

# Effects of Prior Polysaccharide Vaccination on Magnitude, Duration, and Quality of Immune Responses to and Safety Profile of a Meningococcal Serogroup C Tetanus Toxoid Conjugate Vaccination in Adults

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**Extensive use of meningococcal AC polysaccharide (MACP) vaccines has raised concerns about induction of immunologic hyporesponsiveness to C polysaccharide. We investigated the immunogenicity and safety of a meningococcal C-tetanus conjugate (MCC-TT) vaccine in naïve adults and prior MACP vaccinees. Laboratory staff ( $n = 113$ ) were recruited; 73 were naïve to meningococcal vaccination, and 40 had previously received  $\geq 1$  dose of MACP vaccine. Blood was taken prior to MCC-TT vaccination and 1 week, 1 month, and 6 months later. At each time point, proportions of subjects with serum bactericidal antibody (SBA) titers of  $\geq 8$  or  $\geq 128$  were similar ( $P > 0.46$ );  $>94\%$  of subjects achieved titers of  $\geq 128$  at 1 month. However, the geometric mean titer (GMT) of SBA at 1 month was higher in the naïve (1,757; 95% confidence interval [95% CI], 1,102 to 2,803) than in the previously vaccinated (662; 95% CI, 363 to 1,207) group ( $P = 0.02$ ), and similarly at 6 months ( $P < 0.001$ ). Conversely, geometric mean concentrations (GMCs) of serogroup C-specific immunoglobulin G (IgG) were significantly higher in the previously vaccinated group pre-MCC-TT and at 1 week; the groups were similar at 1 month, and there was some evidence that the GMC for the previously vaccinated group was higher at 6 months. Qualitative differences in antibodies between groups were demonstrated by using the SBA/IgG ratio, though avidity measures were similar for the two groups throughout the study. MCC-TT was well tolerated, with similar safety profiles in the two groups. Pain in the arm and headache were the most frequently reported events following vaccination. The study shows that MCC-TT is safe and immunogenic in naïve and previously MACP-vaccinated adults, though the magnitude and persistence of postvaccination SBA responses in the latter group were lower.**

Meningococcal serogroup C (MenC) disease is an important cause of morbidity and mortality worldwide. Until recently the only vaccines available against MenC were plain polysaccharide vaccines, which provide some protection but have two major disadvantages. First, they do not protect those aged  $\leq 2$  years, for whom the burden of disease is high (2, 24). Second, protection in older children and adults is short-lived, with no induction of immune memory (17).

Conjugation of meningococcal polysaccharide to immunogenic protein carriers has resulted in conjugate vaccines that induce T cell-dependent responses with higher antibody titers and increased antibody avidity as evidence of priming for immunologic memory, leading to better protection and longer-lasting immunity even in infants (8, 18, 21). In 1999, the United Kingdom became the first country to introduce MenC conjugate (MCC) vaccines formulated using mutant diphtheria toxin (MCC-CRM<sub>197</sub>) or tetanus toxoid (MCC-TT) protein compo-

nents, and these vaccines have been extensively used for infants, children, and young adults (16).

Reduced responses to repeated doses of MenC polysaccharide vaccine have been reported (12, 20), and the ability of an MCC-CRM<sub>197</sub> vaccine to induce immunologic responses adequate to confer protection has been demonstrated (4, 5). This study is the first to examine the effect of prior vaccination with plain serogroup C polysaccharide on acute responses to MCC-TT and on antibody persistence at 6 months postvaccination.

## MATERIALS AND METHODS

**Study design.** This was a single-group (divided upon analysis by vaccination history—naïve or previously vaccinated), open-label phase IV study. Subjects were National Health Service staff and were recruited pragmatically, with the sample size therefore defined by participant availability. A total sample size of at least 100 was sought. It was anticipated that the naïve group would be larger than the previously vaccinated group. The study power was determined on an absolute minimum of 20 subjects in each group, which would enable only large differences (about sixfold) in postvaccination serum bactericidal antibody (SBA) geometric mean titers (GMTs) to be detected with 80% power at a 5% significance level.

