Dengue fever update

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Dengue Global Epidemiology

Dengue continues to be a global disease, more so than prior to 2000. In the Americas, cases have become more numerous, particularly Dengue 3 infections, with the highest incidence and mortality among adolescents and children[1]. Since beginning operations in 1999, the European Network on Imported Infectious Disease Surveillance (TropNetEurop) has detected an increasing incidence of dengue imported to Europe, mostly from South East Asia (43%)[2].

Now 10 years after the publication of "The development of Dengue vaccines and their military significance"[3] outbreaks in Asia and the Middle East are occurring in Saudi Arabia, Yemen, Brunei, Thailand, and Indonesia[4]. In Australia this year, outbreaks have been declared in Tully (February 2010) and Townsville (April 2010), both of which have been Dengue 2 infections[5].

Despite a number of episodes transiently reducing international travel, the increase in global dengue is related to increased mobility of populations. Dengue is not only emerging with a greater global footprint, but diversifying that footprint in any location with multiple serotypes, thus increasing the risk of complicated dengue infections.

Dengue in the ADF

Since the publication in 2006 the relevance of dengue vaccines to operations of the Australian Defence Force remains high. The ADF experienced a significant exposure to dengue during deployments to East Timor with initial outbreaks in the forward area of operations and in Dili of at least 160 cases at the Army Malaria Institute[6]. This outbreak included cases of all four serotypes, though mostly Dengue 3. Many lessons of field prevention and management of dengue were relearned and new field diagnostic tests and expertise were developed that proved useful in the following years of continued operations in East Timor and subsequently in other near- north operational areas.

The broader military significance of dengue to the ADF was highlighted by the potential importation of dengue to the receptive area of continental Australia in returning military personnel from operations[7]. The ADF demonstrated superlative preventive medicine expertise in the containment of dengue among soldiers returning to Townsville from East Timor. At least nine viraemic cases were returned to Townsville and treated at Lavarack Barracks without any local transmission of the virus.

Progress towards a Dengue Vaccine

The conventional wisdom is that a tetravalent vaccine will be necessary to avoid heterotypic reactions to serotypes against which only marginal immunity is held[8].

Following the outbreak of dengue among ADF personnel in East Timor, the Defence Health Services became involved in the global effort to develop a dengue vaccine. At that time, Aventis Pasteur in collaboration with Mahidol University in Thailand had gathered strains of dengue from South East Asia to attenuate for tetravalent vaccine candidates. A Phase 1b study was conducted at 2HSB to evaluate the immunogenicity and safety of two dengue vaccine candidates[9]. This study well demonstrated the necessary level of attenuation to maintain immunogenicity whilst ensuring safety.

These candidate vaccines and other live attenuated tetravalent dengue vaccine programs have largely been suspended in favour of more sophisticated approaches. These strains have subsequently been used to develop chimaeric vaccines with yellow fever vaccine. Chimaeric dengue vaccines have been developed combining the DNA coding for the envelope antigens of the dengue serotype with the 17D yellow fever vaccine to produce a replicating viral particle manifesting the dengue serotype envelope antigens with the core of the YF vaccine.

In this format, ChimeriVax-DEN2 has been demonstrated to produce neutralizing antibodies to all four dengue serotypes in association with yellow fever vaccine pre-immunity[10]. Whether this translates into clinically protective immunity is not clear. The development of a tetravalent chimaeric vaccine has progressed to be the leading candidate in dengue vaccines having completed Phase 2b trials in adults[11]. Phase 3 trials of the chimaeric tetravalent vaccine are underway in South East Asia by Sanofi Pasteur and are due for first results in 2012[12].

This is the leading vaccine candidate program for a tetravalent dengue vaccine. Aventis Pasteur aim for it to be on the market in 2015. Other programs

continue towards further development of tetravalent vaccines. Hawaii Biotech are in Phase 1 trials of a monovalent Dengue-1 vaccine consisting of envelope proteins expressed by an insect cell system. With successful results, this vaccine will next progress to tetravalent trials.

Another chimaeric dengue vaccine has been developed by CDC on an attenuated Dengue-2 backbone used in the same way as Acambis/Sanofi vaccines have used the 17D Yellow Fever vaccine backbone. The CDC vaccine has been licenced to Inviragen for clinical trials towards a tetravalent vaccine due to begin shortly13. The clinical trial program is becoming typical of dengue vaccine development with initial trials in dengue-free countries, in this case USA, before Inviragen moves to Singapore for later phase clinical trials in an endemic area. The other feature of this dengue vaccine development program and the vaccines discussed here is the partnership with significant biotech companies able to scale vaccine development to the levels that will be necessary to supply the world with dengue vaccines when they do become available.

Australia remains on the list of countries in which dengue vaccines are likely to be licensed early due to the quality of research and regulation, the presence of endemic dengue and the proximity to hyperendemic countries.

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