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Commentary

Proposed new WHO rabies control guidelines (Highlights from the WHO consultation on human and dog rabies prevention and control, Veyrier du Lac, France, October 7-9, 2009)

The World Health Organization convenes a conference of experts on rabies at least once every 5 years in order to determine whether major changes in the current guidelines are indicated. Such a meeting was convened at Annecy, France in October 2009. New recommendations are considered by the WHO Secretariat and, if significant enough, included in a revised version of the WHO position paper on rabies vaccines for submission to the Scientific Advisory Group on vaccines and immunization (SAGE) and, if relevant, to the Expert Committee on Biological Standardization (ECBS). Below is a summary of the meeting that may be of interest to rabies specialist, worldwide.

CE Rupprecht (US-CDC) presented new guidelines originating from the US Advisory Committee on Immunization Practices (US-ACIP) on post-exposure rabies prophylaxis. It was accepted in June of 2009 [1]. It recommends a change in the "Gold Standard" Essen intramuscular schedule, shortening it to two weeks by omitting the final day 28 injection. The US-CDC regimen for WHO category III patients now consists of rabies immunoglobulin (RIG) injected into wounds and vaccination on days 0, 3,7, and 14; omitting the day 28 dose. This revision was based on extensive reviews of experimental, epidemiological, and clinical data [2]. There is little doubt that compliance with this new schedule will become routine in North America.

DC Anderson presented his strong criticism of the current WHO and US-CDC guidelines for the use of immunoglobulins (RIG) for post-exposure prophylaxis, which was based on a 2007 paper [3]. He argues that the portion of a calculated dose injected intramuscularly at a site distant from the wounds is a waste of these scarce and expensive products. His reasoning is that human and equine rabies RIG is often virtually unavailable in most rabies endemic countries. Wasting the RIG by injecting the remnant of the calculated dose, not used for effective wound injection, into a distant intramuscular site may deprive the next patient of receiving this life saving product. DC Anderson, MK Sudarashan, and SN Madhusudana presented data that led to extensive discussions of this important issue. Past animal and some human data showed that intramuscularly injected RIG, at the calculated weight-based dose alone, does not result in significant circulating antibody titers [4]. Delegates were aware of these results and raised the need for further controlled prospective studies that would determine whether injecting the wounds alone is effective in preventing human rabies deaths. However, such studies are impossible to carry out ethically today. Heated discussions focused on Anderson's suggestion to define a maximum dose for wound injection that is unrelated to the patient's weight and to do away with RIG injection at a distant site altogether. The consultation did not come up with a consensus regarding this suggested change other than to firmly acknowledge the paramount importance of wound injection with RIG. Only the physician at the bed-site can determine the optimal dose of the RIG that can and must be injected safely into and around the wounds without compartment syndromes or other complications. To determine this dose arbitrarily was considered impossible. The physician in an impoverished region must therefore make a decision whether to inject RIG into all wounds alone and then, either save the remnant of the calculated total dose for the next patient, or inject it intramuscularly at a site different from vaccine as is currently

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recommended by WHO. This current and decades old WHO and US-CDC recommendation clearly ask for a fixed weight-based calculation of the total dose. The part not injected into wounds is injected intramuscularly elsewhere. This was never changed, even though there is experimental evidence in animal models that RIG injected intramuscularly in animals alone is not protective [4]. There is, however, no convincing evidence that this might also be the case in humans. Very rare human rabies deaths, where WHO and US-CDC guidelines have been followed, and have been reported and will have to be expected in the future [5]. This clearly raises the probability that a physician, who does not use the total calculated RIG dose, may be held responsible if the patient dies of rabies. This threat further complicates decision making on how to solve the dilemma of avoiding waste of valuable excess RIG after wound injection. Animal bite centers, which experience extreme shortages of RIG and have no choice but to inject wounds only, should collect prospective data. This may allow making evidence- supported-changes in current RIG injection guidelines. There was no consensus among the delegates and this problem remains as is for future resolution.