Prior to enrollment, eligibility was assessed against inclusion and exclusion criteria. The inclusion criteria were informed written consent and an age of  $\geq 18$  years. The exclusion criteria were known hypersensitivity to vaccine components,

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TABLE 1. GMCs and GMTs of MenC antibody, and proportions of naïve versus previously MACP vaccinated recipients of MCC-TT achieving titers above set cutoffs

| Measure                        | Naïve                      | Previously vaccinated  | <i>P</i> value <sup>a</sup> |
|--------------------------------|----------------------------|------------------------|-----------------------------|
| No. recruited <sup>b</sup>     | 73                         | 40                     |                             |
| SBA GMT (95% CI)               |                            |                        |                             |
| Prevaccination                 | 4.6 (2.9, 7.3)             | 48.2 (19.3, 120.3)     | <0.001                      |
| 1 wk postvaccination           | 160.7 (80.1, 322.1)        | 84.9 (30.6, 235.6)     | 0.32                        |
| 1 mo postvaccination           | 1,757.6 (1,102.1, 2,803.0) | 662.3 (363.2, 1,207.0) | 0.02                        |
| 6 mo postvaccination           | 1,625.5 (1,108.5, 2,383.7) | 349.3 (164.6, 741.4)   | <0.001                      |
| No. (%) with SBA of $\geq 8$   |                            |                        |                             |
| Prevaccination                 | 13 (19.4)                  | 24 (61.5)              | <0.001                      |
| 1 wk postvaccination           | 47 (77.0)                  | 22 (81.5)              | 0.64                        |
| 1 mo postvaccination           | 65 (95.6)                  | 34 (97.1)              | 0.70                        |
| 6 mo postvaccination           | 66 (100)                   | 27 (93.1)              | 0.82                        |
| No. (%) with SBA of $\geq 128$ |                            |                        |                             |
| Prevaccination                 | 6 (9.0)                    | 20 (51.3)              | <0.001                      |
| 1 wk postvaccination           | 42 (68.9)                  | 14 (51.9)              | 0.46                        |
| 1 mo postvaccination           | 65 (95.6)                  | 33 (94.3)              | 0.96                        |
| 6 mo postvaccination           | 65 (98.5)                  | 25 (86.2)              | 0.68                        |
| ELISA GMC (95% CI)             |                            |                        |                             |
| Prevaccination                 | 1.00 (0.6, 1.5)            | 13.0 (7.4, 22.9)       | <0.001                      |
| 1 wk postvaccination           | 6.1 (4.1, 9.1)             | 16.9 (9.2, 31.1)       | 0.01                        |
| 1 mo postvaccination           | 39.2 (25.8, 59.5)          | 44.5 (28.3, 69.9)      | 0.71                        |
| 6 mo postvaccination           | 12.1 (8.8, 16.6)           | 21.3 (13.8, 33.0)      | 0.05                        |
| No. of samples                 |                            |                        |                             |
| Prevaccination                 | 67                         | 39                     |                             |
| 1 wk postvaccination           | 61                         | 27                     |                             |
| 1 mo postvaccination           | 68                         | 35                     |                             |
| 6 mo postvaccination           | 66                         | 29                     |                             |

<sup>a</sup> For comparison of SBA GMTs or ELISA GMCs between groups.

<sup>b</sup> Differences between number recruited and number with prevaccination blood samples were due to failed venipuncture, not to withdrawal from the study.

known pregnancy, previous receipt of an MCC vaccine, history of meningococcal infection, any vaccination in the previous month, or receipt of any immunoglobulin or blood product in the past 3 months, or any immunodeficiency. Vaccination was deferred for acute illness or an aural temperature of  $>38^{\circ}\text{C}$ .

**Treatment schedule.** A single dose, 0.5 ml, of MCC-TT (Baxter Bioscience, Vienna, Austria) was administered intramuscularly in the deltoid muscle of the nondominant arm. All doses were from one batch and contained 10  $\mu\text{g}$  of de-O-acetylated purified serogroup C meningococcal polysaccharide conjugated with 10 to 20  $\mu\text{g}$  of tetanus toxoid protein, adsorbed to 0.5 mg of aluminum hydroxide per dose. Blood samples were taken prior to vaccination and 1 week, 1 month, and 6 months later.

To fulfill a duty of care, an extra dose of MCC-TT was offered if the 1-month postvaccination blood sample had an SBA titer of  $<8$  (considered to indicate susceptibility to disease with respect to the proposed correlate of protection) (3, 6). These subjects were excluded from the 6-month analysis.

