxvirus egress inhibitor that is effective against monkeypox and can be delivered both orally and intravenously. Plans are to develop a second antiviral that has a different mechanism of action.

Diane E. Griffin (Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA) reviewed the status of measles and prospects for eradication. Although there has been substantial progress in measles control, and eradication is technically feasible, cases are now increasing in many parts of the world due to failure to vaccinate. Because measles virus is efficiently transmitted, high levels of population immunity (> 90%) are required to eliminate endemic spread. Achieving this level of population immunity requires 2 doses of the live attenuated vaccine. The first dose is delivered between 9 and 15 months of age and the second at school entry or through supplemental vaccine activities that have been difficult to sustain. The vaccine is safe and provides protection from infection, but this protection is less robust and long-lasting than wild-type infection that provides life-long immunity. The difference in immune responses may be related to the fact that infection with wild-type measles virus results in long-term persistence of viral RNA in lymphoid tissue, while vaccine virus infection does not. Barriers to achieving the levels of immunity required for eradication include lack of political will, logistical difficulties for vaccine delivery and unfounded fears of vaccine hazards.

Michel Zaffran (World Health Organization, Geneva, Switzerland) reviewed the current status of efforts to eradicate polio. The Global Polio Eradication Initiative is a public-private partnership launched in 1988 based on vaccination with the trivalent live oral poliovirus (OPV) vaccine. There has been considerable success with a > 99% decrease in cases of paralysis and apparent elimination of both wild poliovirus (WPV) types 2 and 3. However, 2018 has seen an increase in cases of WPV type 1, with 28 cases confirmed to date, all in Pakistan or Afghanistan, associated with many chains of transmission along the border between the two countries. Conflict zones and lack of trust have complicated surveillance as well as vaccine delivery. In addition, there is an ongoing problem with circulation of vaccine-derived PV (usually OPV type 2) in many regions. To counter this problem, type 2 was removed from OPV in 2017, and all but three countries have initiated vaccination with inactivated trivalent vaccine (IPV) rather than OPV.

Leo Poon (University of Hong Kong School of Public Health, Hong Kong, China) reviewed the history of the 2002-3 outbreak of severe acute respiratory syndrome (SARS) coronavirus that caused almost 800 deaths, with the biggest impacts in China, Hong Kong, Singapore and Canada. Control was achieved by case isolation, prevention of nosocomial spread and contact tracing with quarantine. There remains a risk of return, as the viral reservoir is in Chinese horseshoe bats that may transmit infection to other species.

Joaquim Segales (CRESA/Center de Recerca en Sanitat Animal, Barcelona, Spain) presented an overview of virus transmission from animals to humans and noted that most emerging and re-emerging diseases are caused by RNA viruses, of which 70% are vector-borne or zoonotic. Prevention requires a “One Health” approach to control at the origin, with a focus on the virus reservoir at the segment of the infection chain most amenable to intervention. However, reservoir identification is not always easy, and new methods use large genomic and ecological datasets, machine learning and evolutionary criteria to predict animal reservoirs for RNA viruses. These approaches can decrease the time between virus discovery and control.

Georges Thiry (Coalition for Epidemic Preparedness and Innovations (CEPI), Toulouse, France) explained plans for CEPI to facilitate and fund development of vaccines for priority pathogens. CEPI was founded in 2017 and is a partnership between public, private, philanthropic and civil organizations. The first group of targeted pathogens are MERS coronavirus (4 candidate vaccines), Lassa virus (5 candidates) and Nipah virus (2 candidates), which were chosen based on public health impact, risk of outbreak and vaccine feasibility. The plan is to bring vaccine candidates from late preclinical development through to manufacture of 100,000 doses. A second call is planned for proposals to develop platforms that can decrease vaccine development against new pathogens to < 16 weeks.

3.2. Retroviruses: emergence and intervention strategies

Sharon Lewin (The Peter Doherty Institute for Infection and

Immunity, The University of Melbourne and Royal Melbourne Hospital, Melbourne, Australia) presented recently published and unpublished work on the natural variation of HIV transcription in HIV-infected individuals on antiretroviral therapy (ART), specifically the effects of time, circadian proteins which vary over the course of the day and stress. There is currently high interest in understanding how HIV persists in individuals on ART, in order to develop novel strategies to eliminate long-lived latent virus, with the overall goal for individuals to safely stop ART without virus rebounding. Lewin was one of the first to demonstrate many years ago that there is ongoing transcription of virus in individuals on fully suppressive ART, which can be detected as cell-associated unspliced and multiply spliced RNA (Lewin et al., 1999). Her group has now demonstrated that HIV transcription on ART varies with time and that the circadian proteins Circadian-locomotor-output-cycles-kaput (CLOCK)- and Brain-and-muscle-ARNT-like-1 (BMAL-1) bind to the E-box in the HIV long terminal repeat (LTR) promoter and enhance transcription (Chang et al., 2018). These proteins could potentially be exploited for latency reversal. She also presented recent data from an interventional study of a stress stimulus demonstrating that stress can also increase basal levels of HIV transcription in individuals on ART.

Joshua Anzinger (The University of the West Indies, Kingston, Jamaica) reviewed the epidemiology and management of HIV infection in the Caribbean, as defined by the World Health Organisation. He presented published data from UNAIDS demonstrating that the number of people living with HIV in the region is 310,000 with an adult prevalence of 1.2% and a total of 10,000 AIDS-related deaths. Risk factors are predominantly heterosexual transmission (except in Jamaica where men who have sex with men is a more common risk factor) and sex work. Infection from injecting drug use is rare (except in Puerto Rico and Bermuda). The prevalence in sex workers is highest in Haiti at 8.7%. In relation to reaching the UNAIDS 90:90:90 targets of 90% of people aware of their diagnosis, 90% on treatment and 90% with a suppressed viral load, the Caribbean is currently at 73:57:40 but the progress towards these targets vary in different countries. In Jamaica, recent advances include a policy of test-and-treat, introduced in January 2018, and a pilot program of pre-exposure prophylaxis will start in 2019. Seven countries in the Caribbean have achieved elimination of mother-to-child transmission of HIV.

