Dose sparing effects of novel adjuvants and alum on two different vaccines in a neonatal mouse model

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Introduction

Childhood vaccination provides protection against infectious diseases. In epidemics and pandemics vaccine demands may exceed production capacity, highlighting the need for dose-sparing strategies. Adjuvants are immune-stimulating agents used to boost and modulate immune responses to vaccines and can reduce antigen doses needed.

Aim

To assess the dose-sparing effects of adjuvants dmLT, mmCT, CAF01, CAF08b and alum on primary neonatal IgG antibody (Ab) response and % above protective Ab levels and IgG antibody secreting cells (ASCs) elicited by two vaccines; a pneumococcal-conjugate-vaccine (Pn1-CRM_{197}) and an influenza-hemagglutinin vaccine (HA).

Results

- Antibody levels of neonatal mice immunized once with a full dose of Pn1-CRM_{197} or HA without adjuvants were low (Fig 1 and Fig 2) and not protective against pneumococcal infections.
- mmCT and CAF08b significantly enhanced Pn1-specific Abs ($P<0.05$ to <0.001) elicited by fractional doses of Pn1-CRM_{197} providing 8-fold dose-sparing of the vaccine, with good protection against pneumococcal bacteremia, whereas dmLT and CAF01 provided 5-fold and 2-fold dose-sparing, respectively (Fig 1).
- For the influenza HA vaccine, CAF08b provided 40-fold dose-sparing effect whereas CAF01 and mmCT provided 8-fold dose-sparing (Fig 2).
- CAF08b and CAF01 induced high hemagglutination inhibition titers after one immunization, reaching seroprotection against influenza for 63% and 38% of the mice, respectively, with 2µg of HA.
- mmCT, CAF01 and CAF08b significantly enhanced Pn1- and HA-specific IgG antibody secreting cells (ASCs) in the bone marrow 8 weeks after immunization compared with full dose vaccine only (Fig 3).
- Alum did not induce dose sparing with either vaccine (Fig 1, 2 and 3).

Figure 1. Dose sparing effects of the adjuvants with Pn1-CRM_{197}. Kinetic of vaccine-specific IgG antibody levels elicited by Pn1-CRM_{197} vaccine with or without adjuvants.

