# SAFETY AND IMMUNOGENICITY OF TYPHOID FEVER AND YELLOW FEVER VACCINES WHEN ADMINISTERED CONCOMITANTLY WITH QUADRIVALENT MENINGOCOCCAL ACWY GLYCOCONJUGATE VACCINE IN HEALTHY ADULTS

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## BACKGROUND & OBJECTIVES

- It is often desirable to complete pre-travel immunization in a single visit and simultaneous administration of vaccines is recommended.[1] Providing vaccines concomitantly will simplify the process of acquiring pre-travel prophylaxis and may help ensure that all required vaccines are administered.
- However, concomitant vaccination could potentially compromise immunogenicity and/or safety of the individual vaccines and, therefore, possible vaccine interaction should be carefully assessed.
- This phase 3b randomized, open-label study assessed the immunogenicity and safety of travel vaccines including vaccines for typhoid fever (TF) and yellow fever (YF) when administered with or without a quadrivalent meningococcal glycoconjugate vaccine (MenACWY-CRM) (NCT01466387). Results of concomitant administration of MenACWY-CRM with Japanese encephalitis and rabies vaccination are reported separately.

## METHODS

- In this study, overall 552 healthy adults aged 18 through 60 years were enrolled, of which 301 subjects were randomized to 1 of 3 vaccine regimens presented here.
  All vaccines were administered on day 1.
  - TF + YF + MenACWY-CRM (n=100)
  - TF + YF (n=101)
  - MenACWY-CRM (n=100).
- Immunogenicity at baseline and 4 weeks (day 29) following vaccination was assessed by serum bactericidal assay using human complement (hSBA), enzyme-linked immunosorbent assay (ELISA) or neutralization test.
  - The primary immunogenicity objective was to demonstrate non-inferiority of the immune responses to TF + YF + MenACWY-CRM regimen as compared to TF + YF alone, as measured by geometric mean titers/concentrations (GMTs/GMCs) to TF and YF at day 29 post-vaccination.
  - Secondary immunogenicity objectives were to evaluate the seroprotection rates elicited by YF vaccine at day 29 post-vaccination and to assess the immune responses to MenACWY-CRM vaccine given concomitantly with TF and YF vaccines versus given alone.
- Adverse events (AEs), serious AEs (SAEs) and AEs leading to study withdrawal were recorded throughout the study period.

## RESULTS

- The three vaccine groups were comparable with respect to age, weight and height. Subjects were predominantly Caucasian and 50% to 56% across groups were males (**Table 1**).
- Of all subjects, 99% to 100% across groups completed the study protocol. Reasons for premature withdrawal were loss to follow-up (n=1) and protocol deviation (n=1).

**Table 1:** Baseline demographics and characteristics

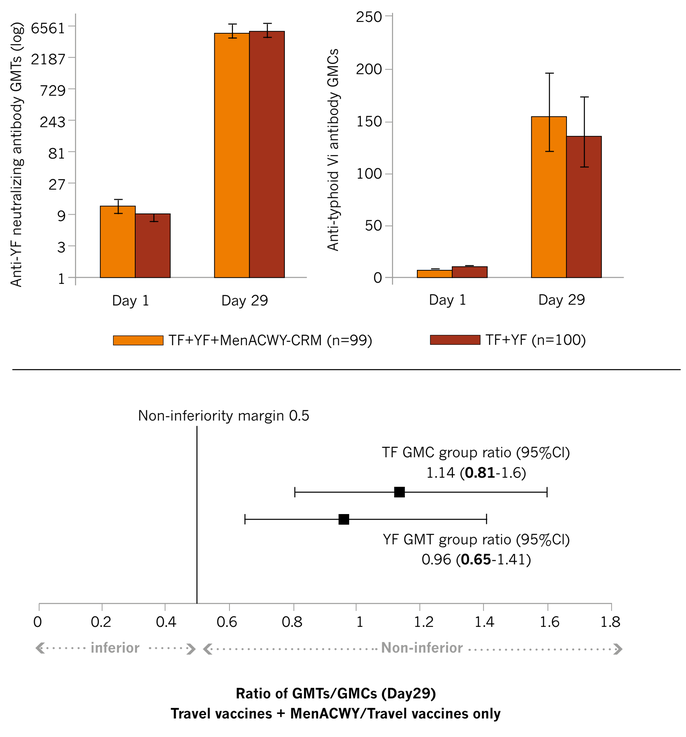
| | TF+YF+MenACWY-CRM n=100 | TF+YF n=101 | MenACWY-CRM n=100 |
|---|---|---|---|
| **Age**, years (Mean±SD) | 35.0±11.0 | 36.5±10.8 | 36.9±11.2 |
| **Male**, n (%) | 56 (56%) | 52 (51%) | 50 (50%) |
| **Female**, n (%) | 44 (44%) | 49 (49%) | 50 (50%) |
| **Ethnicity**, n (%) | | | |
| Asian, n (%) | 1 (1%) | 1 (<1%) | 0 |
| Black or African American, n (%) | 3 (3%) | 0 | 0 |
| Caucasian, n (%) | 96 (96%) | 99 (98%) | 99 (99%) |
| Other, n (%) | 0 | 1 (<1%) | 1 (1) |
| **Weight, kg** (Mean±SD) | 77.7±18.1 | 77.8±15.7 | 76.1±15.9 |
| **Height, cm** (Mean±SD) | 175.2±9.5 | 173.6±10.2 | 173.8±9.7 |
| **Met entry criteria**, n (%) | 100 (100%) | 100 (99%) | 100 (100%) |