Antoine Gessain (Institut Pasteur, Paris) presented an update on HTLV-1. Gessain highlighted the significant prevalence of HTLV-1 in indigenous communities in central Australia. Shortly following the significant public and media interest in HTLV-1 in indigenous Australians, that followed the GVN meeting held in Melbourne in September 2018 (Catton et al., 2017), the Australian government announced the establishment of a task force to respond to HTLV-1, with funding of 8 million Australian dollars. This is a bold investment. Gessain also presented preliminary data from a new, large prospective study of HTLV-1 infection in Gabon. Preliminary data from the first 2060 participants enrolled showed that the prevalence of HTLV-1 infection increases with age, is higher in women than in men, and is higher in Pygmies than other ethnic groups. The likelihood of HTLV-1 infection was also marginally higher in individuals with a history of a bite from a non-human primate (Djuicy et al., 2018). The predominant subtype in central Africa was subtype 1b. He emphasized that aside from Japan, the true prevalence of HTLV-1 in most of the world urgently needs further evaluation.

Robert C. Gallo (Institute of Human Virology, University of Maryland, Baltimore, MD) highlighted that many viruses have been mechanistically associated with human cancers. However, the associations of bacteria with cancer, other than for *Helicobacter pylori*, are poorly understood. Multiple strains of *Mycoplasma*, a bacterium capable of intracellular infection, have been associated with the development of cancer in mice and humans. He showed that a type of *Mycoplasma fermentens* infects mouse and human lymphocytes and produces lymphoma in immunodeficient mice. There was no evidence of the *Mycoplasma* after tumor development except for small (less than 1 KB) DNA fragments in a very small number of tumor cells. The fragments included a component of the DnaK protein which is produced by multiple bacteria. This protein markedly reduced pro-apoptotic p53 activity and interacted with proteins of the DNA repair complex. In addition, this protein impaired the activity of anti-cancer drugs that are dependent on p53 enhancement (Zella et al., 2018). Preliminary data showed that the same fragment was detected in some human lymphomas, but the sequence was different from that found in mice. He concluded that these findings are consistent with a ‘‘hit and run’’ strategy by the mycoplasma in causing malignancy.

3.3. Arboviruses: emergence and intervention strategies

Johan Neyts (University of Leuven, Leuven, Belgium) discussed the antiviral drug development program at his institution. Despite successes with HIV, hepatitis B and C, and herpesviruses, there are no licensed antivirals for the vast majority of viral pathogens. Using cell-based antiviral screens and a high containment BSL-3+ robotized “lab-in-a-box,” antivirals are being pursued against a wide variety of viruses. An example presented was a potent NS4b-targeting compound that targets all four dengue virus serotypes at nanomolar concentrations. Another is a novel class of chikungunya virus inhibitors that are also active against the Venezuelan equine encephalitis virus at micromolar concentrations. This compound targets the RNA capping function of the nsP1 alphavirus protein. The influenza virus inhibitor favipiravir has also been shown to be active against flaviviruses, arenaviruses, bunyaviruses and filoviruses. Additional efforts have evaluated capsid-binders as well as novel compounds with binding sites targeting rhinoviruses/enteroviruses, in order to prevent excretion of wild-type or vaccine poliovirus strains from immunocompromised individuals; these strategies have been evaluated in conjunction with inactivated poliovirus vaccination. Other novel enterovirus and rhinovirus inhibitors that show an unusually high barrier to the development of resistance and target the 2C protein, are highly effective in mouse models. Finally, 2’C-methylcytidine can protect mice from fatal mouse norovirus infection and also prevent transmission, with promise to control human noroviruses that are major etiologic agents of human diarrheal disease. Johan collaborates with many international virology research groups and hopes to use his unique “lab-in-a-box” facility to partner with additional GVN centers.

Mauricio Nogueira (Faculty of Medicine, Sao Jose do Rio Preto), presented an update on yellow fever (YF) outbreaks in Africa and Brazil. He began by pointing out that our understanding of YF virus transmission ecology and possible control strategies was already established over a century ago, with little progress or new developments in recent decades. Due to enzootic transmission cycles in non-human primate (NHP) populations on both continents, eradication of the virus is an impossibility, and the risk of spillover emergent epidemics will always remain a constant threat. Ever since development of the 17D YFV vaccine in the 1930s, efforts to mitigate the threat of emergence have focused on preventative vaccination of human populations at risk. In Brazil, several genera of NHPs serve as enzootic hosts, and *Haemagogus*, *Sabethes* and *Aedes* spp. mosquitoes serve as vectors. The majority of human infections are asymptomatic, but 10–20% develop life-threatening hemorrhagic disease. A 2016 epidemic in Angola and the Democratic Republic of the Congo involved ca. 1000 confirmed cases with over 130 fatalities and many more suspected cases. Approximately 30 million people were vaccinated, depleting international vaccine stockpiles, including those in Brazil, the largest manufacturing country. Outbreaks then ensued in Brazil from 2016-present, with over 2000 confirmed cases and 744 deaths, along with thousands of fatal NHP infections. Deficits in YF vaccination coverage in known endemic regions combined with spread into regions without outbreaks in many decades, and consequently with minimal vaccination, were responsible for the largest epidemic in many years. The etiologic YFV strain appears to have originated in Sao Paulo State, and enzootic

amplification has occurred in forested urban pockets where marmosets are particularly abundant. Fractional doses of the YF vaccine appear to have been efficacious, probably because most manufacturers include larger virus titers than required. However, the 17D vaccine occasionally produces serious, sometimes fatal adverse reactions, which prompted the development of an inactivated version. Other vaccine platforms have been developed but the sporadic nature of outbreaks will make efficacy trials challenging. Mauricio also discussed evidence of NHP infections with Zika virus in Brazil, and the potential that Zika, like YFV, will establish an enzootic sylvatic cycle in the Amazon region of South America.