**Data collection.** Subjects completed a health diary to record oral temperature, local reactions, and/or systemic symptoms daily for the week following vaccination. Serious adverse events were monitored by use of standard adverse event questionnaires completed by study personnel at each postvaccination visit.

**Serological assessments.** Sera were analyzed by standardized SBA assays as previously described (15). The SBA target strain was MENC11 (C:16:P1.7-1.1), and the complement source was baby rabbit sera (Pel-Freez Biologicals, Rogers, Ark.) SBA titers were expressed as reciprocals of the final serum dilution giving  $\geq 50\%$  killing at 60 min. For computational purposes, titers less than 4 were assigned a value of 2.

Serogroup C-specific immunoglobulin class G (IgG) antibodies were quantified by using a standardized enzyme-linked immunosorbent assay (ELISA) (9). Results were expressed in micrograms per milliliter, and the lower limit of detection was 0.06  $\mu\text{g}/\text{ml}$ .

Antibody avidity was measured by an elution ELISA using the chaotropic thiocyanate as described previously (10), modified for a meningococcal IgG assay (19). Avidity indices could be measured only for samples with serogroup C-specific IgG levels of  $\geq 0.6 \mu\text{g}/\text{ml}$  as measured by a standard ELISA (9). The lower limit of quantitation was an avidity index of 62.

**Data analysis.** Geometric mean fold rises between time points and the geometric mean concentrations (GMCs), GMTs, and geometric mean avidity indices (GMAIs) of meningococcal antibodies, all with 95% confidence intervals (95%

CI) were calculated using log-transformed data and compared between groups by using *t* tests and regression. Changes between time points were compared by using paired *t* tests. For each serum sample, the SBA/IgG concentration ratio was determined (23), and the averages for the naïve and previously vaccinated groups were calculated by using log-transformed ratios. The proportions achieving defined SBA titers were compared between groups by using chi-square tests. The proportions of vaccinees reporting symptoms were compared between groups by using chi-square tests, as well as Fisher's exact test where appropriate. To test whether preexisting antibodies had an effect on local reactions experienced post-MCC-TT, the log-transformed SBA titer from the prevaccination samples was regressed against various measures of local reactions.

## RESULTS

In total, 113 subjects were recruited. The mean age at vaccination for the 73 naïve recruits was 36 years (range, 22 to 64 years), compared to 34 years (range, 23 to 50 years) for the 40 previously vaccinated subjects, for whom the mean interval since polysaccharide vaccination was 4.7 years (range, 0.1 to 15.8 years). The female-to-male ratio was 60 to 13 (ratio, 4.6) for naïve recruits, compared with 27:13 (ratio, 2.1) for previous vaccinees. This difference was taken into account in the multivariable regression analyses. In practice the sample size obtained was larger than expected, allowing for smaller differences than anticipated (threefold differences) to be detectable. With the eventual sample size, differences such as 75% in one group and 95% in another could be detected in the proportion above various cutoffs.

**Compliance with study procedures.** A proportion of subjects did not provide samples (Table 1). The proportions submitting diaries, 91.8% of naïve recruits and 82.5% of previous vaccinees, were similar for the two groups ( $P = 0.71$ ).

TABLE 2. SBA/ELISA ratios and GMAIs for MenC antibody for naïve versus previously MACP vaccinated recipients of MCC-TT

| Measurement                               | Naïve                   | Previously vaccinated  | <i>P</i> value <sup>a</sup> |
|---|-------------------------|------------------------|-----------------------------|
| SBA/ELISA ratio (95% CI)                  |                         |                        |                             |
| Prevaccination                            | 4.7 (3.3, 6.7)          | 3.7 (1.8, 7.5)         | 0.52                        |
| 1 wk postvaccination                      | 26.3 (13.9, 49.7)       | 5.3 (2.0, 13.9)        | 0.009                       |
| 1 mo postvaccination                      | 44.8 (29.5, 68.0)       | 14.9 (9.0, 24.6)       | 0.002                       |
| 6 mo postvaccination                      | 135.1 (95.4, 191.2)     | 16.4 (9.7, 27.6)       | <0.001                      |
| GMAI (95% CI); no. with evaluable avidity |                         |                        |                             |
| Prevaccination                            | 110.9 (96.4, 127.6); 32 | 94.0 (79.3, 111.3); 36 |                             |
| 1 wk postvaccination                      | 93.0 (79.4, 108.9); 48  | 84.2 (67.2, 105.5); 29 |                             |
| 1 mo postvaccination                      | 86.8 (75.2, 100.2); 60  | 86.1 (70.8, 104.6); 39 |                             |
| 6 mo postvaccination                      | 95.1 (84.7, 106.7); 59  | 85.3 (69.9, 104.2); 35 |                             |

<sup>a</sup> For comparison between groups.

