Five accelerated schedules for the TBE vaccine FSME- Immun® in last-minute travellers: an open-label, single-centre, randomized controlled trial.

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Funded by the Royal Higher Institute for Defense Brussels ("HFM 18-1: FASTBEPROTECT")

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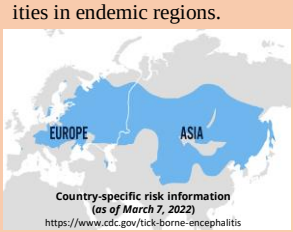
Introduction

Tick-borne encephalitis (TBE) is a viral disease, mainly transmitted by the bite of an infected tick (Ixodes sp.). It is endemic in Asia and Eastern Europe. Every year 10,000 to 15,000 new cases are reported with increasing numbers. The flavivirus can affect the central nervous system leading to meningitis and menigoencephalitis with potential death or long-term neurological sequelae. The lack of a standard effective treatment emphasizes the importance of disease prevention through vaccines. Since 2011, the World Health Organization recommends vaccination for travellers with outdoor activities in endemic regions.



Country-specific risk information (as of March 7, 2022)
https://www.cdc.gov/tick-borne-encephalitis

Methods

A single-centre, open-label trial with FSME-Immun® in TBE-naïve Belgian soldiers, randomized to five intramuscular (IM) or intradermal (ID) schedules:

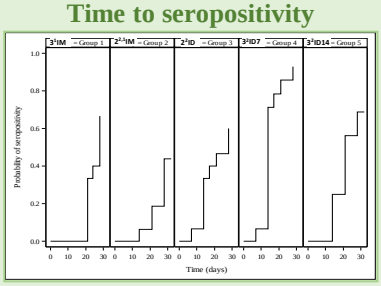
	Group	N	Dose	Screening	Day 0	Day 7	Day 14	Day 21	Day 28	Month 3	Month 6	Month 12	Month 12 + 21 d	Total volume
Blood sampling	All groups		10 mL / sample	✎		✎	✎	✎	✎	✎	✎	✎	✎	90 mL
Vaccination IM	1: 3^1IM	15	0,5 mL / injection		💉		💉					💉		1,5 mL
Vaccination IM	2: $2^{2\text{-}1}$IM	15	0,5 mL / injection		💉💉							💉		1,5 mL
Vaccination ID	3: 2^1ID	15	0,1 mL / injection		💉							💉		0,4 mL
Vaccination ID	4: 3^1ID7	15	0,1 mL / injection		💉	💉						💉		0,6 mL
Vaccination ID	5: 3^1ID14	15	0,1 mL / injection		💉		💉					💉		0,6 mL

Primary objective: Time-to-seropositivity of the different schedules based on reactogenicity data up to 28 days after the first dose.
Secondary objective: Proportion of patients with seropositivity at every visit.

Serology
TBE virus neutralizing antibodies were measured in a plaque reduction neutralization test (PRNT) at ITM. A PRNT90 titre of ≥ 10 was defined as seropositivity.

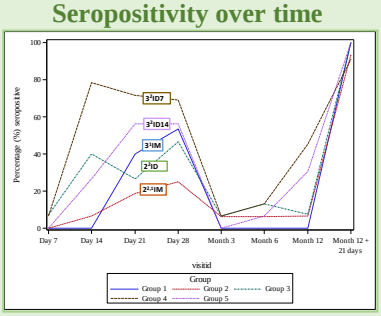
Results

Time to seropositivity

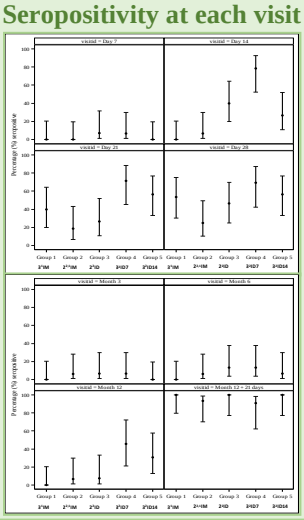


Time-to-seropositivity was shorter in ID than IM groups. Seropositivity was observed at day 7 in group 3 + 4. Group 4 peaked highest and earliest at day 14 (74.7%, 95% CI 49.4-89.9). No group showed sufficient protection at day 28.

