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Urgent call for action: avoiding spread and re-urbanization of yellow fever in Brazil

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Yellow fever (YF), a haemorrhagic viral disease with a high fatality rate, is considered one of the greatest scourges of mankind. Historically, devastating epidemics of this disease have been reported since the seventeenth century in Africa, the Americas and Europe (WHO 2017).

The control of urban yellow fever in Rio de Janeiro in the beginning of last century is recognized as one of the most successful public health initiatives in the world. Oswaldo Cruz's successful campaigns with strong and enforceable fight against the domestic mosquito vector *Aedes aegypti* dramatically dropped the number of urban yellow fever cases in the city. The measures were applied with success across the country. The elimination of the urban transmission in Brazil and all over the Americas was achieved in the early 1940's with the vaccine campaigns and *Ae. aegypti* eradication (Franco 1969). However, the ineradicable zoonotic sylvatic transmission cycle maintained between *Haemagogus* and *Sabethes* mosquitoes and non-human primates (NHP) has annually caused people infections and deaths.

The recent sylvatic YF outbreak in Brazil has been the most severe in the last seven decades and turned into an epidemic. Up to May 31 2017, a total of 3240 cases have been reported in Brazil: 792 confirmed, 1929 dismissed and 519 remain under investigation,

including 435 deaths (274 confirmed, 124 discarded, and 37 under investigation). The case fatality rate (CFR) among confirmed cases is 34,5% (MS 2017). For non-human primates, 3850 epizooties were reported (642 confirmed, 96 dismissed and 1448 under investigation).

The rapid spread of the YF cases in Brazil has led to a major concern: infections were no longer reported just in the jungle and remote inland rural areas, but sylvatic transmission also occurred in the surroundings of the most densely populated cities in the states of São Paulo (SP), Minas Gerais (MG), Espírito Santo (ES), Bahia (BA) and Rio de Janeiro (RJ) (MS 2017). It started in MG late in 2016. Despite of being an area with recommendation for routine immunization and having a good vaccination coverage in the young population, the epidemic reached and hit with severity the rural area of northeastern MG, due to poor vaccine coverage of adults. The rapid spread to the coastal state of ES, an area where YF vaccine was not routinely recommended, led to a severe epidemic with 260 and 85 confirmed cases and death, respectively. Subsequently, the virus also spread to RJ, which also had no previous recommendation for routine YF vaccination. Fortunately, some of the areas at higher risk in RJ had already been partially vaccinated at this time. Nevertheless, 17 confirmed cases and 7 deaths were recorded in the state from March to June 2017 (MS 2017).

The YFV circulating in Brazil since 2008 belongs to the South American Genotype I, lineage 1E (Sousa et al 2010, Cardoso et al 2010). The whole genome of YFV causing the 2017 outbreak in ES was sequenced and phylogenetic analysis revealed that it clusters in the 1E sub-clade along with recent Brazilian and Venezuelan strains (Mir et al. 2017). However, it was discovered that this virus strain displays seven new mutations, which role in host infectivity and virus replication and spreading is still under investigation (Bonaldo et al. 2017). The unique amino acid signatures carried by the 2017 YFV occur in non-structural proteins, being one change in the capsid protein and the other in components of the viral replicase complex, the NS3 (two changes) and NS5 (five changes) proteins; no change was detected in the envelop protein. Although the amino acid changes may affect the viral fitness, they would not potentially impact in the efficacy and effectiveness of the available vaccines (Bonaldo et al. 2017).

A complex combination of ecological, social and behavioral factors may help to explain the severity and efficient spread of the YFV in Southeast Brazil, particularly its dissemination to the Atlantic coast. Among them, ecological issues, such as changing environmental and climate conditions, favoring a high density of competent sylvatic and urban vectors and primary amplifier vertebrate hosts (NHP); the

uncontrolled occupation of forest areas by human populations; the large number of susceptible non-human primate populations and non-vaccinated people in peri-urban areas in close contact with forests, mainly the adult human populations from rural areas in Northeastern MG affected by the recent YFV outbreak as well as in vast coastal receptive zones (Vasconcelos 2010, Couto-Lima et al. 2017). In these zones, lack of access of populations to sanitation and garbage collection in urban areas, favoring *Aedes* proliferation, is contributing to increase the potential for re-urbanization of yellow fever in Brazil.

Yellow fever epidemics are not acceptable and are an ethical issue. Brazil is the largest producer of yellow fever vaccine, which is provided free of charge. Vaccination was not recommended universally in Brazil due to the serious adverse events associated with it. But now the risk of transmission increased, and the risk-benefit balance favors universal vaccination. This decision has already been taken, but its implementation is urgent, taking advantage of the temporary relief in YFV transmission in most of Brazil caused by the reduced rainfall and lower mean temperature recorded during the dry season (July-October). These environmental conditions reduce the availability of mosquito larval sites, larval developmental time, mosquito adult longevity and viral replication. YFV epizooties and human cases will potentially reemerge in the following rainy season. The last two epidemics in Brazil spanned more than one year: from 1988 to 2003, and again in 2008 and 2009, despite vaccine campaigns (Vasconcelos 2010; MS, 2017; Jentes et al 2011).

On this aftermath, the decision by the Ministry of Health to vaccinate all the Brazilian population against YFV was obvious, and received strong support from the Brazilian scientific community and the international health authorities. Due to sudden increase on demand and limited vaccine supply, the decision by the Ministry of Health to administer only one dose of vaccine, as recommended by WHO, was provisionally endorsable. Nevertheless, booster doses are necessary to ensure longer protection for all YFV vaccines (CGSYF 2014, Campi-Azevedo et al. 2016). Therefore, the emergent decision to administer only one dose of vaccine recently taken by the Brazilian Ministry of Health should be reevaluated as soon as the current sanitary situation normalizes and new information on duration of immunity is available.

Yellow fever vaccination needs to be urgently intensified before the next rainy summer, chiefly on the states with the highest risk, such as RJ and other coastal receptive and vulnerable Brazilian zones. Rio de Janeiro has the largest urban forest in the world. Large remains of the Atlantic rainy forest extend in a vast territory from South to Northeast Brazil, along which millions susceptible people live in cities,

villages and farms under influence of this biome. Competent sylvatic mosquito vectors and susceptible NHPs are largely distributed in this area. All together, these features render this large territory very receptive to sylvatic YFV re-emergence in the next rainy season. Alarmingly, this territory also reports high infestation by *Ae. aegypti*, but also of experimentally YFV susceptible *Aedes albopictus* populations. The proximity with the YFV sylvatic transmission foci and the intense people movement in this territory combined with high density of these urban vectors increase the risk of YFV reemergence in an urban cycle, which needs to be urgently be prevented with vector control measures and vaccination campaigns.

The YF vaccine should be included in the immunization schedule of all the Brazilian population, with specific recommendations for groups at risk. Mobile immunization units should be urgently provided to reach the more vulnerable rural populations, with limited access to immunization in health centers.

In addition, as the demand for yellow fever vaccine will continue to increase due to the epidemiological context in Brazil and elsewhere, there is an urgent need to strengthen public manufacturer's capacity to provide the YF vaccine to all who need it by an affordable price.

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