The issue whether there is need to define a potency per dose injected intra-dermally at each site was discussed. The volume of 0.1 mL is now the accepted standard per site when using WHO recommended regimens. MJ Warrell, DJ Briggs, and B Quiambao collected data dealing with recommended potency of vaccines used for intra-dermal regimens. They could not find any published prospective immunogenicity study of vaccines with potency near the 2.5 IU minimum. The WHO and US-CDC requires that all tissue culture vaccines must have a minimum potency of 2.5 IU per intra-muscular dose (whether reconstituted in 0.5 or 1.0 mL). WHO also recommends that vaccines to be used intra-dermally fulfill that potency requirement and have been shown to be immunogenic in humans using WHO recommended intra-dermal regimens and volumes per intra-dermal site. WHO has a short list of vaccines that fulfill all these conditions [6, 7]. Most current WHO recognized vaccines are of considerably greater potency than 2.5 IU per dose. Thailand, nevertheless, requires that vaccines used for ID schedules must have an antigen content of at least 0.7 IU per 0.1 mL dose (7.0 IU per full reconstituted dose whether in 0.5 or 1.0 mL). Similar requirements exist in other Asian countries using intra-dermal schedules. There has been formal discussion of this subject at past WHO conferences [7]. The discussion during this meeting reiterated earlier conclusions saying that a potency dose per intradermal site was not adding value to existing recommendations on vaccines for intradermal usage. It would seem very timely to conduct an independent prospective immunogenicity trial on volunteers using a WHO recognized vaccine at a potency of 2.5 IU (0.25 IU per ID dose).

DJ Briggs and B Quiambao then presented a review of documented studies of the duration of neutralizing antibody after pre- and post-exposure vaccination. They concluded that immune memory, with accelerated immune response following boosters after a potential exposure, last for decades [8]. Consequently, boosters at 1, 2, or 5 years, as sometimes recommended, are not indicated unless the subject is in a continuous high-risk exposure setting (laboratory workers, certain animal handlers etc). In all situations, re-exposure to rabies requires a short post-exposure prophylaxis regimen without RIG consisting of 2 intra-muscular or intra-dermal injections on days 0 and 3 or, alternately, one visit with the new 4-site intra-dermal injections (see below).

P. Shantavasinkul presented a large retrospective study (of 5,116 patients, 65% WHO category III and 5% bitten by laboratory proven rabid animals) who had received the previously published one visit, 4-site intradermal boosters during the past 10 years, after experiencing repeat rabies exposures following reliable pre- or post-exposure vaccination. The longest time interval between primary and booster vaccination was 25 years. Higher initial neutralizing antibody titers were statistically significantly higher in the 4-site booster group than in the conventional day 0 and 3 boosters. The original work was published in a previous study published [9]. None of the 5,116 subjects had any significant adverse reactions and there were no reported rabies deaths. This regimen, though not yet WHO or US-CDC recommended, is now recognized by Thai authorities and regularly applied at Thai Red Cross animal bite centers. The delegates endorsed this regimen and it should be submitted to SAGE for review in April 2010.

MJ. Warrell proposed a new 4-site intra-dermal regimen consisting of 4 intra-dermal injections of 0.1 mL on day 0, 2 on day 7, and 1 on day 28. Her proposal was based on a published study that still included the 90 day booster that was abandoned by all WHO

approved post-exposure regimens [10]. Her data documented immunogenicity results equivalent to those in other studies using the well-estalished intra-dermal Thai Red Cross, conventional Essen or Zagreb 2-1-1 intramuscular regimens. She then proposed that 0.1 mL injections be only used with WHO recognized vaccines reconstituted in 0.5 mL. However, a study by A Ambrozaitis et al. [11] used PCEC at 1.0 mL reconstitution and it showed that there was no statistically significant difference between PVRV diluted in 0.5 mL and PCEC diluted in 1.0 mL using 0.1 mL per dose. Warrell's presentation again raised the old dispute of what is a minimum safe potency for intradermal injection. After lengthy discussions, without total consensus, it was agreed that the intra-dermal dose should remain uniform at 0.1 mL for all vaccines that fulfill WHO requirements for the intradermal route. All new rabies vaccines, to be used for intra-dermal use, should demonstrate their immunogenicity at the 0.1 mL dose. The consultation did endorsed the proposed "4 sites" regimen as a potential replacement for the "eight sites Oxford" schedule, which may consequently disappear from the WHO list of recommended schedules.

