The handling and production of dairy products, *Mycobacterium bovis* infection is quite unusual in developed countries of the Western hemisphere [1]. However, in recent years, outbreaks of multidrug-resistant *M. bovis* infection in patients with AIDS have been reported from Spain and elsewhere [2–5]. These reports have described the disseminated nature of *M. bovis* infection in HIV-infected patients and have emphasized the associated high mortality rate, which approaches 100% at 3 months after diagnosis [2]. Here, we describe an immunocompetent host who developed pulmonary tuberculosis caused by multidrug-resistant *M. bovis*.

A 32-year-old woman who was a social worker at Fundación Jiménez Díaz (Madrid) was admitted to the hospital because of fever and chest pain. One week before admission, she had developed a cough, malaise, fever, and sweats, and, later on, she experienced pleuritic chest pain. The findings of physical examination, blood tests, and biochemical studies were normal. The patient’s erythrocyte sedimentation rate was 41 mm/h. Radiography of the chest revealed infiltrates in the upper right lobe. The results of a tuberculin test were positive (15-mm induration). The patient had a mild course of infection in which symptoms rapidly subsided and pulmonary infiltrates abated, despite the patient having received treatment with a combination of drugs that were proven to be inactive in vitro against the isolate. Obviously, the immune integrity of this patient had to be of paramount importance to achieve the cure.

The patient continued to receive therapy with rifampin and isoniazid until she completed a 12-month course. The findings of chest radiography and the erythrocyte sedimentation rate became normal. Three years after discontinuation of treatment, the patient is doing well, and there are no signs of residual tuberculosis.

In immunocompromised patients with AIDS, *M. bovis* infection is a very severe disseminated infection with an awful prognosis. However, the situation could be completely different in immunocompetent hosts. To the best of our knowledge, only 1 immunocompetent patient with multidrug-resistant *M. bovis* infection has been described to date [6]. That patient developed pulmonary tuberculosis that relapsed after cessation of treatment. Our patient had a mild course of infection in which symptoms rapidly subsided and pulmonary infiltrates abated, despite the patient having received treatment with a combination of drugs that were proven to be inactive in vitro against the isolate.

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Reprints or correspondence: Dr. Pablo Robles Ruiz, Div. of Infectious Diseases and Clinical Microbiology, Fundación Jiménez Díaz, Virgen de la Paz nº 2, 28027 Madrid (roblesruiz@yahoo.com).

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**Intradermal Regimens for Rabies Postexposure Prophylaxis: More Confusion**

Sirs—We applaud the efforts of Dr. Henry Wilde and colleagues in publicizing the crisis in the global supply of rabies immunoglobulin (RIG) [1]. This is an old and familiar problem that seems to be getting worse. In 1998, the World Health Organization (WHO) reported that only 1.6% of 7.5 million patients who were given postexposure vaccination against rabies also received RIG [2]. Because most postexposure treatments (PETS), by default, consist only of wound cleaning and vaccine administration, rapid induction of active immunity by vaccine is vital in the attempt to compensate for the lack of passive immunization in the early days after exposure to rabies. The cost and, therefore, the amount of modern cell culture vaccine must be kept to a minimum in order that the vaccine can be used in developing countries.

Two economical, multiple-site, intradermal methods used for rabies PETS are currently recommended by the WHO: a 8-site regimen and a 2-site regimen that use the same amounts of vaccine [3]. In their article, Dr. Wilde and colleagues stated that, for the 2-site regimen, the intradermal dose per site "consists of 0.1 mL of any potent tissue culture vaccine" [1, p. 478]. This is clear and simple advice,
but, unfortunately, it is incorrect because it does not address the differences in the volume of ampoules and, hence, the differences in the amount of rabies antigen per unit volume of the recommended rabies vaccines. For the 2-site regimen, the dose is 0.1 mL per site if the ampoule contains 0.5 mL of vaccine or 0.2 mL per site if the ampoule contains 1 mL of vaccine [3]. The WHO recommendation for these intradermal regimens is restricted to 4 commercial rabies vaccines.

On the basis of findings from an immunogenicity study from Thailand [4], use of a 2-site regimen that involved administration of a dose of 0.1 mL per site, of a vaccine for which the ampoule volume was 1 mL (one-half of the currently recommended volume) was proposed to a WHO working group in 2000; however, this regimen was not recommended for general use because no data were available on the efficacy of the regimen among patients who were bitten by animals proved to be rabid. WHO advice on PETs remained unchanged, but the WHO report of the meeting included a new phrase that indicated that the regimen could “be considered for use by national health authorities,” if they judged fit [5, p. 22]. This applied to one vaccine only: purified chick embryo cell vaccine (Rabipur/RabAvert; Chiron Behring) [5]. This half-dose regimen has since been used in Thailand in a PET study in which all the patients received the added protection of RIG; the results of this study, however, have yet to be published.

Semple and suckling mouse brain vaccines of nervous tissue origin (NTVs) are currently given to 1 million patients in Asia annually, principally in India, Vietnam, Bangladesh, and Pakistan [6]. The WHO is encouraging the replacement of NTVs by cell culture vaccines. Accumulated serological data suggest that even the half-dose intradermal regimen would be more immunogenic than the NTVs. Introduction of the half-dose intradermal regimen as a step toward the elimination of NTV use may be logical, and follow-up surveillance could eventually indicate the degree of protection that this regimen confers in the absence of RIG.

However, the concern expressed by Dr. Wilde and colleagues about diminishing supplies of RIG is based on the knowledge that the currently used PET vaccine regimens will not protect all patients against death. Halving the dose of the less immunogenic [7] of the 2 approved intradermal regimens will further narrow the margin of safety.