Marc Lecuit (Institut Pasteur, Paris, France) presented an overview of an international collaborative research program to address the diverse etiologies of pediatric infectious encephalitis in Southeast Asia. The project was conducted in 4 referral hospitals between July, 2014 and December, 2017, from Hanoi, Vietnam; Phnom Penh, Cambodia; Vientiane, Lao PDR; and Yangon, Myanmar. Children with a clinical acute encephalitis syndrome were prospectively enrolled, and comprehensive laboratory diagnostics were performed using molecular and serological tests targeting ~70 encephalitis-causative pathogens. Of 695 enrolled children, 663 (95%) met the AE case definition. Median age was 4.3 (1.7–8.8) years and 56% were male. MRI was abnormal in 84%, 28 causative pathogens were identified in 405 (61%). Preliminary results showed that Japanese encephalitis virus (JEV), herpes simplex virus 1, influenza virus, dengue virus, enterovirus 71, *Streptococcus pneumonia*, *Orientia tsutsugamushi* and *Mycobacterium tuberculosis* were the most common pathogens detected. Outcome was fatal in 13% and neurological sequelae present in 54% of patients. A low Glasgow score and shortness of breath on admission were significantly associated with death. Of identified etiologies, 64% were preventable and 20% curable, underscoring the clinical relevance of strengthening local capacity to conduct pathogen-specific diagnostics. The presentation highlighted the fact that despite the widespread use of JE vaccines across the SE Asian region, JEV remains the most predominant pathogen identified during differential diagnosis., and was detected in approximately 1/3 of cases across all sites. Further analysis will be required to assess if any of the JE cases involved vaccine failures; however, it was mentioned that routine delivery of JE vaccine within EPI programs remains weak, particularly in Cambodia. Interesting preliminary data were presented regarding co-detections of respiratory syncytial virus (RSV) in nasopharyngeal samples from AE cases, suggesting the possibility that some encephalopathies may be associated with RSV infections. Despite very extensive laboratory testing using pathogen-specific molecular and serological assays, etiologies remained undetermined in as many as 40% of patients. Further analysis of residual specimens by next generation sequencing is planned.

Masayuki Saijo (Department of Virology 1, National Institute of Infectious Diseases, Tokyo, Japan) provided an update on JE epidemiology in Japan and in the region. He noted that routine immunization programs in Japan still deploy the inactivated JE vaccine from Biken (Vero cell-culture-derived, requiring 3 doses), whereas the live attenuated SA14-14-2 vaccine manufactured in China (single dose) has now become the most widely used JE vaccine in endemic countries. The average number of patients reported annually for last several years has been < 10. Interestingly, studies to detect antibodies to JEV NS1 (an indication of natural infections) have demonstrated that 2.5% of the population in central and southern Japan may be infected annually, highlighting the importance of continued vaccination. Although JEV species is genetically diverse and comprised of 5 genotypes, all recognized strains within the species are serologically cross-reactive, and thus considered as a single 'serotype'. JEV genotype III is believed to have been the predominant circulating genotype throughout Asia in the 1990s, with a subsequent shift to more frequent detections of genotype 1 in the early 2000s. Masayuki presented data showing that genotype V was detected for the first time in 65 years from China and South Korea. Experiments conducted using recombinant viruses evaluated in mouse models suggest that genotype V may have increased virulence over reference genotype I and III strains. Additionally, the protective efficacy of current vaccines against genotype V was questioned, based on the observed relative neutralizing titers of sera from vaccinated mice that were challenged with JEV strains from genotypes I, III, and V.

Xavier de Lamballerie (Aix-Marseille University, IRD – INSERM, Marseille, France), provided a seminar on the compelling need for improved clinical diagnostics of arboviral diseases, with investments needed during interepidemic periods, as an essential component of preparedness against current and recurring threats. He emphasized that the largest burden of disease from 'emerging' pathogens is associated with well-known pathogens for which effective prevention and control measures have yet to be deployed. His talk addressed classical scenarios of emergence patterns, e.g. examples of 'anthropomorphic' transitions from sylvatic to urban cycles (e.g. YFV); 'non-anthropomorphic' transitions whereby widespread dissemination occurs even in the absence of human-to-human transmission (e.g. West Nile Virus); and 'non-anthropomorphic' transitions in which viruses may broaden their host range and ecological niches through changes in land use and exposure patterns (e.g. Tick Borne Encephalitis). Finally, a generic approach for preparedness efforts was proposed, aligned with the model of the GLOPID-R (https://www.glopid-r.org) working group on chikungunya disease.

Annelies Wilder-Smith, consultant for arboviral vaccines, WHO-IVB, reported on the complex issues surrounding dengue vaccine development and current usage. She provided an overview of basic concepts regarding heterologous and homologous immunity in response to serial infections with different serotypes, and a comprehensive update on current understanding of performance characteristics of the only licensed dengue vaccine (CYD-TDV, ®Dengvaxia, by Sanofi-Pasteur). Dengue is the single most important arboviral infection in terms of disease burden, with more than 3.6 billion people at risk for infection and an estimated 390 million infections annually in over 120 tropical and sub-tropical countries. In the absence of truly effective and sustainable vector control measures, dengue vaccines are considered a key component in prevention programs. Deployment of Dengvaxia has been complicated by significant controversy because vaccine responses are driven by an individuals' serostatus; vaccination of individuals who are seronegative at the time of inoculation will elicit immunity akin to that following a primary infection, and thus generate risk for antibody-dependent enhancement, with higher risk of severe disease upon subsequent dengue infection. In contrast, vaccination of individuals who are seropositive has been shown to have at least 72% efficacy to protect against subsequent symptomatic infection (Sridhar et al. N Engl J Med 2018 Jul 26:379(4):327–340). The WHO initially recommended (April 2016) that the vaccine should be deployed only in areas with seroprevalence > 70%. However, in 2017, more definitive evidence from a retrospective analysis of clinical trial data revealed an excess of severe dengue in seronegative vaccine recipients. The WHO SAGE (Strategic Advisory Group of Experts) working group was therefore obliged to reconsider guidelines for how to best use the vaccine (http://www.who.int/immunization/sage/previous/en/index.html) and to evaluate under which circumstances there may be a net public health benefit versus individual risk. The key consideration was whether WHO should recommend countries to conduct population seroprevalence studies to measure endemicity levels prior to vaccine introductions; or rather to develop individual-based pre-vaccination screening programs. Both approaches present challenges due to cross-reactive dengue seroassays. The talk concluded with a discussion of other dengue vaccines under development, including chimeric vaccines from Takeda and Butantan, for which clinical phase III trials are underway.

