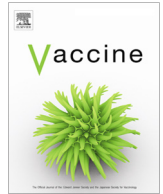




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Conference report

Arboviruses: A global public health threat

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ABSTRACT

A conference on «ARBOVIRUSES, A GLOBAL PUBLIC HEALTH THREAT» was organized on June 20–22, 2018 at the Mérieux Foundation Conference Center in Veyrier du Lac, France, to review and raise awareness to the global public health threat of epidemic arboviruses, and to advance the discussion on the control and prevention of arboviral diseases. The presentations by scientists and public health officials from Asia, the Americas, Europe and Africa strengthened the notion that arboviral diseases of both humans and domestic animals are progressively becoming dominant public health problems in the world. The repeated occurrence of recent deadly epidemics strongly reinforces the call for action against these viral diseases, and the need for developing effective vaccines, drugs, vector control tools and strong prevention programs.

1. Introduction

Declaring a dengue pandemic in the 1990's was a sentinel call to action in the fight against a range of emerging arboviral diseases of humans [1,2]. The past 50 years have seen a dramatic emergence/re-emergence of epidemic arboviral diseases [3,4]. The recent outbreak of neurological disorders and neonatal malformations associated with Zika virus (ZIKV) infection in Latin America [5], the yellow fever (YFV) epidemics in Angola and Brazil with importation to China [6], the ever-expanding West Nile virus (WNV) epidemic in the Americas [7], the recent emergence in East Africa and global spread of chikungunya virus (CHIKV) [8], as well as the ongoing and expanding dengue virus (DENV) pandemic in the tropics and subtropics [9] have reinforced the call for action in the fight against emerging and re-emerging arboviral diseases.

These epidemics underscore the urgency and need for integrated control and prevention of arboviral diseases, especially

those transmitted by *Aedes* mosquitoes in urban areas [10,11]. Prevention and control strategies currently focused on vector control, including insecticide treatment, environmental management and social mobilization have not been effective in practice. It is widely recognized that no strategy alone can fully address the problem. However, some intervention tools have helped reduce the disease burden. For example, timely access to clinical services and appropriate care can reduce mortality dramatically [12], indoor residual spraying (IRS) and indoor space spraying (ISS) may be effective in reducing mosquito populations and exposure to arboviruses [11]. In addition, personal protection, clinical diagnosis and management, laboratory-based surveillance and vaccination, can be effective [12]. Vaccines are available to protect against Japanese encephalitis and yellow fever [13], and the first dengue vaccine, even though limited in its applications, was licensed in 2015 [14].

2. Epidemiology, surveillance and diagnostic tests

Dr Duane Gubler (Duke-NUS Medical School, Singapore) reminded the audience that the frequency and magnitude of the arboviral epidemics and the extent of their geographic spread have progressively increased over time, accelerating in the past 30 years and now occurring globally in the tropics [3,4].

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As an illustration, DENVs were found in the 1960's in less than 10 endemic countries and only a few thousand cases were reported each year. In contrast, in 2017 the virus had become endemic in 124 countries, causing an estimated 400 million yearly infections and 100 million symptomatic cases [9]. In the 1970's, DENV serotypes 3 and 4 could be found only in South-East Asia. But in the early 1980's, all four serotypes of DENV had dramatically spread to all regions of the tropics [9]. Similarly, a new strain of CHIKV emerged in East Africa in 2004, spreading to Asia and then to the rest of the tropical world in 10 years [8]. And epidemic ZIKV emerged in the Pacific and spread around the world in only 7 years [5]. All of these viruses are transmitted by the urban mosquito, *Aedes aegypti*.

West Nile virus (WNV), transmitted primarily by bird feeding *Culex* mosquitoes, was introduced to the western hemisphere for the first time in 1999, rapidly spreading from the east coast of the USA to the rest of the country and to Canada before invading the Caribbean, Central and South America [7]. In 2002, 14,000 cases of WNV encephalitis in horses and 4,000 cases in humans were reported in the USA. WNV is now enzootic in the region.