SD, standard deviation.

### *IMMUNOGENICITY*

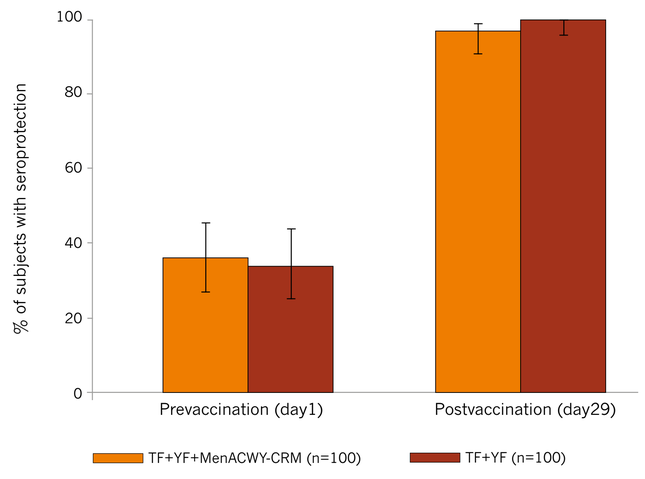
- Pre-specified criteria for non-inferiority of post-vaccination GMCs and GMTs were met for TF and YF vaccines, respectively, when given concomitantly with MenACWY-CRM vaccine versus when given alone. At day 29 post-vaccination, the lower limits of the 95% confidence interval for GMT/GMC group ratios were above the non-inferiority margin of 0.5: TF GMC group ratio: 1.14 (95% CI: **0.81**-1.6), YF GMT group ratio: 0.96 (95% CI **0.65**-1.41) (**Figure 1**).
- Post-vaccination TF GMCs were 153 (TF + YF + MenACWY-CRM) and 134 (TF + YF). YF GMTs following vaccination were 5022 (TF + YF + MenACWY-CRM) and 5244 (TF + YF) (**Figure 1**).
- The percentages of subjects with seroprotective anti-YF neutralizing antibody titers ≥1/10 at day 29 post-vaccination were 97% when TF and YF vaccines were administered with MenACWY-CRM and 100% when these vaccines were administered without MenACWY-CRM vaccine (**Figure 2**).
- Percentages of subjects achieving post-vaccination hSBA titers ≥8 for meningococcal serogroups A, C, W-135 and Y were 77%, 76%, 97%, and 91% (TF + YF + MenACWY-CRM) and 76%, 77%, 95%, and 89% (MenACWY-CRM group), respectively (**Figure 3A**).
- Post-vaccination GMTs against serogroups A, C, W-135 and Y were generally in the same range when MenACWY-CRM vaccine was given alone or co-administered with TF and YF vaccines (**Figure 3B**).

