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The Benefit of Japanese Encephalitis Vaccination? [1]

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Abstract
The use of Biken Japanese encephalitis (JE) vaccine (JE-Vax) by the Australian Defence Force (ADF) for service personnel deploying to JE endemic areas has consumed a significant proportion of the total ADF vaccine budget. Consideration of the benefit this has provided may be obtained by a cost-benefit study. The risk to ADF personnel in East Timor of acquiring JE has been estimated to be less than 1/12000. With a vaccine effectiveness assumed to be 72%, the number needed to vaccinate to prevent one additional case of clinical JE has been estimated at 4695 persons. As the vaccine cost for initial JE vaccination in the ADF is $130, the cost of preventing one additional case of clinical JE is $610,350.

Introduction
Japanese encephalitis is caused by a mosquito- borne virus. The disease is reported to extend from India to the Korean Peninsula, through the Japanese and Philippine islands, throughout Southeast Asia and into Melanesia. It is the leading cause for viral encephalitis in Asia with adult exposure thought to produce a clinical/asymptomatic infection ratio of 1:200 and permanent neurological outcomes for the clinical cases[1].

Entry of the virus to the Australian geographic region was heralded by clinical cases in the Torres Strait in 1995[2]. With the first clinical case presenting on continental Australia in 1998[3]. The Australian Defence Force embarked on large-scale vaccination of deploying forces with consideration of the distribution and expansion of the virus in southeast Asia.[4] Vaccinating service personnel with an initial course of three subcutaneous injections, at a cost of $130 for the course, represented 42% of the budget for vaccines in the ADF in FY98/99[5]. This paper will review the data and, by utilising cost-benefit analysis[6]. will consider whether this has been a good investment or not.

The Vaccine
The Biken JE-Vax is an inactivated vaccine. The vaccine virus, the Nakayama-NIH strain, was originally isolated in 1935 from a human case of JE and is now grown in mouse brain before being inactivated with formalin. The vaccine was subject to efficacy studies prior to availability in Australia. In a pivotal study involving 65224 Thai volunteers, Hoke et al.[7] found a cumulative attack rate for JE in the control group of 51 / 100 000 (51 x 10.5) while the vaccinated group had 5 cases/100 000 (5 x 10.5). This established the relative risk reduction (RRR= (Initial risk - Modified risk) / Initial risk) or efficacy of vaccine at 91% (95%: CI 70%-97%)[6]. This trial, however, used only two vaccinations one month apart. This confirmed earlier work in Taiwan finding the inactivated mouse brain vaccine had over 80% efficacies.

One possible confounding factor of analysis of this data. in extrapolation to efficacy in Australian soldiers, is that the populations vaccinated in these previous trials had a higher level of flavi- virus exposure. Both countries have endemic JE and dengue. The volunteers, therefore, will enter the study of a flavi-virus vaccine "primed". Also, the newly vaccinated volunteers living in a JE and dengue-endemic country will be challenged more frequently than Australian soldiers who are based in a non-endemic area (Australia) and only occasionally visit endemic areas on operations where many other precautions are taken to prevent exposure. Such an effect has also been observed in infections among laboratory personnel [9]. The effect potentially acts as a boost for the immunised.

The efficacy of the vaccine has not been determined in Australian service personnel as no field trials have been conducted in the face of wild virus. Nevertheless, effectiveness may be assessed by serological assessment after vaccination [10]. The inactivated vaccine after injection will be phagocytosed by antigen-presenting cells, the viral peptides presented on MHC II (major histocompatibility complex type II) for CD4 T lymphocytes that, through a type II response, produce B lymphocytes and Plasma cells to develop neutralising antibodies to JE. In summary, the nature of this immune response is such that the objective endpoint of vaccination is neutralising antibody, thus inferring effectiveness from seroconversion rates. In previous work at the Army Malaria Institute (AMI), it has been found that approximately 70-80% of flavi-naive soldiers will develop antibodies two weeks after the initial vaccination course.

