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Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial.

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Abstract

BACKGROUND: Serological non-response can be present after **hepatitis B** vaccination in healthy adults. We aimed to establish which of three revaccination regimens is most effective at inducing protective immunity
METHODS: Healthy adults (aged 18-80 years) from 16 Dutch centres (13 public health services, two university hospitals, and one travel clinic) were included in this multicentre, parallel group, randomised, controlled, superiority trial. The inclusion criterion was **vaccine** non-response (**hepatitis B** surface antibody [anti-HBs] titre <10 IU/L) after a primary series with three doses of one type of recombinant **vaccine** against **hepatitis B** virus (either HBVaxPro-10 or Engerix-**B** at months 0, 1, and 6). Participants were individually randomly assigned (1:1:1:1) to a vaccination series of repeated initial vaccination (HBVaxPro 10 µg or Engerix-**B** 20 µg) as the control, or to Twinrix 20 µg, Fendrix 20 µg, or HBVaxPro 40 µg. We used a web-based randomisation programme, stratified by centre, with a block size of four. Participants and centres were unmasked to assignment after randomisation. Laboratory staff and investigators were masked to **vaccine**-group assignment. All revaccination schedules were identical, with intramuscular vaccinations at 0, 1, and 2 months. Anti-HBs was measured at 0, 1, 2, and 3 months. The primary outcome was the percentage of responders (anti-HBs titres ≥10 IU/L) at 3 months. Immunogenicity and safety analyses were based on an intention-to-vaccinate analysis, the immunogenicity analysis with last observation carried forward for missing data, and the Bonferroni and the Benjamini-Hochberg method were applied to correct for multiple testing. The trial was registered in the Dutch National Trial Register and inclusion has been stopped (identifier NL3011; EudraCT-number 2011-005627-40).

FINDINGS: The participants were recruited between Nov 1, 2012, and Sept 1, 2017. 480 participants were randomly assigned and included in intention-to-vaccinate analyses: 124 (26%) to control, 118 (25%) to Twinrix, 114 (24%) to HBVaxPro-40, and 124 (26%) to Fendrix. At month 3 the percentage of responders was 83 (67%) of 124 (95% CI 57·9-75·1 in the control group, 94 (80%) of the 118 (71·3-86·5) in the Twinrix group, 95 (83%) of 114 (75·2-89·7) in the HBVaxPro-40 group, and 108 (87%) of 124 (79·9-92·4) in the Fendrix group. Compared with the control group, the percentage of responders was superior for the HBVaxPro-40 group (adjusted difference 21·6% [95% CI

10·4-32·7], p=0·0204 [Bonferroni corrected p value]) and the Fendrix group (26·3% [15·4-37·3], p=0·0006), but not the Twinrix group (25·0% [13·0-37·0]; p=0·0846). One serious adverse event occurred (herpes zoster ophthalmicus) in the Fendrix group, which was not attributed to the **vaccine**.

INTERPRETATION: Revaccinating healthy non-responders with Fendrix or HBVaxPro-40 resulted in significantly higher proportions of responders and therefore indication for these vaccines should be expanded to enable revaccination of non-responders.

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