**Figure 1.** GMTs against YF, GMC against TF (days 1 and 29) and day 29 post-vaccination ratio of GMCs/GMTs (95% CI) for TF and YF travel vaccines given simultaneously with MenACWY-CRM vaccine versus given alone. Criteria for non-inferiority: lower limit of 95% confidence interval should be >0.5



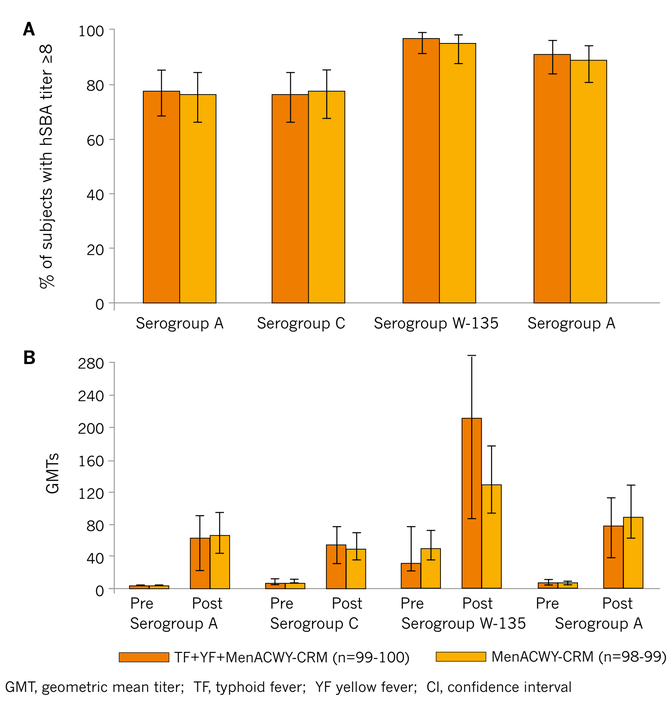

GMT, geometric mean titer, GMC, geometric mean concentration; TF, typhoid fever; YF, yellow fever; CI, confidence interval

**Figure 2.** Percentage of subjects (95% CI) achieving anti-yellow fever neutralizing antibody titers ≥1/10 at baseline and day 29 post-vaccination, by vaccine regimen




TF, typhoid fever; YF yellow fever; CI, confidence interval

**Figure 3.** Percentages of subjects with hSBA titers ≥8 at day 29 post-vaccination (A) and GMTs at baseline and day 29 post-vaccination (B) (95% CI) against meningococcal serogroups A, C, W-135 and Y, by vaccine regimen




GMT, geometric mean titer; TF, typhoid fever; YF yellow fever; CI, confidence interval

### *SAFETY*

- The percentage of subjects reporting AEs was the same for TF and YF vaccines with or without MenACWY-CRM vaccine.
- Any AEs were observed in 41% of subjects in groups TF + YF + MenACWY-CRM and TF + YF; 30% to 34% of these events were considered at least possibly related to study vaccination. In the MenACWY group, 14% of subjects reported any AE, of which 8% were considered at least possibly related (**Table 2**).
- By preferred term, the most common at least possibly related AEs in TF + YF + MenACWY-CRM and TF + YF groups were injection site pain (8% and 12%) and headache (10% and 7%), respectively. In MenACWY-CRM, the most common possibly related AEs were headache (4%) and injection site pain (2%).
- Most of the AEs were of mild to moderate severity, with only 2 to 3 subjects across groups reporting AEs of severe intensity.
- There were no SAEs, premature study withdrawals or deaths in any of the vaccination regimens (**Table 2**).

**Table 2:** Number and percentage of subjects with spontaneous adverse events (AEs)

| n (%) | TF + YF + MenACWY-CRM n=100 | TF + YF n=101 | MenACWY-CRM n=100 |
|---|---|---|---|
| **Any AEs** | 41 (41%) | 41 (41%) | 14 (14%) |
| **At least possibly related AEs** | 34 (34%) | 30 (30%) | 8 (8%) |
| **SAEs** | 0 | 0 | 0 |
| **At least possibly related SAEs** | 0 | 0 | 0 |
| **Any AE leading to premature withdrawal** | 0 | 0 | 0 |
| **Deaths** | 0 | 0 | 0 |

TF, typhoid fever; YF, yellow fever; AE, adverse event; SAE, serious adverse event.

## CONCLUSION

- MenACWY-CRM can be administered concomitantly with typhoid Vi polysaccharide vaccine and live attenuated yellow fever vaccine without compromising antibody responses or safety to these individual vaccines and can be incorporated into existing pre-travel vaccination programmes.

## REFERENCE

[1] General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and mortality weekly report Recommendations and reports (MWRR) / Centers for Disease Control 2011; 60(2): 1-64

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