A common approach to tackling mosquito-borne viruses to pre-empt epidemics

London, 5-7 October 2016

Executive summary

Mosquito-borne viruses, most of them transmitted in the urban environment, pose a threat to half the world’s population and a serious public health challenge in many developing countries.

The global expansion of dengue, chikungunya and most recently Zika, as well as the recent epidemic of urban yellow fever in Central Africa, raise numerous questions over patient management, prevention and control. Indeed, Zika has made us aware that other viruses with poorly-known pathologies may be waiting in the wings, poised to enter the urban transmission cycle.

Many of these diseases are under-researched and few tools exist to combat them, as shown by the current Zika outbreak in Latin America. When effective tools exist, as is the case with yellow fever, there are often production or supply vulnerabilities, as seen in the recent outbreak in parts of Africa.

These issues were the subject of a WHO and Wellcome Trust three-day meeting in London, on 5-7 October 2016, bringing together a wide range of international experts. The aim of the consultation was to review the science on mosquito-borne viral diseases and explore common research approaches in order to promote development of medical products capable of combating several of these diseases, thereby saving precious time during research and improving cost-effectiveness.

The meeting was organized under the WHO R&D Blueprint effort, which aims to reduce the time between declaration of a public health emergency and the availability of effective diagnostic tests, vaccines, antivirals and other treatments that can save lives and avert a public health crisis (http://www.who.int/csr/research-and-development/en/).

Mosquito-borne viruses: exploring a common approach

Mosquito-borne virus outbreaks seem set to increase in occurrence and geographic range in the future, largely due to demographic changes, urbanisation, agricultural and land use practices, deforestation, and husbandry practices. This inevitable trend presents numerous challenges and requires the development of well-integrated strategies for prevention and control, effective surveillance systems, stronger health systems in affected countries and research preparedness, especially to develop better diagnostics that can diagnose and differentiate between the different mosquito-borne diseases.

At the same time, clinical management for mosquito-borne viruses are starting to improve, with a new understanding of pathogenic processes. A vaccine approach with the potential for broad-spectrum flavivirus activity has been described. More work is still needed to understand how cross-neutralisation and cross-enhancement can affect disease transmission and pathogenesis. There is
also a need for better methods of vector control, and how the environment is affecting mosquito ecology.

**Vaccines**

A major topic of discussion at the meeting was the way existing flavivirus immunity in a patient affects immunity to other pathogens, and the potential for antibody dependent enhancement (ADE). ADE has been documented for various flaviviruses in *in vitro* models (for yellow fever, Japanese encephalitis and Dengue), but apart from Dengue has never been plausibly documented in humans as a means to modulate disease susceptibility or severity of disease. Discussions also covered: the possibility of inferring from existing flavivirus vaccines; the need for a standardized way to measure neutralization in evaluating vaccines; and exploration of various vaccine technology platforms to achieve sterilizing immunity. The very similar structures of a particular epitope near the E protein in both Zika and Dengue provoked discussion on the potential for a universal flavivirus vaccine. The question was also raised on whether transmission-blocking vaccines might curb spread during a flavivirus outbreak, or work as a preventive measure.

**Vector control**

Meeting participants broadly agreed that vector control for diseases transmitted by the *Aedes* mosquito should be sustained and scaled up, particularly where vaccines and specific therapeutics are not available. Findings from the meeting were: highly concentrated urban areas are particularly challenging as they require holistic solutions; insecticide resistance is important and requires increased monitoring; and the levels of effort and investment previously seen in malaria control now need to be replicated to curb *Aedes* mosquitoes. This will require political will and commitment; to gain the necessary support and win public backing. Field studies on the efficacy of vector control tools are needed, measured against epidemiological outcomes and containing economic evaluations; and evidence for current methods should be reviewed. Meanwhile, new, improved strategies must be explored. Innovation should also extend to involving communities, with the help of social scientists, and to surveillance tools and techniques. All this also requires advocacy, and increased capacity and training in public health entomology.

**Medicines and blood products**

While a broad spectrum anti-viral would be welcomed, there are several challenges to its practical use. These include: delayed case identification; patients’ late presentation for care; overlapping syndromes; the fact that disease is generally not life-threatening while progression to severe disease is unpredictable; and incomplete understanding of disease pathogenesis. Any effective treatment would rely on better diagnostics and diagnostic strategy in order to be effective. Virus-specific monoclonals could be developed for targeted use, such as Zika prophylaxis in pregnant women, or treatment of viscero-invasive yellow fever vaccine.

**Diagnostics**

Good diagnostic tests for mosquito borne diseases also face challenges. Viraemia is often over at clinical presentation, necessitating serological diagnosis; and available assays have poor specificity, due to cross reactivity among arboviruses and differing arbovirus backgrounds in different regions, which make validation challenging. Experts discussed the importance of validated international
reference standards for different mosquito-borne viruses. The problem of access to biomaterials (pathogen strains, specimens, and reagents) was seen as an ongoing challenge.

**Regulatory issues**

The meeting discussed alternative regulatory pathways that can be adapted for emergency situations and their limitations, and explored the work of Brazilian agency ANVISA in cooperating with other regulatory agencies to expedite processes during the Zika emergency. Regulators face particular issues with Zika given the gaps in the science and data usually needed for regulatory assessment. In this context the need for international reference standards was again raised, as was WHO’s important role in coordinating different regulators and pathways.

**Yellow fever**

The recent African outbreak has exposed vulnerabilities in vaccine supply, but also provoked successful innovation in the use of fractionated doses. Making the business case to vaccine developers for a new vaccine was already challenging (with the current vaccine conferring lifelong immunity with a relatively safe profile) and the successful use of fractional dosing adds to this challenge. Research to evaluate this approach further is now a priority. Plans are also in place to address supply issues in the near future, not least of which is the Eliminating Yellow fever Epidemics (EYE) strategy (http://www.who.int/csr/disease/yellowfev/eye-strategy/en/).