Dr Joao Bosco Siqueiras (Institute of Tropical Pathology and Public Health, Goias, Brazil) described another dramatic example, that of yellow fever, which is also transmitted by *Aedes aegypti*. The mosquito is widely prevalent in the tropics including tropical America and most countries in sub-Saharan Africa. In 2007–2010 yellow fever emerged and expanded into the south and southeastern parts of Brazil, where yellow fever vaccination was not common. Then, in 2014–15, it emerged in Central Brazil, infecting many travelers. Cases of yellow fever were exported from Brazil to Europe, Peru and the USA. The virus continued to spread in 2017–18 into the areas of Bahia, Rio and Sao Paulo and was detected in 4266 municipalities, causing small urban epidemics [15]. The death toll increased to 235 persons in 2017 and 409 in the first half of 2018. In Africa, yellow fever spread from Angola to the Democratic Republic of Congo in 2016–17, and emerged in Nigeria and Uganda in 2018 [16]. More dramatically, 11 cases were imported from Angola to China, which is the first time in history that confirmed yellow fever was introduced to Asia [6]!

As outlined by Dr Duane Gubler, the new and worrisome aspect of emerging arbovirus epidemics is that they can occur in urban centers, as was observed with dengue fever, Zika, chikungunya and yellow fever. The urban vectors are *Aedes* mosquitoes, primarily *Aedes aegypti*, which has spread around the world in past centuries, and secondarily *Aedes albopictus*, whose spread began in the 1980s [17]. The emergence and spread of dengue, Chikungunya and Zika infections actually reflect the growing geographical spread of *Aedes spp* across all continents.

The fact that arboviral diseases have become a major threat to urban populations is the result of: 1) population growth and urbanization, which results in crowding of humans, inadequate housing, waste management and accumulation of trash, including used automobile tires, plastics, tins, etc, creating ideal ecological conditions for urban *Aedes* populations to thrive; 2) the spread of *Aedes spp* mosquitoes around the world and throughout the tropics and subtropics; 3) the lack of effective vector control and infectious disease prevention; and 4) the globalization of air transport, which facilitates the rapid spread of pathogens and the diseases they cause (more than 3 billion passengers have travelled on air lines in the year 2018) [2,3,18,19]. As these trends will continue, epidemic arboviral diseases will increasingly threaten global, national and local political and economic security and could create a global public health emergency, similar to or even greater than the current SAR-CoV-2 pandemic. One should not forget that over 3.6 billion people live in areas exposed to urban *Aedes* mosquitoes.

Dr Duane Gubler also noted that since arboviral diseases represent a major threat to urban populations, it is necessary to reassess

surveillance strategies. Currently, surveillance systems are based on passive reporting of loosely defined clinical syndromes with infrequent laboratory confirmation. He suggested that all at-risk countries should have an enhanced passive disease surveillance system based on well-defined case definitions supported by serological and virological laboratory testing. Three major arbovirus pathologies should be monitored: systemic febrile syndrome, haemorrhagic disease syndrome, and meningo-encephalitis syndrome. An active laboratory-based syndromic surveillance network is also badly needed. Weekly reports by local physicians, as done in Brazil, where they have turned out to be most useful, should also be encouraged.

However, as discussed by Dr Elizabeth Hunsperger (CDC, Atlanta, USA), differential diagnosis in the clinical setting may be difficult, especially outside of seasonal disease, as mild and asymptomatic infections are common. As an example, laboratory testing for dengue is important in order to distinguish the disease from other febrile illnesses such as malaria, leptospirosis or influenza, other arbovirus diseases such as Chikungunya, Zika, West Nile, Japanese encephalitis or yellow fever, and even from typhoid/paratyphoid (*Salmonella typhi* or *Salmonella paratyphi spp* bacteria). Recently, WHO has recommended the serotesting of individuals in dengue vaccination settings to screen out those with no evidence of past infection.