**Serology.** The GMTs of SBA and the GMCs of serogroup C-specific IgG before vaccination were significantly higher for the previously vaccinated group than for the naïve group (Table 1). SBA GMTs for the two groups were similar 1 week postvaccination, though the IgG GMC was higher in the previously vaccinated group. At 1 and 6 months postvaccination, SBA GMTs for the naïve group were higher than those for the previously vaccinated group, whereas IgG GMCs were similar at 1 month, but there was some evidence of a higher GMC for the previously vaccinated group at 6 months. Univariable analysis showed that age and sex were not associated with differences in any serologic measure when the groups were compared at any time point, so these parameters are not reported further. Significant increases in antibody levels over time were noted for both groups in comparisons of the prevaccination and 1-week samples and of the 1-week and 1-month samples ( $P < 0.001$  in all cases). For both the naïve and previously vaccinated groups, there was no significant decline in SBA GMTs between 1 and 6 months ( $P = 0.80$  and  $P = 0.19$ , respectively), though there was a decline in specific IgG GMCs ( $P < 0.001$  and  $P = 0.03$ , respectively). The proportion of subjects attaining SBA titers of  $\geq 8$ , the putative correlate of protection (3, 6), or  $\geq 128$  was calculated at each time point (Table 1). For proportions with SBA titers of  $\geq 8$ , significant differences between the groups were seen only prior to vaccination; however, the study was powered to detect only large differences between such proportions.

The two study groups showed different patterns in their SBA/IgG ratios over time, with a continued increase for the naïve group but little change for the previously vaccinated group (Table 2). The groups had similar SBA/IgG ratios before vaccination, but significant differences were noted between them at each postvaccination sampling ( $P \leq 0.009$  in all cases).

In the prevaccination serum samples, the majority of naïve subjects did not have sufficient IgG to allow assessment of avidity whereas the majority of those previously vaccinated did, consistent with the persistence of antibody from meningococcal AC polysaccharide (MACP) vaccination. By 1 month postvaccination, all samples had sufficient IgG levels for measurement of avidity indices. The GMAIs for the two groups did not differ significantly at any time (Table 2). The naïve group was split into subsets of those who did and those who did not have measurable antibody avidity prior to vaccination. Responses were assessed over time to determine whether these subsets behaved differently with regard to the eventual avidity indices.

The GMAIs of the subsets were similar at 1 week (97.6 versus 90.1 [ $P = 0.64$ ]), 1 month (86.0 versus 88.4 [ $P = 0.88$ ]), and 6 months (98.5 versus 97.7 [ $P = 0.95$ ]) postvaccination.

Four subjects were offered an extra dose of MCC-TT following detection of an SBA titer of  $< 8$  in the 1-month-postvaccination sample. Three, from the naïve group, consented to revaccination and blood sampling a month later, from which it was established that all had mounted protective antibody titers (SBA titers of 256, 2,048, and 4,096, respectively). The fourth, a previous vaccinee, declined the extra dose.

**Reactogenicity.** The primary source of safety data was the subject-completed diary (Table 3). The majority of subjects in both groups did not report any redness or swelling at the injection site, but a third did note some pain. The proportions of subjects reporting redness, swelling, and pain, and the duration and maximum size of these measures, were similar for the naïve and previously vaccinated groups. The SBA titers prior to vaccination did not affect the maximum measures of redness ( $P = 0.30$ ) or swelling ( $P = 0.12$ ), the proportions of subjects reporting redness of  $> 0.5$  cm ( $P = 0.94$ ) or  $> 2.5$  cm ( $P = 0.10$ ) or swelling of  $> 0.5$  cm ( $P = 0.17$ ) or  $> 2.5$  cm ( $P = 0.17$ ), the number of days of pain ( $P = 0.24$ ), or the pro-