The Risk

The actual risk of JE to which Australian soldiers are exposed is not well defined. Rates of up to 2.1110,0001 week have been seen in unvaccinated military personnel (US) in endemic countries[11.13]. When the ADF entered East Timor as part of InterFET. JE had not been recorded in the Province. The presence of the virus has subsequently been confirmed with viral studies by ICPMR, Westmead, of samples derived from clinical cases in Vikeke and surveillance samples from Dili. The risk to ADF personnel may be estimated from using the denominator of those exposed during Operations Warden and Tanager and assuming a single case for mathematical purposes despite the absence of such a case. Approximately, 7500 soldiers served with InterFET. Three further Battalion groups of approximately 1100 persons have deployed to the area of operations with around 400 additional service persons in other Units. This period covers two years with an estimated total of 12000 persons exposed.

Australian Defence Force personnel benefit from significant vector control programs and personal protection measures in addition to vaccination. The additional protection will reduce the overall risk of being exposed to the vector of the JE virus. This will bias the effectiveness of the vaccine away from the null; that is, improve the apparent efficacy. That accepted the apparent overall risk of JE to ADF personnel serving in East Timor is less than 1/12000 (8.3 x 10-5). Notably, this is comparable to that observed by Hoke et al.[7] among the vaccinated group.

Risk Reduction

Taking the efficacy of the vaccine from the two field studies conducted in endemic countries, vaccination is 80-90% effective and assuming 80% seroconversion among Australia soldiers, the RRR from vaccination will be assumed to be 72%. Notwithstanding continual use of other personal protection measures and vector control, the actual risk (72% = {Initial risk - 8.3 x 10-5} I Initial risk) is estimated to be 29.6 x 10-5, giving an absolute risk reduction (ARR = Initial risk - Modified risk)6 of 21.3 x 10-5.

Number Needed To Vaccinate

For the ADF, the cost of preventing one additional case of JE, in statistical terms is the "number needed to treat" (NNT. or vaccinate in these circumstances)[6] and is derived from the inverse of the absolute risk reduction (NNT = 1IARR). From the absolute risk reduction of 21.3 x 10-5, the number needed to vaccinate would be (at least) 4695 persons to prevent one case of clinical JE.

The current policy for the ADF for personnel serving in East Timor is to receive all three subcutaneous JE vaccinations prior to deployment. The approximate vaccine cost for this countermeasure is $130 for the initial course. The estimated cost of preventing one case of JE based on these data is $610,350.

Conclusion

There are many estimations inherent in these calculations; however, in planning population interventions with limited resources, including limited funding, the process of determining the "number needed to treat" (or vaccinate) is a valuable method to allow comparison of interventions. Ultimately, the decision to vaccinate against JE must also include the impact of one case. Such ramifications are the possibility of a soldier, sailor or airman suffering permanent neurological impairment following clinical JE, as well as the public awareness that a virus previously only seen once on continental Australia has again been introduced, this time by the Defence Force.

With the availability of an internationally accepted JE vaccine, not vaccinating the deploying force to a JE endemic area and sustaining a non-battle casualty from this virus is likely to be unacceptable to media-aware Australians.

Further research

There are opportunities to reduce the cost of preventing one case of operational JE. The AMI has been researching the prospects of intradermal vaccination with the existing Biken JE-Vax. Dual intradermal vaccination has been found to be comparable to conventional subcutaneous vaccination with markedly reduced costs in initial studies[14]. Alternative vaccines available now are not suitable for Australian circumstances. In China, Primary Dog Kidney grown live attenuated vaccines from the SA14-14-2 strain JE virus are available[15-17]. Live attenuated vaccines are not acceptable for Australia while the continent remains largely JE receptive and inactivated vaccines are available. The Walter Reed (United States) Army Institute of Research (WRAIR) has inactivated the SA14-14-2 strain for a vaccine and conducted a successful phase I trial [18]. The AMI will be involved in the phase II trials of this vaccine late in 2002. AMI will also be involved in the phase II trials of the chimeric JE vaccine[19]. This is a vaccine built on the backbone of the successful 17D Yellow Fever vaccine (17D YF) with the PreM and E sections of the genome replaced by JE sections[20]. Potentially, this vaccine will give JE protection with YF vaccine performance (one vaccination for an extended immunity).

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