Each of these objectives requires different test characteristics. Standard dengue diagnostics assays include RT-PCR, virus neutralization assays, immunoassays to detect DENV NS1 antigen, and assays to detect anti-DENV IgMs [ref]. The most sensitive and specific assays are RT-PCR and the NS1 ELISA assay. Low-cost point-of-care (POC) rapid diagnostic tests (RDTs) are currently not adequate for the clinical and vaccination settings, while ELISA, RT-PCR and other strategies with much higher levels of performance are too slow and costly. The latter tests are needed in public health surveillance and research settings. These diagnostic approaches are instrument-dependent and require appropriate facilities and highly trained technical staff to perform complex diagnostic tests, unfortunately none of which are available in resource-limited areas. Dengue diagnostics will greatly benefit from a Dengue POC test that meets the WHO ASSURED criteria (Affordable, Sensitive, Specific, Rapid, User-friendly and Delivered to those in need) [20]. Note that laboratory diagnosis of dengue can be achieved with a single serum specimen obtained during the febrile phase of the illness by testing for DENV nucleic acid, non-structural protein 1 (NS1) and anti-DENV IgMs. The current POC RDTs detect both anti-DENV IgMs and IgGs as well as the NS1 antigen. This has the potential to change the current situation in resource-limited areas and improve dengue clinical management.

DENV viremia occurs for up to 12 days following the onset of fever, and anti-DENV IgMs begin to appear around 3 days after fever onset. Detection of DENV nucleic acid by RT-PCR is the most sensitive and specific means to confirm acute infection, but it may not necessarily reflect infectious virus as it only detects viral RNA, which may persist in biologic fluids after infectious virus is cleared. Immunoassays to detect DENV NS1 antigen also provide acceptable levels of sensitivity and specificity. Both these diagnostic approaches are instrument-dependent and require appropriate facilities to perform complex diagnostic tests.

Recently, it was found that Apoprotein H (Apo H) can be efficiently used to detect bacteria and viruses in blood samples. As described by Dr Francisco Veas (French Institute for Development (IRD), Montpellier, France), beads coated with Apo H can readily capture viruses with a glycoprotein-rich envelope such as influenza virus, Ebola virus, DENV and other arboviruses, or even HCV. The beads are easy to use, the process is very fast and shows high sensitivity: one can readily detect 1 PFU of virus in 5 mL of whole blood.

3. Disease update: The example of Zika virus infection

Dr Rome Buathong (Bureau of Epidemiology, Dept of Disease Control, Thailand Ministry of Public Health) reminded the audience that until the Brazilian outbreak in 2015–16, ZIKV was a little known arbovirus presenting with a mild dengue-like illness without any major complications [21]. It initially spread from sub-Saharan Africa to Asia without detection. Thus, although the virus was present in Thailand, it was not detected until May 2013, when a Canadian traveler returning from Thailand was diagnosed with the disease. A ZIKV surveillance program was launched in the country (from January 2016 to December 2018) revealing a yearly peak of ZIKV infection during the rainy season, occurring 6–8 weeks after the peak of dengue disease. A total of 1698 confirmed cases of ZIKV infection was recorded in Thailand during this two year period. The age groups most affected were the 11–20 followed by the 21–30 year groups. A total of 121 cases of ZIKV infection was recorded in pregnant women, leading to 4 miscarriages and 4 birth abnormalities, including 3 cases of microcephaly.

Aedes mosquitoes in the country were found to be ZIKV positive, but other routes of transmission included blood transfusion and sexual intercourse. ZIKV RNA could readily be detected from plasma, saliva and urine of infected patients. Sexual transmission of ZIKV has been documented to occur up to three weeks after onset of illness in the male partner. Shedding of the viral RNA in semen has been well documented, but only 4% of semen samples that were PCR positive could be shown to contain infectious virus by cell culture.

Dr Nikos Vasilakis (University of Texas Medical Branch) reviewed the explosive emergence of ZIKV in 2015–16 in the South Pacific and South America, with a focus on Brazil where major clinical outcomes in pregnant women were common. The alarming numbers of ZIKV associated microcephaly and other gestational and neonatal complications brought the virus into the spotlight. Increased reporting of Guillain-Barré syndrome (GBS) and other neurological manifestations was also associated with ZIKV infections.