TABLE 3. Comparison of the frequencies of local reactions and oral temperatures reported at any time in diaries completed for the week after vaccination by naïve and previously MACP vaccinated recipients of MCC-TT<sup>a</sup>

| Reaction and measure                  | Naïve      | Previously vaccinated | <i>P</i> value <sup>b</sup> |
|---------------------------------------|------------|-----------------------|-----------------------------|
| Redness at injection site             |            |                       |                             |
| No. (%) with no redness               | 48 (72)    | 26 (79)               | 0.45                        |
| No. (%) with $\geq 3$ cm              | 3 (5)      | 1 (3)                 | 1.00                        |
| No. (%) with $\geq 10$ cm             | 0 (0)      | 0 (0)                 |                             |
| Swelling at injection site            |            |                       |                             |
| No. (%) with no swelling              | 55 (82)    | 27 (82)               | 0.97                        |
| No. (%) with $\geq 3$ cm at any time  | 4 (6)      | 4 (12)                | 0.43                        |
| No. (%) with $\geq 10$ cm at any time | 1 (2)      | 0 (0)                 |                             |
| Pain in arm or at injection site      |            |                       |                             |
| No. (%) reporting no pain             | 21 (31.3)  | 9 (27)                | 0.68                        |
| No. (%) with $\geq 3$ days of pain    | 18 (27)    | 14 (42)               | 0.12                        |
| No. (%) with $\geq 5$ days of pain    | 5 (7.5)    | 6 (18.2)              | 0.17                        |
| Mean duration (days) of pain (range)  | 2.52 (1–7) | 2.30 (1–7)            | 0.15                        |
| Oral temp                             |            |                       |                             |
| No. (%) with $> 37.5^\circ\text{C}$   | 1 (2)      | 1 (2)                 | 1.00                        |
| Duration (days)                       | 1          | 1                     |                             |

<sup>a</sup> The denominators for percentages were the numbers of diaries returned: 67 for naïve and 33 for previously vaccinated subjects.

<sup>b</sup> For comparison between groups.

TABLE 4. Comparison of the frequencies of systemic symptoms reported in diaries completed for the week after vaccination by naïve and previously MACP vaccinated recipients of MCC-TT<sup>a</sup>

| Symptom and measure              | Naïve     | Previously vaccinated | <i>P</i> value <sup>b</sup> |
|----------------------------------|-----------|-----------------------|-----------------------------|
| <b>Headache</b>                  |           |                       |                             |
| No. (%) of subjects reporting    | 9 (13.4)  | 5 (15.2)              | 1.00                        |
| Median day of onset              | 1         | 2                     |                             |
| Mean duration, days (range)      | 1 (1–2)   | 1 (1)                 |                             |
| <b>Nausea and/or vomiting</b>    |           |                       |                             |
| No. (%) of subjects reporting    | 2 (3.0)   | 0 (0)                 | 1.00                        |
| Median day of onset              | 2         |                       |                             |
| Mean duration, days (range)      | 1.5 (1–3) |                       |                             |
| <b>Fatigue and/or malaise</b>    |           |                       |                             |
| No. (%) of subjects reporting    | 4 (6.0)   | 2 (6.1)               | 1.00                        |
| Median day of onset              | 1         | 2                     |                             |
| Mean duration, days (range)      | 1 (1–2)   | 1 (1)                 |                             |
| <b>URTI<sup>c</sup> symptoms</b> |           |                       |                             |
| No. (%) of subjects reporting    | 9 (13.4)  | 8 (24.2)              | 0.18                        |
| Median day of onset              | 4         | 2.5                   |                             |
| Mean duration, days (range)      | 2 (1–3)   | 1 (1–2)               |                             |

<sup>a</sup> The denominators for percentages were the numbers of diaries returned: 67 for naïve and 33 for previously vaccinated subjects.

<sup>b</sup> For comparison of proportions reporting symptoms between groups.

<sup>c</sup> URTI, upper respiratory tract infection.

portions of subjects reporting pain lasting >3 days ( $P = 0.22$ ) or >5 days ( $P = 0.22$ ).

Systemic symptoms were reported by a minority of subjects (Table 4) but were too few to allow robust regression analyses. The symptoms included headache, nausea and/or vomiting, fatigue and/or malaise, and upper respiratory tract infection symptoms. There were no significant differences in proportions reporting these between the two study groups. All systemic symptoms were mild and were resolved within the diary period.