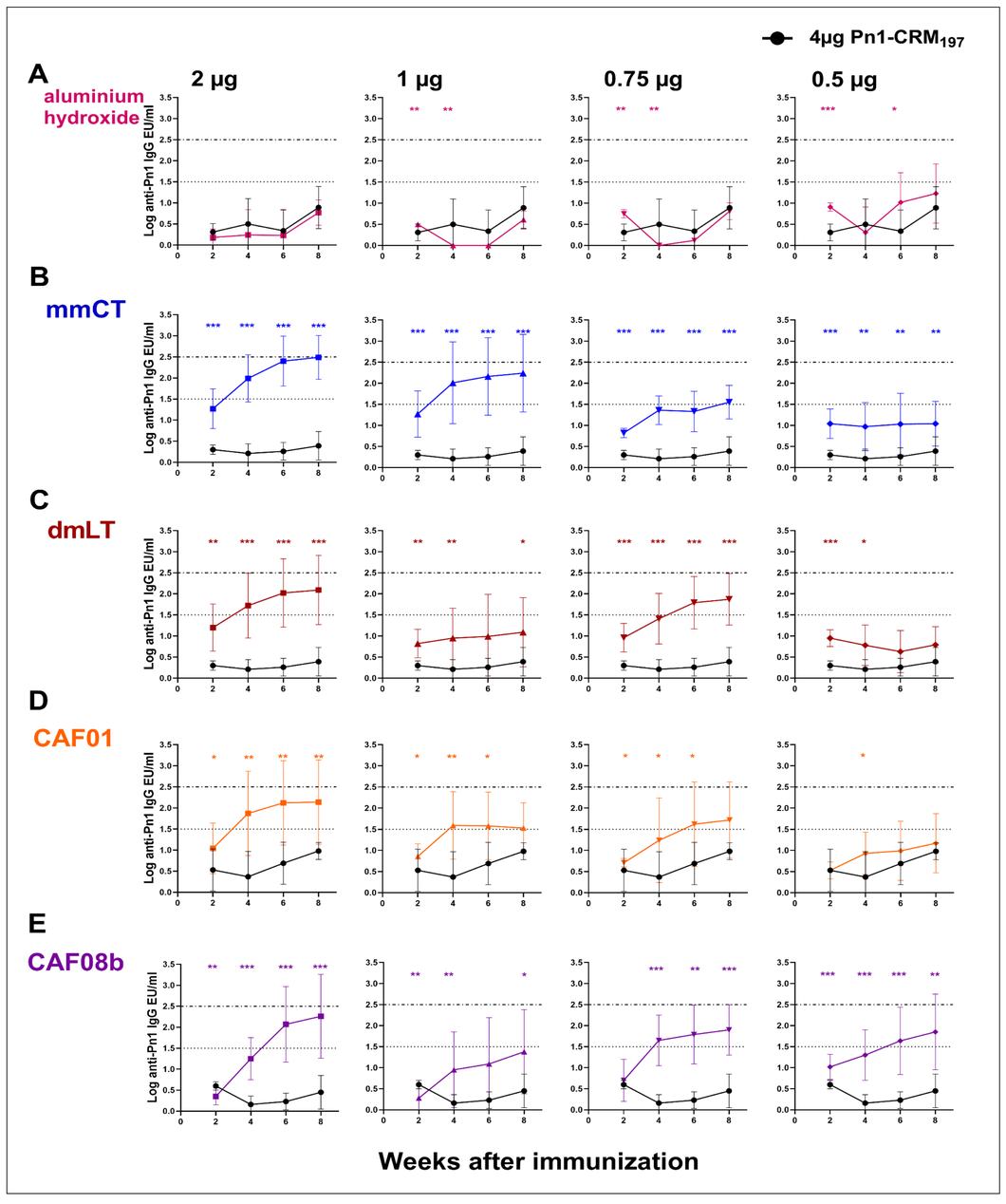


Figure 2. Dose sparing effects with influenza hemagglutinin vaccine. Kinetic of vaccine-specific IgG antibody levels elicited by influenza HA vaccine with or without adjuvants.

