

Low-Cost Intradermal Rabies Vaccination Is Indeed Very Promising

TO THE EDITOR—We read with great interest the recent article by Wieten et al in *Clinical Infectious Diseases* [1] and, being involved in ongoing research strictly related to this topic, we wish to bring our contribution to their reflections.

First, we fully agree that a lower-dose, abbreviated intradermal pre- and postexposure vaccination schedule may constitute a valid, shorter, and cheaper alternative to the current intramuscular

or intradermal 3- to 4-week schedules. If proven to be effective, such a schedule would be highly advantageous both for prevention in international travelers and for expanding vaccination in resource-poor endemic countries. We also agree that further studies are needed to determine precisely which intradermal preexposure regimen is ideal for life-long boostability and which intradermal postexposure regimen gives high effective serology titers at day 7 after exposure.

In their literature review, Wieten et al selected 9 studies and described the effects of the different schedules [1]. They stated that direct comparisons of various studies was not possible because of the different timing, dosing, routes of administration, and, in our opinion, also because of the small sample size and of the differences in serologic testing. The 2 most promising intradermal studies were designed by Khawplod [2, 3]: In 5 of the 10 study arms, exclusively intradermal regimens (0.1 mL) were used, with a total dose between 0.4 mL and 0.8 mL. In 2 other studies, authors declared that a total dose of 0.4 mL or 0.6 mL, respectively, of preexposure rabies vaccine administered over a minimum of 2 visits gives an adequate antibody response, irrespective of the time interval since the last dose [4, 5].

Concerning serology, in fact, the World Health Organization guidelines recommend the use of either the rapid fluorescent focus inhibition test (RFFIT) or the fluorescent antibody virus neutralization test. In particular, an RFFIT titer of > 0.5 IU/mL after booster vaccination is considered to be the best surrogate marker to determine protection from rabies infection after an animal bite in endemic zones [6]. Thus, we suggest that studies using only the enzyme-linked immunosorbent assay (ELISA), although reliable as an alternative, should be excluded in future analyses assessing or comparing the boostability of preexposure and postexposure rabies vaccination schedules. For instance, a recent case

series study of 420 subjects that used a highly effective abbreviated (7-day) intradermal preexposure schedule showed promising results [7], with an overall seroconversion rate after initial vaccination of 94.3% (14 days after the last vaccination). However, the rabies antibody ELISA was used instead of the gold standard (RFFIT), and the methodological design was a case series study, with known limitations (no randomization); thus, such findings should be further confirmed.

Concerning the sample size, it is worthwhile to note that even if local mild adverse side effects after intradermal schedules have been described in small studies, larger sample sizes are now needed to assess and compare more accurately the safety profile of such schedules.

Meanwhile, the need for further studies should not slow down the attempts to improve the cost-effectiveness and the time-to-boostability of rabies vaccination. Pharmaceutical industries should in particular make available ampoules of 0.1 mL for direct intradermal injection, with special intradermal needles to improve quality of care. Also, ad hoc research plans should be designed for children in endemic countries, who can be considered a neglected population owing to great risk exposition.

Finally, we would like to note that our study, "Simplifying the Preexposure Rabies Schedule" (EudraCT 2011-001612-62; clinical trials registration identifier NCT01388985) [8], in contrast to that of Wieten et al, is not evaluating intramuscular schedules, but is comparing 2 intradermal preexposure regimens with total doses of 0.4 mL versus 0.5 mL (day 0: 0.1 mL, day 7: 0.1 mL, day 28: 0.1 mL vs day 0: 2 × 0.1 mL, day 7: 2 × 0.1 mL, and 1 booster vaccination between day 365 and day 1095 of 0.1 mL). Recruitment started in October 2011 and as of 31 December 2012 we had recruited 415 subjects of the planned 480. The seroprotection by RFFIT is tested on day 35 after initial vaccination and 7 days after booster between 365 and 1095 days. Our primary endpoint,

boostability after a single intradermal booster, will be analyzed in 3 years (at the end of the study).

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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