

## **Yellow Jack knocking on Asia's door! A Report on the Meeting on the Risk of Yellow Fever autochthonous transmission in the Asia-Pacific region**

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Following the return of 11 Chinese (non-vaccinated) workers infected with Yellow Fever Virus (YFV) from Angola between March 2016 to April 2017 (Chen *et al.*, 2016; Ling *et al.*, 2016; Cui *et al.*, 2017), a series of articles and commentaries appeared underlining the historic nature of these introductions into Asia, but more crucially they stressed that these imported cases demonstrate how critical it is to recognize the risk now in order to take adequate preemptive action so that a catastrophe can be averted (Wasserman *et al.* 2016; Elsevier Health Sciences, 2016; Butler, 2017) Wasserman and colleagues consider that these

conditions raise the alarming possibility of a Yellow Fever epidemic in Asia, with a case fatality rate of up to 50%, in a region with a susceptible population of two billion people and where there is extremely limited infrastructure to respond effectively (Wasserman *et al.* 2016).

Acting on this potentially dangerous situation, virologists, medical entomologists, epidemiologists and immunologists from 13 Instituts Pasteur within the Institut Pasteur International Network (IPIN) Asia-Pacific and Africa regions, the Chinese Center for Disease Control and Prevention and Nature Communications gathered at the Institut Pasteur of Shanghai-Chinese Academy of Sciences on the 6th and 7th December 2017 to assess the present situation and to: 1) plan research strategies to better analyze the risk of Yellow Fever Virus (YFV) introduction and autochthonous transmission in the Asia-Pacific region, 2) to improve existing direct and indirect YFV diagnostic techniques and assure that regional Instituts Pasteur are able to differentially diagnose YFV from the plethora of other Flavivirus species circulating in Asia (Dengue Virus, Japanese Encephalitis Virus, Zika Virus, Tick Borne Encephalitis Virus, Yokosé Virus, Sokuluk Virus etc.), and 3) to discuss Yellow Fever epidemic preparedness and prevention in the Asia-Pacific region, as well as how to address weaknesses in abiding to the International Health Regulations.

The majority of the Yellow Fever-infected Chinese workers returned to Beijing, Fujian and Shanghai, China during the month of March 2016 when average temperatures were too low to support Yellow Fever vector, *Aedes aegypti* or *Aedes albopictus* biting activities and extrinsic viral development. However, if these human Yellow Fever introductions were to have taken place during the hot and humid rainy season when Yellow Fever vectors are abundant and actively biting in China, a localized outbreak could not have been excluded. However, at present, given the fact that these were the first documented Yellow Fever introductions in Asia, there is insufficient evidence-based data to adequately assess the risk of YF autochthonous transmission in Asia.

Because there has never been documented autochthonous transmission of YFV in Asia or at least in the past century, most public health authorities have and still consider Asia as “off limits” to YFV transmission and this perception has by all means integrated the collective consciousness. A common hypothesis put forth to explain this lack of YFV establishment in Asia is that strains of dengue and other related flaviviruses offer cross protection and reduce viral loads for efficient transmission (Butler, 2016). However, the rapid spread of Chikungunya virus and Zika virus transmission these past few years are unnerving reminders of what can happen during this age of ever increasing air travel and the continual and expanding colonization of *Aedes (Stegomyia)* mosquitoes due to rampant urbanization and climate change. Given the Yellow Fever scare in China, it is now urgent and indispensable to provide the scientific community and public health officials with evidence-based results concerning the vectorial competence of Asian and Pacific Island strains of *Aedes aegypti* and *Aedes albopictus* to YFV, with the caveat that these experiments be carried outside the Asia-Pacific region to avoid unintentional introduction. We need to update the spatial and temporal distribution of *Aedes aegypti* and *Aedes albopictus* in the Asia-Pacific region to better decipher their biology in a context of environmental, social, economic, climatic change and most importantly to evaluate and map their resistance to insecticides. Furthermore, it is important to evaluate other putative peri-urban and sylvatic arboviral vectors, such as *Aedes malayensis*, *Aedes scutellaris* and *Aedes niveus* to avoid YFV spillover into simian populations that are prevalent in Southeast Asia. It should not be forgotten that YFV was in fact first introduced into the Americas centuries ago by *Aedes* spp. mosquitoes and slaves coming on ships from West Africa. The YFV spread from the coastal areas into the jungle where sylvatic vectors: *Sabethes* sp. and *Haemogagus* sp. have been the YFV to non human primates ever since. (Bryant *et al.*, 2007).

For YFV surveillance, direct (YF genome) and indirect (serological) diagnostic capacities are requisite. Today readily available commercial and customized diagnostics for YFV serology are lacking; moreover, the paucity of reliable diagnostics is further complicated by the numerous *Flavivirus* species circulating

in Asia, hence making confirmation specificity and sensitivity difficult and serological YFV confirmation solely reliant on sero-neutralization assays. Finally, to our knowledge no rapid diagnostic test for YFV is yet available. Therefore, renewed research and development on YFV diagnostics are warranted and should be pursued.

Another area of serious concern is that the global YFV vaccine supply remains constrained due to limited production capacity. Furthermore, the high demand generated by the outbreak in Angola in addition to potential increased outbreak response requirements in other geographic regions; outweigh supply, which is indeed worrisome (Barrett, 2016; UNICEF, 2016; Shearer *et al.*, 2017). A reassessment of the present situation needs to be taken into consideration by the WHO, GAVI UNICEF and other stakeholders.

The Institut Pasteur International Network with 33 institutes on 4 continents is uniquely positioned, with its local and international partners to tackle these renewed challenges concerning the entomo-virological research and diagnostic improvements to assess eventual YFV introduction and autochthonous transmission in Asia-Pacific region. The IPIN with its global expertise in virology, medical entomology and epidemiology, has served the Asia-Pacific region for over a century. Today member institutes in the Asia Pacific region are present in: Shanghai, Hong Kong, Seoul, Hanoi, Ho Chi Minh City, Nha Trang, Vientiane, Phnom Penh, Tehran, and Nouméa. The Asia Pacific regional institutes also benefit from the invaluable support of the Institut Pasteur Dakar (World Health Organization Reference Center for Yellow Fever in West Africa), the historic and present day hub for Yellow Fever research and vaccine production. The IPIN is engaged to help address these research and diagnostic issues to increase Yellow Fever preparedness in the Asia Pacific region.

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