Author’s response to reviews

Title: Safety and efficacy of tetanus vaccine in anticoagulated patients: is intramuscular administration appropriate? A randomized clinical trial.

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Author’s response to reviews: see over
Despite its low incidence, tetanus is a major public health problem with a high fatality rate (40-50%). Tetanus is a disease that can be fully controlled, as it can be prevented by vaccination. However, it cannot be eradicated, because *Clostridium tetani* is a widely distributed microorganism in the environment. Immunization is highly effective [1], providing long-term protection and is recommended for the whole population in general, even though booster doses are required to maintain immunity, after the first vaccination Most cases of tetanus occur in previously unvaccinated adults, especially among those over 60 years of age.

Seroprevalence studies demonstrate that immunity from tetanus is higher than 95% in Spanish cohorts born after 1982 but studies of the elderly have reported seroprevalence of 7.7% in those over 70 years of age. Most anticoagulated patients in primary care consultations are seen due to auricular fibrillation and, on average, they are over 56 years of age [7,8]. Hence, vaccination coverage is probably low [9].

In anticoagulated patients, because of the hypothetical risk of bleeding after injection, use of the intramuscular route has been traditionally discouraged, with the subcutaneous route being recommended, even for vaccines that are routinely administered intramuscularly, as for tetanus [10-12]. In studies comparing the effectiveness of the two routes [14-15], vaccine efficacy studies have used the intramuscular route [1,10,14], and subcutaneous administration may be less effective compared to intramuscular administration. Moreover, for most vaccines, local adverse reactions are more frequent with subcutaneous administration than with the intramuscular route.

The safety of the intramuscular route for the hepatitis B [17] and influenza vaccines [18], which are also administered intramuscularly, has been demonstrated in patients with alterations in coagulation. But we have not found any study in the literature that assesses the safety and efficacy of intramuscular (IM) and subcutaneous (SC) administration for the Td vaccine in patients treated with oral anticoagulants.

As consequence, the objective of this study was to compare the safety and efficacy of the intramuscular and subcutaneous routes of administration for tetanus-diphtheria (Td) vaccine in patients treated with oral anticoagulants, and to verify the hypothesis that IM administration is safer and has greater efficacy.

This project respected ethical principles for medical research involving human subjects, as set out in the World Medical Association Declaration of Helsinki, together with the clinical research rules of the Spanish Research Act Regulations, and was granted permission by the Clinical Research Ethics Committee of Galicia (Spain) with approval obtained on 07/06/2009 with number 2007/089 (Nº EudraCT 2007-001073-29), which was subsequently modified and extended on 26/02/2009, 10/09/2009 and 13/10/2010 by successive expansion in the number of participating health centres (from the initial 6 to 15), to improve recruitment of patients.

The trial registration number is ISRCTN69942081, included as the last line of the abstract of the manuscript.

The enrolment has already begun. At the time of submission, the trial continues the participants’ recruitment.

The study has received a grant from a major government funding body from Galicia Health Department (Spain), No. PS07/114, in public competition involving peer review.

The authors declare that they have no competing interests. It is provided as a separate section of the manuscript, followed by the Acknowledgements.

All authors have read and agreed to its content. I warrant, on my behalf and my co-authors, that:
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COMMENTS TO FIRST EDITORIAL REVIEW

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The study has received ethics approval and a grant from a major funding body. A statement to this effect appears in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

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A declaration of competing interests is provided as a separate section of the manuscript, to follow the Acknowledgements.

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