Dr. Wilde and colleagues have misrepresented the results of our study [8]. Among patients given the 8-site regimen, the true percentage of patients with seroconversion on day 7 of the regimen was 27% [8], not 7% (as stated in table 2 of the article of Wilde et al. [1, p. 479]). Compared with the 2-site regimen, the 8-site regimen induces higher levels of neutralizing antibody from day 7 of the regimen up to 1 year [7], and it is recommended by the WHO for use when no RIG is available [3].

Dr. Wilde and colleagues were wrong to cite the studies mentioned in references 20 and 24 in their article [1, p. 479] as studies of the 2-site and “double-dose” Thai Red Cross regimens. Neither regimen was tested in these referenced studies.

The dose and, therefore, the cost of their suggested “double-dose” Thai Red Cross vaccine regimen are ambiguous because the particular vaccine is not specified. The cost might be the same or double that used in the 8-site regimen. It is not appropriate to compare antibody levels in different studies in this way. Immune responses can only be compared between regimens randomized in the same trial.

In other articles published in Clinical Infectious Diseases in 2000, there was similar confusion about the intraderal dose of vaccines for economical postexposure rabies vaccine regimens [9, 10]. In 2001, Tantawichien et al. [11] incorrectly implied that a 4-site intradermal regimen was recommended by the WHO. When their article was abstracted elsewhere, this implied recommendation was stated as a fact [12]. It is unfortunate that such crucial information should prove so prone to misquotation. The evident complexity of the current treatments emphasizes a need for change. Research is underway to simplify and improve the 2 currently recommended economical PET regimens.

M. J. Warrell and D. A. Warrell
Centre for Tropical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom

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Reprints or correspondence: Mary J. Warrell, Centre for Tropical Medicine, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, United Kingdom (mary.warrell@ndm.ox.ac.uk).

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Reply

Sirs—We thank Drs. Mary and David Warrell [1] for noting the error in the percentage of patients with seroconversion presented in table 2 of our article [2]; the rate should have appeared as 27%, not 7%. On day 7 of the regimens, the levels of neutralizing antibodies (NAb) in all patient groups ranged from undetectable to 0.4 IU/mL (geometric mean titer [GMT], 0.04 IU/mL) [3]. This titer is 10 times lower than the lowest acceptable titer (0.5 IU/mL) recommended by the World Health Organization (WHO) [4, 5].

In our study (P.K., H.W., T epsumeshon S, Limusanno S, Tantawichien T, Wangroonsurb Y, unpublished data), we compared levels of NAb s in patients on days 0, 5, 7, and 14 of each of the 4 regimens followed. The regimens included the Essen regimen, the Thai Red Cross regimen (TRC-ID), the Oxford 8-site regimen, and the “double-dose” TRC-ID (for dosages, see [2]). On day 5 of the regimens, NAb levels were undetectable. On day 7 of the regimens, the GMT was only 0.13 IU/mL (range, 0.03–0.5 IU/mL) in the group receiving the 8-site intradermal regimen. We suggest that these NAb levels are unlikely to intercept the virus before it enters the peripheral nerves [6]. If rabies immunoglobulin (RIG) was unavailable, use of the 8-site regimen was recommended by the WHO, but they cited no scientific evidence to support this recommendation [4].

We had reservations when Briggs et al. [7] performed a study in which only 0.1 mL of vaccine was used per injection site, rather than the WHO-recommended dose of 0.2 mL of vaccine from 1.0 mL of reconstituted purified chick embryo vaccine [7]. TRC-ID was developed for the use of purified Vero cell vaccine that is reconstituted in 0.5 mL of saline. Both vaccines have approximately equivalent antigen contents (6–14 IU), amounts that are several times greater than the WHO-recommended level of 2.5 IU. Briggs et al. [7], nevertheless, demonstrated that their vaccine regimen had good immunogenicity. This led to early application of TRC-ID with 0.1 mL of purified chick embryo vaccine per intradermal dose. There were no treatment failures among 7227 patients treated in a province in which canine rabies was endemic [8]. Only 216 (3%) of these 7227 patients also received RIG.

Unlike the Warrells, we are not aware of any confusion about these issues in Thailand. This country used TRC-ID for 5 years before it became the first intradermal regimen approved by WHO (in 1992). Use of this regimen made abolishment of the use of neural rabies vaccines possible in 1992. We are convinced that RIGs will remain essential biological products. Further manipulation of vaccine administration schedules will not abolish the need to use these vaccines for optimal postexposure treatment, and we hope that an affordable immunoglobulin will soon reappear in the international marketplace.

Henry Wilde, Pakamatz Khawplod, Thiravat Hemachudha, and Visith Sitprija
Queen Saovabha Memorial Institute, Thai Red Cross Society, and Department of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand

References

Reprints or correspondence: Dr. Henry Wilde, Queen Saovabha Memorial Institute, Thai Red Cross Society, 7182 Rama IV Rd., 10330 Bangkok, Thailand (docwilde@toxininfo.co.th).

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Is There Hope for the Prevention of Future Antimicrobial Shortages?

Sirs—Shlaes and Moellering [1] recently described the impact of using a 10% delta for the lower limit of the 95% CI for clinical trials of noninferiority when a newly developed antibiotic is compared with a previously approved agent. The authors discussed the high number of patients required for statistically significant data in clinical trials that use a 10% delta, and they accurately described the impracticality of conducting a clinical trial using a 10% delta for an infection such as acute meningitis, for which >700 patients would be needed. Such a trial would require a large number of sites and would take several years to complete. Shlaes and Moellering [1] emphasized that the costs of conducting such a study and the potentially low financial return to the sponsor are