Scott Weaver (University of Texas Medical Branch Galveston, TX, USA) presented an update on the epidemiology and mosquito vector transmission of chikungunya (CHIKV) and Zika (ZIKV) viruses. Both originated in African enzootic cycles and recently spread to Asia followed by the Americas, where naïve human populations and abundant

urban *Aedes aegypti* mosquitoes facilitated major epidemics with nearly pandemic spread through infected travelers. Although epidemics of both chikungunya and Zika have peaked in many regions, outbreaks continue, especially in the southern cone of South America for both viruses and in regions of Africa, Asia and Europe for CHIKV. Some CHIKV strains of the Indian Ocean lineage have adapted through a series of mutations in the envelope glycoprotein genes to also be transmitted efficiently by the invasive mosquito, *A. albopictus*. Fortunately, epistatic interactions in both CHIKV strains now circulating in the Americas have prevented this adaptation there. Like CHIKV, ZIKV spread from Asia into the South Pacific and appears to be related to adaptive evolution for more efficient transmission by *A. aegypti*, the result at least in part of several reversions of deleterious founder effects associated with its introduction many decades ago into Asia from Africa. Limitations on CHIKV adaptive evolution have been traced to founder effects that presumably occur when individual infected travelers introduce both viruses, accompanied by severe viral population bottlenecks. These stochastic founder effects will make it very challenging to predict future outbreaks. Finally, the hypothesized role of immune enhancement resulting from prior dengue virus infections on severe congenital outcomes of ZIKV infection have been discounted by several epidemiologic studies indicating cross-protection between these two flaviviruses.

Aaron Mweene (University of Zambia, Lusaka, Zambia) closed the session by presenting on surveillance of viral zoonoses in Africa. His talk addressed the recent examples of emergence of highly dangerous virus from unexpected habitats, presenting specific examples of how such emergence events have high health and socio-economic impact and pose serious biosafety and biosecurity challenges. Surveillance of bats has been a major effort, with some seroprevalence detected for Ebola and Marburg viruses. Recent, major findings include the discovery of a highly pathogenic, Old World arenavirus (Lujo virus) following air transport of a fatally ill patient from Zambia to South Africa. Despite the association of arenaviruses with rodents, the reservoir of Lujo virus has not yet been identified. Another finding based on phylogenetics is the apparent spread of Zaire ebolavirus associated with severe and widespread outbreaks of Ebola virus disease in West Africa in 2014. Aaron described efforts to strengthen research in Zambia through cooperative grants with Japanese research institutions, including Hokkaido University. The University of Zambia with financing from the World Bank has established the Africa Center of Excellence for Infectious Diseases of Human and Animals (ACEIDHA) to achieve the regional goal of understanding the natural history of some infectious diseases and promoting training opportunities for young investigators. A range of diagnostic research technologies were described for detection of bat viruses, including filovirus-specific IgG ELISAs, rapid tests (lateral flow assays), and field-deployable isolation mini-labs. Ongoing investigations of avian influenza within wild bird reservoirs, and arenaviruses in rodents, was also presented, including detection of a novel nonpathogenic arenavirus among *Mastomys natalensis*, temporarily named Luna (after Lusaka-Namwala).

3.4. Filo- and other hemorrhagic fever viruses: outbreaks and preparedness

Stephan Becker (Philipps-Universität, Marburg, Germany) started the session with an overview of Marburg virus (MARV) and Ebola virus (EBOV). He noted that the first documented outbreak of a filovirus disease took place in Marburg, Germany in 1967 amongst lab workers who contacted tissues of imported monkeys from Uganda. In this first outbreak there were 32 cases, including secondary cases, with a 25% case fatality rate (CFR). Subsequent filovirus outbreaks in Africa have typically had higher CFRs, likely due to the unavailability of advanced supportive measures. With the exception of cases of Tai Forest virus infection in chimpanzees and one human case in Ivory Coast in 1994 known outbreaks of MARV and EBOV infections over the next four decades were confined to Central Africa. The massive 2013-16 West African Ebola virus epidemic showed that Ebola outbreaks can be very difficult to contain, can have severe consequences for the health infrastructure of whole countries and have a significant impact on economies. This outbreak was finally stopped by education and behavior changes, emphasizing that community engagement is key to containing outbreaks. It was also a wake-up call that has driven further development of Ebola virus antivirals and vaccines, and reversed attitudes about the necessary role of research during outbreaks. The frontrunner vaccine, recombinant vesicular stomatitis virus expressing the surface glycoprotein of Ebola virus subtype Zaire, protected macaques from lethal challenge. Importantly, treatment one hour after infection protected half of animals, suggesting potential utility in post-exposure therapy or in ring vaccination. Becker discussed the ongoing (as of this writing) Ebola outbreak in North Kivu and Ituri provinces of the Democratic Republic of the Congo. The area of this current outbreak is densely populated and borders Uganda, Rwanda, and South Sudan. Despite intense threats to security and a humanitarian crisis involving over a million internally displaced people nearly 40,000 people have already been vaccinated. Remarkably, a randomized, controlled clinical trial of three different monoclonal antibody treatments and an antiviral drug has been undertaken. Throughout his talk, Stephan highlighted the need for improving preparedness for known as well as unknown emerging viruses, an important goal of the GVN.