The first association between ZIKV infection and microcephaly was reported in 2015 in Recife, Brazil where three women infected with ZIKV during their pregnancy delivered babies with microcephaly. It was retrospectively discovered that neurological diseases, including microcephaly, in babies born to ZIKV-infected mothers, had been observed in French Polynesia as early as 2014. As reported by Dr Patricia Brasil (Oswaldo Cruz Foundation, Rio de Janeiro), a prospective cohort study for ZIKV infection in pregnant women and infants was initiated in Rio de Janeiro in early 2016. ZIKV was recovered from the amniotic fluid and placenta of the pregnant women, and also from the cerebral spinal fluid of their babies. Microcephaly was observed in 4%–6% of the newborns, while structural birth defects such as hypertonicity, cardiac defects, ophthalmic abnormalities, elbow abnormality, and seizures were observed in up to 11.9% of the newborns. A follow-up of Brazilian babies born to mothers infected by ZIKV during pregnancy showed that up to 25% had abnormal hearing or other manifestations, and 47% showed signs of abnormal behavior. At 18 months of age, only 21% of the babies displayed normal neurodevelopment.

Dr Mauricio Lacerda Nogueira (Faculty of Medicine, Sao Jose do Rio Preto Brazil) talked of the interplay between various flaviviruses. Given that Brazil is hyperendemic for arboviruses, there was concern that previous heterotypic flavivirus (e.g. dengue) exposure could exacerbate Zika disease pathogenicity. DENV antibodies (Ab) bind to ZIKV. Could they drive greater ZIKV replication through antibody-dependent enhancement (ADE)? The phe-

nomenon was initially described for DENV, but it has also been found to exist for rabies virus, coxsackievirus B3, coronaviruses, and even HIV.

To answer the question, a cohort of healthy volunteers in Vila Toninho, Brazil, was followed up from 2015 to 2018, looking for evidence for a possible ADE phenomenon. In spite of the fact that 74% of the cohort had DENV Ab at the start of the study, no significant clinical difference could be observed in ZIKV infections between DENV Ab positive and DENV Ab negative persons. Thus, the epidemiological evidence in Brazil did not support the hypothesis that previous exposure to DENV infection could enhance ZIKV pathogenicity. By contrast, it has been reported that DENV-1 and DENV-2 Ab might be protective against ZIKV infection. Similarly, the presence of YFV Ab has recently been associated with a better prognosis of ZIKV infection in pregnant women.

Other hypotheses, such as enhanced infectivity of ZIKV for *Aedes* mosquitoes, have not been confirmed. Interestingly, a A226V mutation in the E1 gene of CHIKV has recently been described which is associated with enhanced infectivity of the virus for *Aedes albopictus* mosquitoes.

As discussed by Dr Nikos Vasilakis, the most convincing explanation for the sudden aggressivity of ZIKV lies in the discovery by Yuan et al [22] in 2017 of a mutation in the prM gene of the Brazilian strain of ZIKV, which could strongly contribute to the generation of fetal microcephaly. The mutation was also found in ZIKV strains from French Polynesia, where numerous cases of microcephaly have been recorded, but not in virus strains from Africa, where microcephaly has never been observed.

Dr Marc Lecuit (Pasteur Institute, Paris), addressing the question of the cellular and molecular mechanisms of microcephaly, reminded the audience that, in contrast with CHIKV, which does not cross the placental barrier, ZIKV can readily penetrate and infect placental cells. Inoculation of ZIKV in the brain of mouse embryos triggers an endoplasmic reticulum stress which perturbs the physiological unfolded protein response (UPR) within apical cortical progenitor cells that control neurogenesis. Sustained endoplasmic reticulum stress leads to apoptosis. Thus, it is likely that, in pregnant women, ZIKV crosses the placental barrier, gets to the brain of the fetus and crosses the blood–brain barrier, then targets apical cortical progenitor cells, which leads to the blockade of UPR and the arrest of neurogenesis, and, as an obvious consequence, to microcephaly. Microcephaly has not been observed in Africa; it appears to be a specific property of the Brazilian ZIKV strain, and is most likely related to the prM mutation identified by Yuan et al [22].

Dr Michael Gaunt (London School of Hygiene and Tropical Medicine) reported a series of experiments done on ZIKV and DENV to identify potential genetic determinants of ADE. A 10 amino acid long motif in the DENV glycoprotein was identified which might be associated with ADE.