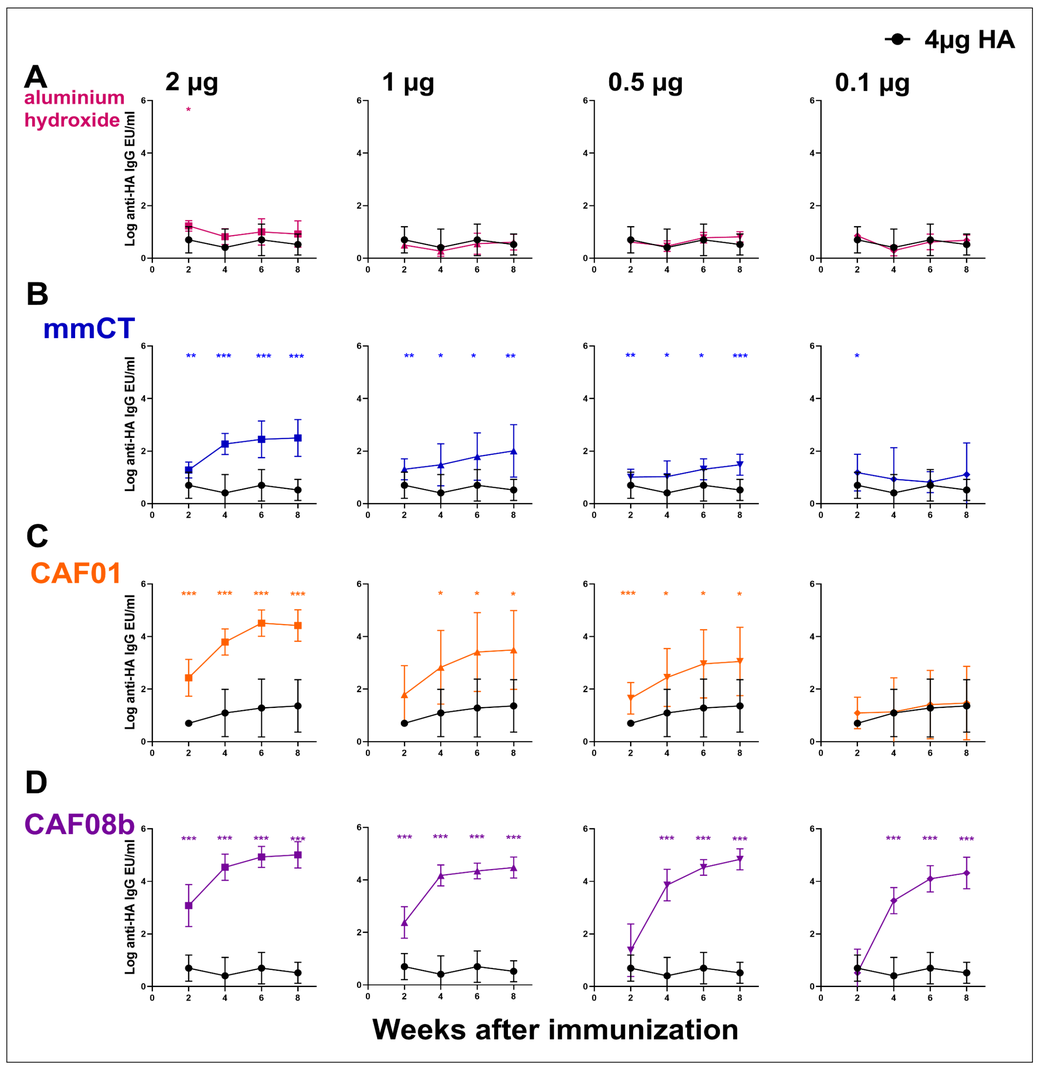
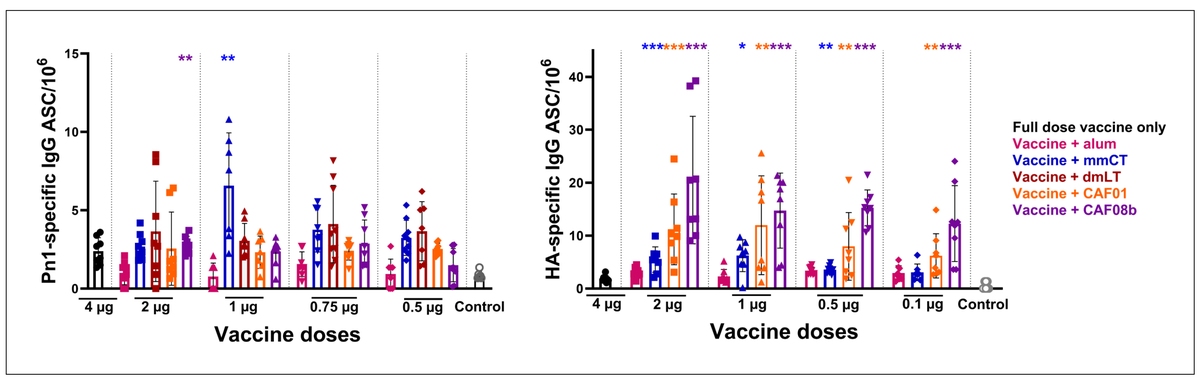


Figure 3. Effects of the adjuvants on persistence of vaccine-specific IgG^+ antibody secreting cells (ASCs) in bone marrow.



Methods: Pn1- and HA- specific IgG antibody levels in serum were measured by ELISA 2, 4, 6 and 8 weeks after subcutaneous immunization of neonatal mice (7 days old) with fractional doses of Pn1-CRM_{197}, (0.5, 0.75, 1 and 2 µg) with alum (0.48% aluminium hydroxide per 1µg of protein/mouse), mmCT (5 µg), dmLT (5 µg), CAF01 (250 µg DDA/50 µg TDB), or CAF08b (125 µg DDA/25 µg TDB/ 1 µg 3M-052); and compared with a full dose of Pn1-CRM_{197} (4 µg) without adjuvants; or fractional doses of HA (0.1, 0.5, 1 and 2 µg) with alum, mmCT, CAF01 or CAF08b and compared with a full dose of HA (4 µg). The dotted lines show levels of Pn1-specific Abs protective against pneumococcal blood (····) and lung infection (·– ·–).

IgG^+ antibody secreting cells (ASC) in bone marrow 8 weeks post-immunization were enumerated by ELISpot. Statistical differences were calculated using Mann-Whitney U-test where adjuvanted groups were compared to full dose vaccine only group.*$p \le 0.05$, **$p \le 0.01$, ***$p \le 0.001$.

Conclusion

mmCT, CAF01 and CAF08b enhanced protective humoral responses and had large dose-sparing effects on both Pn1-CRM_{197} and HA vaccines, although the adjuvant effect was clearly vaccine-dependent. The results support potential use of safe adjuvants in situations when vaccine production capacity is limited, including vaccination of pediatric populations that may be of high risk.

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