Noel Tordo (Antiviral Strategy Unit, lnstitut Pasteur, Paris, France) began his talk by describing renovations, equipment and training at the Institut Pasteur de Guinee, Conakry, Guinea. The facilities that opened in June, 2018 include research units with BSL-3 laboratories for work on hemorrhagic fever viruses, rabies, arboviruses (Rift Valley fever, Crimean Congo hemorrhagic fever, YFV and ZIKV) and other agents. This site is a good model for initiatives envisioned by GVN. Tordo then provided an informative overview of the molecular and functional diversity of hantaviruses, noting that these enveloped stranded tri-segmented RNA viruses circulate persistently and asymptomatically in small mammals such as rodents, insectivores (shrews and moles) and bats. Hantaviruses are distributed worldwide and may be transmitted to humans by aerosols of contaminated rodent excreta. During the Korean War (1951-54) more than 3000 United Nations soldiers became ill with the Korean hemorrhagic fever and there was a 10–15% CFR. Other notable hantaviruses affecting humans include Hantaan, Seoul, Puumala and Sin Nombre viruses. Noel made a convincing case that hantaviruses are excellent models to evaluate virus-host co-evolution. He also presented genetic data suggesting a possible insect origin. The basis for different disease outcomes of hantaviruses in humans and rodents (pathogenicity versus tolerance) is a focus of investigation. Their results also reveal an increase in neutrophils upon Puumala virus infection resulting from a delay in apoptosis. Non-pathogenic hantaviruses did not exhibit such an effect. This observation supports a role of neutrophils in the development of human nephropathy induced by Puumala virus infection. Because of the growing concern regarding the zoonotic risk for humans, hantaviruses should be kept in mind in any unexplained human epidemics.

Erica Ollmann Saphire (Scripps Research, La Jolla, California USA) presented an update on antibody therapeutics against EBOV and Lassa virus (LASV). She asked: What are the best therapeutic antibodies against these viruses, what makes them “good” and how do we find them? She also pointed out that a key need is to understand what leads to protection by protective antibodies. Protection can result from either mechanical neutralization, the less well understood Fc effector function or a combination of both. Another need is for therapeutic antibodies that are broadly reactive against divergent filoviruses and arenaviruses. Erica leads a global effort - the Viral Immunotherapeutic Consortium (VIC) - by previously competing groups. The VIC changed the normal paradigm for discovery of immunotherapeutic antibodies, which typically involved “funneling” the favorite antibodies of a single group through mice, guinea pigs and nonhuman primates. This traditional approach favored the selection of neutralizing antibodies. The VIC

comprises 43 laboratories on 5 continents that conducted a comprehensive, multidisciplinary study of 230 monoclonal antibodies to filoviruses and uses glycoprotein structures to interpret antibody responses. The answer of whether to develop neutralizing or non-neutralizing antibodies is not either/or. There may be an optimal strategy of combining neutralizing antibodies with those that mediate certain Fc effector functions. Erica's group also recently solved several structures of broadly active anti-filovirus antibodies, finding that they recognize a continuum of epitopes that extend in a band across a central portion of the glycoprotein. lmmunogens designed to highlight these key features may yield more broadly active immune responses. In contrast to filoviruses, antibodies that neutralize LASV predominately belong to a single competition group, and recognize a quaternary epitope, bridging multiple subunits and monomers together. Her group solved an array of structures to understand what features of this principal neutralization site led to greatest activity. Rational structure-guided substitutions can now increase potency and breadth of neutralization to include all major lineages of LASV. Similar approaches can be applied to other pathogens to develop broadly reactive antibodies for post-exposure therapy and vaccines for broad protection.

In the final talk of the session, **Robert Garry** (Tulane University, New Orleans, Louisiana USA) provided an update on Lassa fever, which was first described in 1969 following the deaths of two missionary nurses during a hospital outbreak in northeastern Nigeria. Subsequent studies demonstrated that humans acquire LASV primarily via exposure to virus-containing urine and feces of its main reservoir *Mastomys natalensis,* the natal mastomys or multimammate mouse. Human-to-human transmission occurs less frequently, a finding confirmed during genetic analysis of LASV in this year's surge of cases in Nigeria. The potential for further geographic expansion of *Mastomys natalensis* and other rodent reservoirs, the frequent importation of LASV to North America and Europe, and the emergence of novel LASV strains in densely populated West Africa have driven new initiatives to develop countermeasures for LASV. These new initiatives include development of a Lassa vaccine by CEPI, featured in an earlier talk. The Viral Hemorrhagic fever Consortium has established unique clinical and basic research programs in West Africa where LASV is hyperendemic. The team initially focused on improved diagnostic assays based on recombinant LASV proteins, which have greatly expanded the ability to perform LASV serology and surveillance. VHFC also derived a large set of human monoclonal antibodies to LASV proteins. A combination of human monoclonal antibodies to the LASV glycoprotein was able to cure macaques challenged with viruses from two diverse lineages of LASV, even when treatment was delayed for more than a week (Cross et al., in preparation). Despite these advances, fundamental gaps in our knowledge of the immunology, pathogenesis and ecology of Lassa fever persist and hamper efforts at quantifying risk and designing effective control programs.

3.5. Respiratory viruses

Peter Openshaw (Imperial College, London, UK) reported on the impact and pathogenesis of respiratory viruses in humans. First he documented that acute lung infection causes a major global burden of disease and compared differences in pathogenesis and intervention strategies between two major human respiratory pathogens: influenza virus and RSV. He gave an overview of the different mechanisms by which RSV interferes with the host immune system and highlighted the global burden of RSV in children under 5 years of age and in other age categories, such as the elderly. He then addressed the current status of RSV disease prevention by monoclonal antibodies and the advent of first-generation vaccines and the hurdles that still should be taken before their introduction. He compared the forced respiratory volume (FEV) in individuals with COPD, with persistent and intermittent RSV infections and without RSV infections. The differences observed in the respective groups clearly showed that RSV infection has a major impact on the FEV and therefore on the severity of COPD exacerbations. Subsequently he showed the importance of a balanced immune response against RSV. In a clinical study in children with bronchiolitis, with and without an RSV infection, viral loads, immune mediator and gene expression levels were measured in mucosal samples, comparing mild, moderate and severe infections. Finally, he presented a network of scientists working on experimental infections of human volunteers with several pathogens including RSV and influenza virus, and elaborated on the potential of this approach.