Dr Annelies Wilder-Smith (London School of Hygiene and Tropical Medicine) reviewed the EU research program on ZIKV (the 'ZikaPLAN'), which oversees 25 institutional global partners with plans to set up a sustainable Latin American research preparedness network for emerging diseases. A longitudinal cohort study of 17,000 subjects aged 2–59 is being followed for three years in 14 different locations in Brazil, to further refine the full spectrum and risk factors of congenital Zika syndrome, including neurodevelopment milestones, mental retardation, etc, during the first 4 years of life. Also to be addressed is whether neurological problems associated with ZIKV infection, such as meningoencephalitis or acute Zika myelitis, are the direct consequence of ZIKV infection, or are mediated by immune responses. Novel ZIKV diagnostic tests will also be developed.

4. Vector biology and control

Dr Louis Lambrechts (Pasteur Institute, Paris) reminded the audience that *Aedes aegypti*, which is distributed throughout the tropical and sub-tropical world on all continents, serves as the major vector to transmit urban arboviruses, including the 4 DENVs, ZIKV, YFV, CHIKV, etc. Whereas most female mosquitoes take only one blood meal a day, *Aedes aegypti* females need multiple blood feedings every day, which makes them more efficient at transmitting epidemic disease. The comparison between *Aedes aegypti* and *Ae albopictus* also shows that, although *Ae albopictus* is often more susceptible to infection by DENV than *Ae aegypti*, it appears to be significantly less efficient at transmitting the virus. In addition, factors such as the mosquito genotype, its geographical location, and the strain of arbovirus, influence the transmission dynamics of the disease. For example, ZIKV infection of *Ae aegypti* mosquitoes seems to be influenced by the sequence of the NS1 protein of the virus.

As reported by Dr Scott Ritchie (James Cook University, Cairns, Australia), the use of *Wolbachia* infection of *Aedes* mosquitoes has great potential to control the spread of the arboviruses they transmit. *Wolbachia*-infected male *Aedes* mosquitoes become sterile and, if sterile males are repeatedly introduced in a given area, the resident *Aedes* populations can be suppressed. Alternatively, *Wolbachia*-infected male and female mosquitoes can be introduced together, which leads to a progressive replacement of the resident *Aedes* population, which could then show a much reduced capacity at transmitting DENV, ZIKV, CHIKV, YFV and possibly other viruses [23,24].

The use of *Wolbachia* is recommended by the World Mosquito Program to eliminate dengue. A trial in Australia has demonstrated that, shortly after release of *Wolbachia*-infected *Aedes* mosquitoes, over 90% of the mosquitoes population at the site became *Wolbachia*-infected, and the transmission of DENV was stopped [25]. Similar trials are being conducted in Viet Nam, Indonesia and Brazil. The fear that *Wolbachia* infection of *Ae aegypti* would lead to its replacement by *Ae albopictus* seems unwarranted so far, but it requires further studies.

5. Vaccines

5.1. Yellow fever

Dr Joao Bosco Siqueira reported that Brazil had suffered from a shortage of yellow fever vaccine. Fortunately, the usual dose of the Brazilian vaccine contains 40,000 pfu of attenuated YFV (strain 17D), when only 5,000 pfu is a sufficient protective dose [26]. It has therefore, been possible to use fractional doses of vaccine with evidence of protection and relatively no difference in reported adverse events. Faced with the spread of yellow fever throughout the country, the Brazilian Government has updated its vaccination policy and now recommends that the entire population should be vaccinated. As part of this effort, a change in schedule for children was implemented from a single dose at 5 years of age to a 2 dose schedule with the first dose administered at 9 months and a second dose at 4 years. This effort is complicated by inadequate vaccine supply and also false rumors that the vaccine would not be protective. Fake news is unfortunately powerful and, as a result, vaccine refusal has been rising in the population!

5.2. Dengue

As reviewed by Dr In-Kyu Yoon (International Vaccine Institute, South Korea), Dr Christopher Nelson (Sanofi Pasteur, Lyon, France) and Dr Annelies Wilder-Smith, major advances in dengue research

have resulted in development of new vaccines that show promise for use in dengue prevention, such as Sanofi Pasteur's recently licensed CYD-TDV (*Dengvaxia*[®], Sanofi Pasteur, Lyon, France) and six other dengue vaccine candidates in various phases of clinical trials.