Seropositivity over time



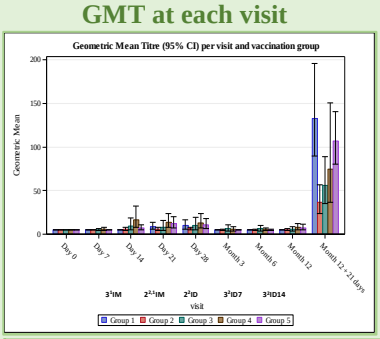
Seropositivity at each visit



All but two were seropositive after the booster dose. Both non-responders (group 2, f, 33 yrs; group 4, m, 33 yrs) developed no antibodies but had a pre-existing yellow fever (YF) vaccination.

Safety The aluminium-adjuvanted vaccine was well tolerated. However, mild to moderate local reactions were reported in 72-100.0% ID vs. 0 - 37.5% IM. No serious adverse events occurred.

GMT at each visit



Intention-to-treat data
Screened: 96, enrolled: 77, booster: 67, LTFU: 10, median age: 19-20 yrs per group, range: 18-49 yrs, male: 83%, female: 17%.

Geometric mean titres (GMT) after the booster positively correlated with the number of vaccination visits. Regimens with priming day 0 and 14 showed best results.

Yellow fever vaccination: geometric mean ab titres, ratio, and percentages

	Geometric mean (95% CI)		Ratio geometric means (95% CI and p-value)		n seropositive % seropositive (95% Wilson CI)	
visit	No yellow fever vaccination	Yellow fever vaccination	Ratio (95% CI)	p-value	No yellow fever vaccination	Yellow fever vaccination
Day 0	5.00 (5.00- 5.00)	5.00 (5.00- 5.00)	1.00 (1.00- 1.00)	.	0/65 0.0 (0.0 - 5.6)	0/12 0.0 (0.0 - 24.2)
Day 7	5.29 (4.87- 5.74)	5.00 (5.00- 5.00)	1.06 (0.97- 1.15)	0.1797	2/64 3.1 (0.9 - 10.7)	0/12 0.0 (0.0 - 24.2)
Day 14	8.43 (6.61- 10.7)	5.85 (4.13- 8.29)	1.44 (0.96- 2.17)	0.0774	21/63 33.3 (22.9 - 45.6)	1/11 9.1 (1.6 - 37.7)
Day 21	10.4 (8.22- 13.2)	5.41 (4.53- 6.46)	1.92 (1.44- 2.55)	**<.0001**	31/65 47.7 (36.0 - 59.6)	1/11 9.1 (1.6 - 37.7)
Day 28	10.9 (8.62- 13.8)	5.41 (4.53- 6.46)	2.02 (1.52- 2.68)	**<.0001**	36/64 56.3 (44.1 - 67.7)	1/11 9.1 (1.6 - 37.7)
Month 3	5.57 (4.85- 6.38)	5.00 (5.00- 5.00)	1.11 (0.97- 1.28)	0.1224	3/65 4.6 (1.6 - 12.7)	0/12 0.0 (0.0 - 24.2)
Month 6	5.64 (5.03- 6.33)	5.00 (5.00- 5.00)	1.13 (1.01- 1.27)	**0.0404**	6/65 9.2 (4.3 - 18.7)	0/11 0.0 (0.0 - 25.9)
Month 12	6.50 (5.56- 7.61)	5.00 (5.00- 5.00)	1.30 (1.11- 1.52)	**0.0015**	11/55 20.0 (11.6 - 32.4)	0/12 0.0 (0.0 - 24.2)
Month 12 + 21 days	82.2 (66.2- 102)	43.7 (22.2- 85.9)	1.88 (1.09- 3.23)	**0.0229**	55/55 100.0 (93.5-100.0)	10/12 83.3 (55.2-95.3)

Exploratory analysis: YF-vaccinated individuals showed at each visit lower GMTs of neutralizing antibodies than yellow fever-naïve vaccinees.

Conclusion

- No sufficient (>90%) protection with any accelerated schedule before the booster was seen.
- Pre-existing YF vaccination might impair TBE immunization outcome.
- Faster and better antibody production but more local reactions after ID than IM vaccination were noticed.
- GMT levels positively correlated with the number of vaccination visits after the booster; priming schedules with day 0 and 14 showed best results.