Ab Osterhaus (TiHo-RIZ, Hannover, Germany) gave an overview of the dozens of human and animal viruses that he and his group have discovered in Rotterdam and Hannover in past decades, largely benefiting from the advent of new molecular technologies. Human viruses included influenza viruses, human metapneumovirus, as well as SARS-MERS- and other human coronaviruses. In addition, he addressed lessons from the recent rinderpest eradication for the eventual eradication of measles and presented a recently documented explanation by their group of measles induced immune suppression caused by the elimination of memory B and T cells through measles virus infection. He explained how the identification and characterization of SARS coronavirus as the cause of SARS by fulfilling Koch's postulates using a monkey model had contributed to the control of SARS shortly after its emergence. Ten years after the discovery of SARS, his group discovered MERS coronavirus as the causative agent of MERS. The Identification of dromedary camels as the source of this infection, the identification of its receptor and the successful testing of a candidate MERS vaccine in this species highlighted the importance of a One Health approach in combatting such human infections at the source. Finally he summarized their work on animal influenza viruses as the source of zoonotic influenza infections, epidemics and eventually pandemics and the importance of the development of preparedness plans for future influenza pandemics was highlighted.

Michelle Crank (Vaccine Research Center, NIAID, USA) gave an update on the results of a Phase I clinical trial with a stabilized RSV prefusion F glycoprotein vaccine (DS-Cav1), showing that the RSV F glycoprotein structure largely determines immunogenicity. After giving an overview of the current knowledge of the F glycoprotein and RSV biology, she presented the development of DS-Cav1, a stabilized pre-F RSV vaccine antigen and the interim results of a clinical trial with this vaccine candidate in healthy adults. First she highlighted the problems with FI-RSV vaccine-enhanced disease 50 years after it had occurred, as well as the mechanism of antibody mediated enhancement that could have had elicited this adverse event. An RSV vaccine and monoclonal antibody development snapshot was presented and it showed that many products are currently in the pipeline. Then she addressed the structure of the pre-fusion F glycoprotein and the importance of the conformation dependent nature of its neutralization-sensitive epitopes in the development of a RSV vaccine. DS-Cav1 was shown to elicit potent neutralizing activity against both RSV-A and RSV-B. It was shown that pre-F specific antibody binds to the apex and site of pre-F site. Finally their ongoing work on B and T cell responses as well as the clinical outcome of the DS-Cav1 vaccine study was addressed.

Adolfo Garcia Sastre (Icahn School of Medicine at Mount Sinai, New York, USA) gave a historical overview of the evolution and spread of influenza viruses, zoonotic events and the human cases, pandemics and epidemics that resulted from animal and human influenza virus infections. He highlighted the need of more universal influenza vaccines that provide broader protection and can be made in preparation for a pandemic but might also serve for the better control of epidemic influenza. Then he introduced the concept of HA-stem-based universal flu vaccines: induction of protective levels of stalk-reactive antibodies with chimeric HA stalk constructs followed by subsequent immunization with chimeric HA stalk constructs of different influenza A subtypes. Protection upon challenge with yet another HA subtype virus, provided prove of concept of this approach in mice and the protection proved to be antibody-mediated in transfer-challenge experiments. Subsequent

experiments in ferrets showed that live attenuated vaccination followed by inactivated chimeric HA vaccination induced HA stem and NA antibodies and high levels of protection towards challenge with heterotypic influenza viruses. Given the promising results obtained with the combination of the different innovative approaches the next step is to prove the validity of the developed concept in human trials.

Meagan Deming (Institute for Human Virology, Baltimore, MD, USA) addressed the major problem of respiratory viral infections in immunocompromised solid organ and haematopoietic stem-cell transplant (HSCT) recipients. The cumulative incidence in the latter group eventually proved to approach 40–50%. Although several viruses proved to be involved, corona- and rhinoviruses appeared to be the most common pathogens in their studies. This also was the case for lung transplant recipients, in which viruses of these two groups tended to persist over prolonged periods of time. In 33–58% patients with haematologic malignancies or HSCT recipients lower respiratory tract infections were seen during the study period, with associated mortality rates of even up to 88% depending on the virus involved. The effects, success rates and limitations of several antiviral and biological response modifying strategies with different therapeutic targets, again depending on the respective viruses, were discussed. It was concluded that the challenges faced with respiratory virus infections in immunocompromised solid organ and HSCT recipients may require unique and multi-pronged strategies, with both potent antivirals and biological response modifiers that target the conserved mediators of pathogenesis.

3.6. Viruses affecting the central and peripheral nervous system

Harry R. Dalton (Truro, United Kingdom) described hepatitis E virus (HEV) as a cause of neurological disease. HEV infections, mainly genotypes 1 (gt1) and gt2, are a major health problem in developing countries in Asia and Africa and considered of little relevance in developed countries ((Purcell and Emerson, 2008). Recent data are presented that refute the latter assumption, showing that HEV infections are also endemic in Europe (Dalton et al., 2015). HEV infections in Europe, mainly gt3 and gt4 and acquired via pigs and wild boar (porcine zoonosis), are commonly asymptomatic, but chronic HEV infection and subsequent cirrhosis may develop in immunosuppressed individuals including transplant patients (Kamar et al., 2017). Various neurological diseases, particularly Guillain-Barre syndrome (GBS) and neuralgic amyotrophy (NA), were discussed as debilitating extrahepatic manifestations of HEV infection, commonly in individuals without overt signs of liver disease (Zheng et al., 2018; Scanvion et al., 2017). Evidence of recent HEV infection was identified in 5–11% of GBS patients and HEV-associated NA has a unique clinical presentation (Mclean et al., 2017). The causal relationship between HEV and neurological syndromes indicates that HEV is a neurotropic virus that warrants future studies to identify key virus and host factors for the development of novel intervention strategies. Finally, the hypothesis that HEV gt3 and gt4 causes miscarriage in humans was discussed.