CYD-TDV is a tetravalent live attenuated chimeric vaccine consisting of a 17D YFV genome with the pre-membrane (pre-M) and envelope (E) genes from each of the four antigenically distinct DENV serotypes. The vaccine has undergone large-scale Phase 3 clinical trials in Asia and Latin America [13,14], demonstrating increasing efficacy with age and higher efficacy in baseline seropositives. Efficacy was highest at preventing severe dengue and hospitalization, and moderate for overall dengue. It also varied with serotype, being higher (75–84%) for DENV-3 and -4 infection, and lower for DENV-1 and -2. Notably, during the third year of the Asian Phase 3 trial, an increased risk of dengue hospitalization was seen in children aged 2–5 years. Efficacy of the vaccine was only 5% or less in 2–6 years old and 65% in 6–8 years old. The vaccine was licensed in 2015 with an age indication of 9–45 years (up to 60 years of age in some countries). The CYD-TDV vaccine is now licensed in 20 countries, and has been introduced into public immunization programs in endemic areas of the Philippines and Brazil.

The vaccine showed high efficacy and good safety in seropositive persons in the 9–45 years age group, but a risk of severe dengue was observed in individuals who were naive for DENV infection at the time they were vaccinated. It was hypothesized that CYD-TDV mimics primary infection among individuals with no prior dengue infection (previously dengue-unexposed, seronegatives) and a secondary-like infection among those with prior dengue infection (previously dengue-exposed, seropositives) [14,27–30]. A retrospective case-cohort study was undertaken to analyze vaccine safety among dengue seropositive and seronegative trial participants. This work used anti-NS1 results from month 13 of follow-up that were obtained using an anti-NS1 IgG ELISA developed for this purpose. The data confirmed the substantial benefit of CYD-TDV vaccination in those who are dengue seropositive and aged 9 years or older, reducing symptomatic dengue, hospitalized dengue and severe dengue by ~80%. However, in individuals of any age without evidence of prior dengue infection, the vaccine elicited an increased risk of severe dengue, as announced by Sanofi Pasteur in November 2017. The vaccine should therefore be administered only to dengue seropositive persons, which obviously implies the need for a pre-vaccination screening strategy [30].

The WHO SAGE Dengue Working Group reviewed these data and, in April 2018, the SAGE Committee recommended to vaccinate only those with evidence of past dengue infection (seropositives) or with medical documentation of past dengue infection. These results have implications for other dengue vaccine candidates in clinical development, and for immunization program policy and program implementation.

Two other dengue vaccine candidates are currently in Phase 3 clinical trials: TDV, developed by the US CDC and manufactured by Takeda, and TV003/005, developed by the US NIH. TDV is a tetravalent live attenuated chimeric vaccine that uses an attenuated DENV-2 backbone with the pre-M and E genes from each of the other three DENV serotypes. The TDV vaccine is undergoing Phase 3 trials in Brazil, Columbia, Nicaragua, Panama, Sri Lanka and Thailand. Preliminary phase 3 data show the vaccine is safe and has good efficacy against DENV-1 and -2, but the results for DENV-3 and -4 are uncertain because there were only a small number of cases of these serotypes [31].

TV003/TV005 is a tetravalent live attenuated vaccine which includes three DENV serotypes (DENV-1, -3, -4) that have undergone attenuation through direct mutagenesis (a 30 base-pair deletion), while the DENV-2 candidate consists of a DENV-4-DENV-2

chimera. The Butantan Institute in Brazil, which is the sponsor of Butantan-DV (TV003), received regulatory approval in December 2015 to begin a Phase 3 trial in Brasil.

Three other DENV vaccines are in less advanced development. They are an inactivated vaccine, a DNA vaccine, and a subunit (the E glycoprotein) vaccine. But the difficulties of developing effective and safe dengue vaccines are multiple, as seen in the CYD-TDV experience, and many issues still remain, including: 1. The vaccine should elicit equal protection against the four DENV serotypes, which has been extremely difficult to achieve, in view of competition between strains and/or ADE of some strains: the question has been raised of whether it really is a must to develop tetravalent vaccines? 2. Whether antibodies are associated with protection or risk (ADE) seems to depend on titer, homotypy versus heterotypy, etc. How can that be understood and controlled? 3. Why does severity of the disease, especially that of the post-vaccination adverse events, vary with age? And 4. What is the feasibility and what will be the cost of a necessary pre-vaccination screening?