No serious adverse events were noted during the study.

## DISCUSSION

This study shows that protective serogroup C antibody responses are induced by MCC-TT in almost all naïve adults and in those who had previously received an MACP vaccine. However, the magnitude of the response and the degree of antibody persistence, as measured by the SBA assay, were lower in those previously vaccinated with MACP than in naïve recipients of MCC-TT. Although the SBA GMTs at 1 and 6 months were lower in the previously vaccinated group, the proportions achieving SBA titers of  $\geq 8$  or  $\geq 128$  (the proposed minimum and the more conservative correlate of protection, respectively [3, 6]) were similar for the two groups (Table 1). Furthermore, the kinetics of the response were similar in the naïve and previously vaccinated groups, with 77.0 and 81.5% of subjects, respectively, achieving an SBA titer of  $\geq 8$  by 1 week, though this comparison may be confounded by the high percentage of prevaccination SBA titers in the group of prior MACP vaccinees. Overall, the differences in the magnitude and persistence of the serologic responses that were seen were unlikely to be clinically significant.

This study confirms earlier findings that prior MACP vaccination may have persisting effects, reducing the serogroup C SBA response either to a subsequent dose of MACP or to a conjugate vaccine. Richmond et al. (20) found that in adults

the SBA response to a second dose of MACP was significantly lower than that to a first given 6 months earlier, confirming the existence of hyporesponsiveness induced by vaccination with plain serogroup C polysaccharide (12). Moreover, those who had previously received MACP vaccine had significantly lower SBA responses to MCC-CRM<sub>197</sub> than a naïve group to which they were compared (20). Borrow et al. found a reduction in the SBA response to MCC-CRM<sub>197</sub> of laboratory staff previously given an MACP vaccine relative to that of naïve individuals (4), and a similar reduction for young children vaccinated with MACP as part of an outbreak control measure in a nursery school and given MCC-CRM<sub>197</sub> 6 months later (5).

As in the present study, the effects of prior MACP vaccination were evident only when the immune response was assessed by SBA assays; IgG responses as measured by ELISA generally were higher in prior MACP recipients. This suggests that functional antibody responses are specifically impaired. Qualitative differences, possibly denoting differences in functional antibody responses, were seen between the groups, as evidenced by the differing ratios of SBA to IgG at each time point. Naïve MCC-TT vaccinees had higher SBA titers than prior recipients of MACP, despite similar concentrations of serogroup C-specific IgG. This difference cannot be explained by the avidity of the antibody, because the avidity indices were similar for the two groups. The reason for this is unclear, though it may be due to the distribution of IgG subclasses or IgM antibodies induced, which are dependent on vaccine history. Alternatively, blocking antibodies induced by previous MACP vaccination may interfere with the IgG induced by the conjugate vaccine (13, 14).

Antibody avidity has frequently been used as a measure of functional antibodies in the evaluation of polysaccharide conjugate vaccines. However, while avidity maturation has been demonstrated following vaccination with MCC in infants and young children (5, 18, 22), when applied to adult populations (11), as found in this study, it is less informative. This may be because antibodies induced by polysaccharide antigens in adults already have high avidity (irrespective of previous vaccination history) and fail to mature further upon immunization with MCC-TT. The likely explanation for this is that all adults are already primed through natural exposure and that this vaccine stimulates predominantly memory B cells.

MCC-TT has previously been shown to be safe and well tolerated by healthy United Kingdom adults in a phase I study where all symptoms reported were mild and no serious adverse events were noted (19). Similar results were shown for naïve subjects in the present study and, importantly, also for those who had previously received the MACP vaccine, with no differences in reactogenicity between the groups despite the much higher prevaccination antibody levels in the latter. Few other data are available on the use of MCC vaccines for adults, though the adverse-event profile observed here is similar to that for inactivated vaccines against hepatitis A virus (25), a combined hepatitis A and B vaccine (7), and the combined low-dose diphtheria-tetanus-acellular pertussis vaccine (1), with pain the most common adverse reaction in this age group.

In conclusion, within the limitations of this study, MCC-TT vaccine was demonstrated to be safe and well tolerated and to induce putative protective antibody titers in similarly high pro-

portions of both naïve and previously vaccinated subjects at 1 week, 1 month, and 6 months postvaccination.

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