Thomas Müller (Institute of Molecular Virology and Cell Biology, Friedrich-Loeffler-Institute, Greifswald - Insel Riems, Germany) described past achievements and current challenges in controlling rabies virus (RABV) infections in wildlife reservoirs. Despite the large variety of RABV reservoir species worldwide, the majority of human rabies cases are due to dog bites that can be prevented by vaccinating dogs in high risk areas. He presented data supporting the concept that immunization of wildlife with an oral rabies vaccine (ORV), consisting of live-attenuated or recombinant live-vectored RABV vaccines with species targeted bait, is an important component of a holistic rabies management program to eliminate RABV from wildlife reservoirs. Long-term, large-scale ORV programs of foxes has led to almost complete elimination of fox rabies in Western Europe and North America (Müller et al., 2015 & Maki et al., 2018). However, RABV will continue to adapt and perpetuate within wildlife species, posing a serious health risk to domestic animals and humans (Freire de Carvalho et al., 2018). He discussed the challenges ahead of the rabies elimination programs, feasible for certain wild reservoir species, that warrants sustained political and financial support for the upcoming decades (Fooks et al., 2017). Challenges discussed included issues on better insight needed into the target species (e.g. multispecies reservoir species and host species shift events) (Wallace et al., 2016), optimal vaccine bait (i.e. no bait fits all species) (Johnson et al., 2016), optimal delivery and distribution systems (e.g. airplane or specific sites) (Sterner et al., 2009), optimal vaccination strategy (e.g. vaccination intervals and bait densities) (Sterner et al., 2009)s and vaccine strain (e.g. minimal effective ORV dose and uptake differs per species) (Zhugunissov et al., 2017).

Justin J.H. Chu (Department of Microbiology and Immunology, School of Medicine, National University of Singapore) described the clinical manifestations and virus-host interactions of hand, foot and mouth disease (HFMD). The incidence of human neurotropic enteroviruses causing HFMD in patients admitted to hospitals, including human enterovirus A71 (HEV-A71) infections associated with severe and even fatal neurological complications in young children, has steadily increased in Singapore during the past decade, causing a significant healthcare and economic burden (Teo and Chu, 2016). Using genome-wide siRNA and miRNA screens, coupled with proteome profiling, his lab identified numerous host susceptibility and resistance factors affecting HEV-A71 infection (Leong et al., 2015; Wu et al., 2016). The host factors and pathways identified are subject of downstream studies at the Chu lab to identify their role in differential disease outcome and to develop novel intervention strategies. Next, he reported on studies addressing the unmet need for an effective and safe antiviral against HEV-A17. The Chu lab developed a high-throughput screening platform leading to the identification of a highly potent and non-cytotoxic antiviral flavonoid (MARVAS-Flavon), a natural compound extracted from citrus fruit peels, which specifically targets the internal ribosome entry site (IRIS) of HEV-A17 (Min et al., 2018). Besides inhibiting replication of other enteroviruses *in vitro*, MARVAS-Flavon appears highly effective in a mouse model, and is a promising candidate for further development.

Georges M.G.M. Verjans (Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands) described virus-host interactions in herpesvirus infections of human nervous tissues. Rodent models are central in studies on the pathogenesis of neurodegenerative diseases, but these models do not fully recapitulate the human diseases under investigation (Ransohoff, 2018). Studies on virus-host interactions of 3 different human herpesviruses in human brain tissue (Epstein-Barr virus, EBV) and sensory ganglia [herpes simplex virus (HSV) and varicella-zoster virus (VZV)] were presented. First, the association between EBV in multiple sclerosis [(MS) (Geginat et al., 2017)] was addressed by demonstrating that, despite the absence of EBV protein and nucleic acids in cerebrospinal fluid (CSF) and brain tissues, EBV reactive T-cells selectively accumulate in both CSF and diseased brain tissues of MS patients, suggesting that local EBV-specific T-cell immunity contributes to MS pathology (van Nierop et al., 2017). Second, the identification and characterization of a novel spliced and protein coding VZV transcript, VZV latency transcript (VL), were presented. VLT is selectively expressed in latently VZV-infected neurons of human trigeminal ganglia (TG) and appears to block lytic VZV infection (Depledge et al., 2018). Third, the role of T-cells controlling latent HSV-1 in human TG was described. In contrast to VZV, HSV-1-specific CD4 and CD8 T cells are selectively retained in dual latently infected human TG (Kinchington et al., 2012). The limited number of HSV-1 proteins recognized, particularly those targeted by T cells in multiple TG donors, were proposed as potential HSV-1 vaccine candidates (van Velzen et al., 2013). The studies presented highlight the importance of studying virus-host interactions of human neurotropic viruses in disease-relevant tissues and species: human nervous tissues (Ludlow et al., 2016).

James J. Sejvar (National Center for Emerging and Zoonotic Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia,

USA) presented an update on the epidemiology and clinical manifestations of flavivirus-induced neurological diseases. Japanese encephalitis virus (JEV) remains the most common cause of epidemic encephalitis in Asia, primarily affecting children, with a 20–30% case fatality rate; about a third surviving children have significant neurologic sequelae. West Nile virus (WNV) emerged as a significant cause of encephalitis in the US, starting with an outbreak in New York in 1999 and subsequently spread throughout the US and Southern Canada, currently the most common cause of encephalitis in North America (Yeung et al., 2017). During the past decade, WNV activity has increased in Central and Southern Europe (Barzon, 2018). JEV and WNV infections are mostly asymptomatic or cause mild disease including fever and headache in about 20% of infected individuals and neuroinvasive disease in < 1%, presenting as encephalitis associated with movement disorders (Yeung et al., 2017). Anterior myelitis appears more common with WNV infections and seizures in JEV infections, which also has a poorer prognosis compared to patients with WNV-associated neurological diseases. Compared to JEV and WNV, the causality of virus-induced neurological signs in DENV-infected individuals remains unclear and warrants advanced neurodiagnostics that is often unavailable in dengue-endemic areas (Li et al., 2017). Whereas the association of DENV and GBS is not formally established, the extremely and unusually high incidence of GBS in areas with ZIKV outbreaks in the South pacific and South and Central Americas support strong evidence implicating ZIKV infection associated with GBS (Sejvar, 2018). Furthermore, ZIKV was presented as an important cause of congenital abnormalities (e.g. microcephaly), and a wide spectrum of neurological diseases including meningoencephalitis and encephalitis, indicating that ZIKV is a neurotropic virus (Mier-Y-Teran-Romero et al., 2018).