Nevertheless, the substantial public health benefits of even a moderately effective dengue vaccine continue to drive all the efforts at developing dengue vaccines [29,30], hoping that safety concerns may be adequately addressed.

5.3. Zika

A large number of Zika vaccine candidates are under development and have entered clinical trials, including: a mRNA vaccine; a DNA vaccine that encodes the ZIKV prM and E genes and is presently entering Phase IIb trials in the USA, Brazil, and several countries in Latin America (Puerto Rico, Mexico, Panama, Peru, Columbia..); a purified inactivated vaccine adjuvanted with alum, which was shown to be immunogenic after two doses by the IM route in a Phase 1 clinical trial; and a chimeric measles virus vaccine that expresses the prM and E genes of ZIKV. As outlined by Dr Anna Durbin (John Hopkins Bloomberg School of Public Health) many hurdles still remain before licensure of a safe and effective ZIKV vaccine can occur. The transmission of ZIKV has declined so much that it will be difficult to perform a Phase 3 efficacy study. In addition, clinical trial efficacy endpoints for a ZIKV vaccine are not well established: one can wonder if a vaccine will not have to fully prevent infection in order to prevent microcephaly, a very high bar for any vaccine indeed!

5.4. Other viruses

Dr Georges Thiry (SAS Senergues, France) reported the creation of the 'Coalition for Epidemic Preparedness Innovations' (CEPI), which was launched in January 2017 in Oslo, London and Washington with the aim to prevent future epidemics by the development of new vaccines. Three major targets have been selected for the manufacturing and testing of candidate vaccines: MERS-CoV, Lassa Fever virus and Nipah virus. CEPI is responsible for vaccine development from preclinical to Phase 2a trial. Several vaccines are being followed up: a Lassa-VSV vaccine, developed by IAVI; a Lassa-DNA vaccine; a Lassa-measles (MV) vaccine, developed by Themis; a MERS-CoV-MV vaccine, also developed by Themis; and a Nipah glycoprotein subunit vaccine with adjuvant. Most Phase 1 studies have taken place in 2018–19 and Phase 2a trials are expected to follow in 2020–22.

6. Concluding remarks

Arboviruses are in the news and at the top of social, political and public health agendas. Arbovirus epidemics will increasingly

threaten global, national and local political and economic security and create a global public health emergency. Not only is there an increased risk of epidemic arboviral diseases in rural areas, but there also is now an increased risk of urban epidemics. Dengue epidemics have recently seen their amplitude increase dramatically: in 2019, there were 10 fold more reported cases of DENV infection in Brazil than during the preceding year, leading to 600 deaths; during the same period, 44,000 dengue-infected persons had to be hospitalized in Bangladesh, where some 100 deaths occurred, and more than 1400 deaths from dengue were reported in the Philippines! An estimated 390 million dengue infections occur annually [9].

The development of vaccines and vector control tools to prevent arbovirus diseases is actively being pursued [32,33], and the possibility of developing a trivalent vaccine against ZIKV, CHIKV and WNV is even being entertained. Many hurdles however, remain before licensure of a safe and effective ZIKV vaccine can occur, as outlined above. Similarly, the difficulties at developing an effective and safe DENV vaccine are multiple, and many questions still arise. What will be the cost of implementing pre-vaccination screening? Whom to vaccinate in places where DENV seropositivity in 9 years of age turns out to be very low (only 10% in Singapore for example)?

The dramatic emergence and spread of epidemic arboviral diseases has made it necessary to reassess surveillance strategies. All at-risk countries should have an enhanced passive disease surveillance system based on well-defined case definitions and supported by serological and virological laboratory testing. An active laboratory syndromic surveillance system, such as was developed in the past by WHO for influenza or for poliomyelitis, is badly needed. It is hoped that such a system will be set up rapidly. But we also need more effective mosquito control tools to use in conjunction with vaccines, timely access to clinical services and appropriate care. Only by using an integrated approach to prevention and control will we be able to successfully reverse the trend of emergent epidemic arboviral diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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