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The development of Dengue vaccines and their military significance!

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Background of Dengue in the South-West Pacific Region

Dengue has become a world-wide disease with more than 100 million cases per year.[1] It is the leading cause of arboviral infection in humans.[2] The current global pandemic of dengue arose from the combination of ecological disruption and demographic changes associated with World War II in Asia and the Pacific.[3] A major regional pandemic occurred around Australia in the final years of the war. With the isolation of the Pacific islands, dengue disappeared until outbreaks of dengue 3 in Tahiti in 1964 and dengue 2 in Fiji in 1971. Dengue 2 subsequently spread to island groups east and west of Fiji. Dengue 1 reintroduced to the area in 1975 and dengue 4 in 1979.

Multiple epidemics of dengue occurred in north Queensland in the late 19th century with the first clinical descriptions of dengue haemorrhagic fever during an epidemic in 1897.[4] Following subsidence of dengue in Australia after World War II, dengue 1 reappeared in 1981 in north Queensland and continued transmission until 1990.[5]

Contemporary Military Significance

The military significance of dengue is multifaceted including loss of manpower through non-battle casualties, loading of the logistic chain with casualties, importation of dengue to Australia during re-deployment and the subsequent deployability of those contracting dengue.

The vector for dengue viruses, Aedes mosquitoes, typically breeds in artificial containers. Suitable breeding sites are the debris remaining from the destruction of urban environments as well as wells, tanks and other storage containers left unmanaged when civil infrastructure breaks down. Under these circumstances, dengue will accompany peacekeeping and peacemaking forces. The INTERFET experienced a significant number of non-battle casualties arising from dengue.[6] The United States peacekeeping and peacemaking forces in Haiti and Somalia also experienced large numbers of dengue cases among deployed personnel serving in similar areas of urban devastation arising from conflict. [7.8]

The operational significance of dengue lies in the nature of the clinical condition. Typically, dengue develops within one to two weeks of transmission from an Aedes mosquito. Common symptoms are fever, macular rash, headache, retro-orbital pain, arthralgia and myalgia, which may last a further one to two weeks or longer with a fatigue syndrome. [9] Most non-immune adults infected will develop the clinical syndrome to some extent.[10] Such debilitation of personnel in this space of time reduce both manpower and manoeuvrability by depletion of the effective fighting force and loading the health service support elements.

With the control of local transmission of dengue in Australia, the possibility of importing dengue into receptive areas of the country by returning soldiers must be of significance to military planners. Importation of dengue from the areas to the immediate north have caused major outbreaks of dengue in north Queensland.[11] The ADF presently has contingents in several dengue-endemic areas immediately north of Australia.

Military significance also arises from the increasing single serotype dengue seroprevalence among the deployable force. Dengue haemorrhagic fever has long been attributed to arising from secondary dengue infections.[12] The implications for subsequently deploying seropositive personnel to dengue-endemic areas, particularly those areas with a different prevalent serotype to that which immunity has been developed is the possibility of antibody-dependent enhanced (ADE) second infections and increased risk of DHF.[13] The risk is probably small, though real.

Vaccine development

Developing a dengue vaccine is important as only symptomatic and supportive treatment are available for the disease and prevention of transmission is the only management for an outbreak. Dengue vaccines were first generated soon after virus isolation towards the end of World War II. The real challenge of dengue vaccination is to develop a tetravalent vaccine capable of providing protection against all four serotypes to prevent sequential serotype ADE infection.

The Walter Reed Army Institute of Research (WRAIR) began attenuating dengue virus in 1971, producing a dengue 2 candidate vaccine, which underwent phase 1 trials causing mild illness in some vaccines. Seroconversion occurred in most (61%) flavi-naive recipients and 90% of those previously vaccinated with yellow fever vaccine.[14]

Upon support from the Regional Advisory Committee for Medical Research of the South East Asian Regional Office of the WHO, efforts were focused into a single laboratory and the concept of a tetravalent vaccine was agreed upon. The Dengue Vaccine Development Laboratory was established at the Department of Pathology, Ramathibodi Hospital, Faculty of Medicine, Mahidol University. With other Governments. Organisations and Institutions, the Australian Government contributes to this endeavour.

Monovalent vaccine phase 1 trial were begun in mountain communities (free of Aedes) in Thailand with flavi-naive individuals. These vaccines were found to be safe. Subsequently, bivalent vaccines and trivalent vaccines were produced by mixing monovalent vaccines prior to subcutaneous injection. These were found to be safe and immunogenic.[15.16] A tetravalent vaccine was produced with concentrations of each element determined by the 50% minimal infectious dose calculated from monovalent vaccine titrations and a small phase 1 trial, this formulation was found to be immunogenic. Subsequently, a larger phase 1 trial in children found after one vaccination, one per cent of recipients experiencing fever and rash. A second vaccination was administered to 22 of these children six months later. Twenty of the children developed neutralising antibodies to all four dengue serotypes.[17]

A collaboration was established with Pasteur Merieux, now Aventis Pasteur, for further development of the vaccine. A phase 2 trial has attempted to establish most likely candidate formulations in terms of safety and immunogenicity. A proposal for phase 2 trial of two candidate tetravalent dengue vaccine formulations has been provisionally approved to be conducted by the AMI in the ADF in collaboration with Aventis Pasteur.[18] This trial will begin later this year with the first of two vaccinations over a six-month period.

Conclusion

Ultimately, the target population of a tetravalent dengue vaccine will be the children of dengue-endemic countries for whom infection is likely and complications are a high risk and carry a high mortality rate. The benefit for the ADF and the military of other nations not endemic for dengue is the possibility of preventing a major cause of non-- battle casualties. Initial results of this trial in the ADF will be presented at the 10th Conference of the Australian Military Medicine Association.

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