3.7. Viral threats in crisis settings

Hubert Endtz (Mérieux Foundation, Lyon, France) gave a talk on respiratory infections among refugees. The United Nations High Commissioner for Refugees (UNHCR) reports of total number of 68 million forcibly displaced persons worldwide. The Syrian refugee crisis is the largest, with approximately 17 million displaced persons. Five million civilians crossed the border of which more than 1.5 million took refuge in Lebanon. The Rohingyas that are forced out of Myanmar into Bangladesh are the fastest growing crisis. They are now surviving on a small and restricted piece of land near Cox's Bazar (Chittagong district) in the south of Bangladesh. Up to 45% of morbidity is associated with acute respiratory infections and acute lower respiratory infections are among the leading causes of mortality among refugee populations. Displaced populations, including refugees, are at risk for negative outcomes secondary to ALRI because of malnutrition, poor living conditions, low vaccination status, rough climate conditions and overcrowding. Understanding the epidemiology and etiologies of ALRI in Africa is important in relation to vaccine development and implementation. Two case-control studies are coordinated by the Fondation Mérieux and local partner institutions that investigate the ALRI etiology. The study involves 1200 patients and controls per country. The principal objective of this study is to estimate the proportion and distribution of community-acquired pneumonia attributable to specific viral and bacterial pathogens (Population Attributal Fraction, PAF). More than 50% of the patients are children. The majority of ARI deaths and severe illness episodes are due to ALRIs. A film-array technique and specific PCR diagnostics was used to identify the various microorganisms involved in ALRIs. While the study among the Rohingyas is still ongoing, preliminary results of the study among the Syrian refugees were reported during the meeting. Overall, influenza, RSV and rhinovirus were the most commonly isolated microorganisms. *Streptococcus pneumoniae* ranked in 7th place. While influenza virus was the most commonly isolated microorganism in children over 5 years of age (PAF 25.6%) and in adults (PAF 36.4%), RSV came first among children under 5 (PAF 30.4%). This study will help us better understand the etiology of ALRI, to optimize treatment algorithms and to rationalize the use of new vaccines among displaced persons.

4. The network in 2018

During 2018, the GVN Network was expanded by the incorporation of the following Centers: University of Nebraska Medical Center (UNMC), West African Center for Cell Biology of Infectious Pathogens (WACCBIP) at the University of Ghana, Colombia-Wisconsin One-Health Consortium (CWOHC), GVN-Singapore Center of Excellence and the Uganda Virus Research Institute (UVRI). The GVN also incorporated one Affiliate institution: the Africa Center of Excellence for Infectious Diseases of Humans and Animals (ACEIDHA) at the University of Zambia in Lusaka. This affiliation is via two GVN Centers of Excellence: Hokkaido University (HU) in Sapporo, Japan and University College Dublin in Dublin (UCD), Ireland.

During the past year, the GVN continued with the Hepatitis C training and Hepatitis B database development programs in India, and the GVN Zika Serum Bank. In regard to training, the GVN hosted the 5th GVN Course for Emerging Leaders in Medical Virology, expanding the community of scholars to 72 scientists from 29 countries in the past 5 years.

The GVN has been active in public information and advocacy. Particularly by communicating to the public the efforts that GVN Centers were carrying out during the Ebola and Nipah outbreaks. The GVN has had a strong advocacy role by issuing an open letter to the WHO requesting the organization to support and promote GVN's prevention strategies for HTLV-1.

This year, GVN's Anticipation and Preparedness Task Force was created. The goals of this Task Force are to provide: 1. Novel approaches to delineating the future of next epidemics by merging mathematics and modelling with epidemiology genomics and medicine and public health; 2. Training and education workshops in Africa for the new generation of scientist and medical doctors;. 3. Contribution to the fight against bioterrorism; and 4. Provide Expert advice on global public health strategies.

Co-chairs of this Task Force are Elodie Ghedin, PhD, Director, Center for Genomics & Systems Biology, New York University, United States and Giuseppe Ippolito, MD, Scientific Director, National Institute for Infectious Diseases Lazzaro Spallanzani, Italy. As a first step and in order to develop a meaningful and long term strategy, we created a questionnaire that will help delineate priorities for research, preparedness, and response to events caused by viral pathogens. Meanwhile we are readily engaging a small scale action to concretely engage GVN and prepare for future action plans.

The aim of this questionnaire is to help develop a common understanding among the GVN centers of excellence of what these priorities are, and, where appropriate, to make practical recommendations for change and to identify the capacity available in the network. The results will be analyzed and published as a position paper.

5. Plans for 2019

The GVN plans to address local needs for training and education by developing Regional GVN Units, which are teams of expert virologists grouped by geographical regions. We are currently taking the first steps towards the establishment of the following regions: Africa, South East Asia, South America, and Europe. The plan is to have Regional Units all over the world.

GVN also plans to host the 6th GVN Course in Baltimore during the week July 28th- August 3, 2019. Much of the focus of the GVN will be in the implementation of GVN's Anticipation and Preparedness Task Force and the partnership with Global public health institutions such as WHO (GOARN network).

The 11th GVN International meeting will take place in Barcelona,

June 9–12, 2019 in partnership with the Spanish Society of Virology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.antiviral.2019.01.013.

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