P. Shantavasinkul et al. also presented a prospective study of an intensive shortened post-exposure schedule completed within one week. It was based on solid prior data that immunity from current tissue culture vaccines is long lasting and that it is very likely that a vigorous initial antibody response, along with RIG wound injection, is of the greatest importance. This study was carried out with and without RIG using healthy volunteers and PVRV from Sanofi with the original Thai Red Cross intra-dermal regimen (2-2-2-1-1) as controls. This proposed new schedule consists of four intra-dermal injections of 0.1 mL at different lymphatic drainage sites (arms and legs) on days 0, 3 and 7. Initial neutralizing antibody responses on days 14 and 28 were significantly higher in this 4-4-4 group with and without RIG than in the control group. The duration of the responses, up to one year, was not significantly different from the control group. This schedule looks very promising as it may reduce travel costs drop-outs, which are a significant factor in developing countries (ranging from 20-30% in the experience of the Thai Red Cross Animal Bite Center). This regimen would provide an alternative option for those who need to complete PEP within one week. It is now being repeated by an independent investigator in at least one other Asian country. P. Shantavasinkul's study has been accepted for publication in the January 15 issue of Clinical Infectious Diseases. The consultation acknowledged the promising results of the above study and decided that the decision on whether to endorse the regimen will be made as soon as results of another study become available.

A resolution was passed that any studies presented to WHO of new schedules or changes in current WHO recommendations should have been designed and conducted using GCP standards and published in an international peer review journal.

South Pacific islands, such as Flores and Ambon in Indonesia were previously rabies free. Rabies was introduced by fisherman importing infected dogs. Local authorities responded by mass killing of owned and community dogs first, and then by inadequate vaccination campaigns after much delay. There were well over 100 human reported deaths. Canine rabies is still present on these islands. Almost one decade later, rabies appeared near Denpasar on Bali. The response was again one of mass killing of dogs in the initially affected district along with circular vaccination using a locally manufactured poorly immunogenic vaccine. Vaccination of dogs by private veterinarians and others was prohibited with the result that canine rabies and human cases have now appeared outside the region initially affected. Some local officials actually believed that canine vaccines might induce rabies infection. This belief had an origin when attenuated live rabies vaccines had been used and may have been justified some four decades ago. The initial official response to the outbreak was first managed using 1927 guidelines written by Dutch colonial authorities. Only sustainable canine and feline rabies vaccination, using a potent vaccine, is likely to make these islands rabies free again. Mass killing of dogs was not able to stop the outbreaks in Flores and Bali [12]. The delegates urge national and provincial authorities to apply only techniques for dog control and rabies prevention that comply with current WHO and OIE guidelines and are in line with modern animal welfare principles.

The issue of whether or not inclusion of pre-exposure rabies vaccination for children in EPI programs in rabies endemic countries should be promoted was considered. T Hemachudha, reviewed three studies dealing with this subject [13-15] that showed that it is possible to integrate rabies vaccination into EPI without significant adverse reactions in

recipients or interference with the immune response to other vaccines as well as with a good rabies immune responses. One model showed that introducing rabies, as part of EPI would be cost beneficial in a very long-term. The problem is that it is costly, would compete with other vaccination priorities, and possibly discourage vigorous vector control. In addition, efficacy and statistically sound cost-benefit analysis would be difficult to carry out due to the low numbers of human rabies cases in the countries where this has been proposed. However, the Consultation recommended further studies of the feasibility of incorporating rabies vaccine into immunization programs for infants, toddlers, and/or schoolchildren in countries where there is no shortage of vaccine for PEP and in areas where canine rabies has not been controlled by the use of conventional methods. Unlike the situation for canine rabies, in Latin America, human populations within inaccessible regions of Amazonia are under routine predation by vampire bats. Application of pre-exposure or PEP to these populations is a major challenge that must be met. Additional research and clinical trials are also needed for application of existing biological and/or new regimens and schedules that could be completed in a few days.

One afternoon was devoted to discussing the most important issue of dog control. S Clkeveland, FX Meslin, and A Wandeler showed convincing evidence that sustained mass vaccination including oral vaccination, together with humane canine population management, are feasible, even in poor countries. They are clearly essential for controlling rabies in dogs and man. The methods were used with success in Europe, the Americas, Japan, Taiwan, Malaysia, Hong Kong and Singapore.

CE Rupprecht and MP Kieny presented exciting data creating hope that extensive experimental work on rabies monoclonal antibody cocktails are close to completion. They are now undergoing human safety and efficacy trials. Monoclonal products are almost certain to replace human and equine RIGs and it is hoped that costs for these new products will be affordable in rabies endemic countries.

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