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Commentary

Rethinking placebo control in infant vaccine trials: A mechanistic and methodological perspective

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Abstract

Placebo-controlled randomized trials are widely regarded as the gold standard in clinical research. However, their routine application in infant vaccine studies has not been systematically re-evaluated in light of advances in immunology, trial design, and ethical frameworks. Infants lack the cognitive capacity required for classical placebo effects, and primary vaccine endpoints—such as immunogenicity, laboratory-confirmed infection, and severe disease—are inherently objective and biologically determined.

Although caregiver-mediated behavioral biases may influence certain outcomes, these effects are limited in scope and can be mitigated through alternative methodological approaches. We propose that placebo control in infant vaccine trials should not be considered a default requirement, but rather a context-dependent tool. A shift toward endpoint-driven trial design would better align methodological rigor with biological plausibility and ethical considerations.

Keywords: Infant vaccines, Placebo control, Immunobridging, Correlates of protection, Clinical trial design, Vaccine ethics

Introduction

Placebo-controlled trials have long been considered the most rigorous approach for evaluating medical interventions [1]. In vaccine research, this paradigm has been broadly applied across populations, including infants [2–4]. However, this practice assumes that placebo control uniformly addresses key sources of bias across all populations. This assumption warrants re-examination in infant populations, where the biological and cognitive context differs fundamentally from that of adults [5].

Here, we present a mechanistic and methodological perspective on placebo use in infant vaccine trials. Rather than arguing against placebo-controlled trials per se, we challenge their routine and uncritical application in this context. We propose that the necessity of placebo control should be determined by biological plausibility, endpoint characteristics, and the availability of alternative methodological approaches. Its role should not be overgeneralized; instead, a shift toward endpoint-driven trial design is both scientifically justified and practically feasible.

The Biological Implausibility of Placebo Effects in Infants

The classical placebo effect is mediated by expectation, belief, and conditioning—processes that require cognitive awareness and prior experience. These mechanisms are well documented in adults and can significantly influence subjective outcomes [6–8].

Infants, particularly in early life, lack the cognitive framework necessary for expectation-driven responses. While non-cognitive mechanisms such as conditioning may exist, there is no evidence that these processes can induce antigen-specific immune responses in the absence of antigen exposure.

Accordingly, placebo lacks a biologically plausible pathway to influence primary immunological outcomes in infant vaccine trials.

Objective endpoints are intrinsically placebo-insensitive

Primary endpoints in vaccine trials are predominantly objective and biologically grounded. These include antibody titers and seroconversion, cellular immune responses, laboratory-confirmed infection [9], and hospitalization or severe disease. Such endpoints are independent of perception and are driven by antigen-specific immune activation [10].

Across randomized trials, placebo recipients consistently exhibit baseline-level immune responses, with no evidence of vaccine-specific activation. This observation supports the conclusion that placebo is functionally equivalent to no antigen exposure with respect to immunological endpoints.

Functional equivalence of placebo and no intervention

Direct randomized comparisons between placebo and no-intervention controls are limited. Nevertheless, converging lines of evidence support their functional equivalence in infant populations.

Infection rates observed in placebo groups closely mirror those reported in unvaccinated populations under comparable epidemiological conditions [11]. Similarly, immunogenicity remains absent in placebo recipients, consistent with the absence of antigen exposure [10]. Moreover, studies employing different designs—including blinded placebo-controlled trials, open-label studies, and immunobridging approaches—yield consistent estimates for objective endpoints [12,13].

Taken together, these findings indicate that placebo and no-treatment controls are functionally indistinguishable with respect to primary vaccine outcomes in infants. While acknowledging the scarcity of direct randomized comparisons, the convergence of mechanistic, immunological, and epidemiological evidence provides strong support for this conclusion.

Caregiver-Mediated Bias: Scope and Limitations

A more relevant source of bias in infant trials arises from caregiver-mediated behaviors, including care-seeking patterns, symptom reporting, and adherence to follow-up [14]. These factors may influence the detection of mild or subjective outcomes.

However, their impact is constrained in several important respects. Severe outcomes, such as hospitalization, are unlikely to be missed. Laboratory-confirmed endpoints are independent of caregiver perception. In addition, active surveillance strategies can decouple case detection from care-seeking behavior [13].

Thus, the influence of caregiver-mediated bias is primarily confined to mild or early clinical presentations. The role of placebo in infant trials is therefore predominantly behavioral rather than biological, and its relevance depends critically on endpoint selection.

Alternative Methodological Approaches

Modern trial designs offer effective alternatives to placebo control. These include active surveillance with routine testing independent of symptoms, prioritization of objective endpoints (such as confirmed infection and severe disease), blinded outcome assessment through independent adjudication, and immunobridging strategies based on validated correlates of protection.

Collectively, these approaches can mitigate caregiver-related bias while preserving methodological rigor, thereby reducing or eliminating the need for placebo control in many settings [12,13].

Ethical Considerations

The use of placebo in infant trials raises important ethical considerations, including exposure to invasive procedures without direct benefit and, in some contexts, the withholding of effective interventions. Ethical guidelines emphasize that placebo use is not required when effective alternatives exist or when withholding intervention poses risk [3,4].

Fleming and colleagues [15] have highlighted the challenges of conducting large-scale randomized controlled trials for new populations when such trials are ethically or logistically infeasible. Similarly, Earle and colleagues [16] provide strong evidence supporting the use of post-immunization antibody titers as correlates of protection, enabling vaccine evaluation without large-scale efficacy trials. The WHO has further advanced this framework by emphasizing immune correlates as a basis for vaccine evaluation, particularly for priority pathogens [17].

When placebo is not methodologically necessary, its routine use becomes difficult to justify. Ethical rigor should be aligned with scientific necessity rather than historical convention. **Box 1** shows when the placebo control in vaccine trials is required.

Placebo control should be considered a context-dependent tool rather than a universal requirement.

1. Most justified when:
- **Endpoints are subjective**
- **Psychological effects are plausible**
- **No correlates of protection exist**

2. Optional when:
- **Endpoints are objective**
- **Participants lack expectation capacity (e.g., infants)**
- **Alternative bias-control methods are available**

3. Generally not justified when:
- **Effective vaccines exist**
- **Ethical concerns outweigh methodological benefit**

Box 1. When is placebo control necessary in vaccine trials?

Implications for Next-Generation Vaccine Evaluation

Vaccine development is increasingly driven by mechanistic insights, including correlates of protection, systems immunology, and AI-assisted antigen design [9,18–20]. As evaluation shifts toward immune signatures and predictive models, reliance on placebo-controlled paradigms is likely to diminish.

Accordingly, the central question is evolving from *"Does it work compared with placebo?"* to *"Does it induce the appropriate immune response?"*

When Placebo Control Remains Important

Despite the arguments presented, placebo control remains important in specific contexts. These include early-phase trials focused on safety and reactogenicity, studies involving subjective or patient-reported outcomes, and settings in which validated correlates of protection are not available.

In such scenarios, placebo provides valuable baseline comparisons and helps disentangle nonspecific effects. The objective is therefore not to eliminate placebo use, but to define more precisely when it is methodologically necessary.

Conclusion

The routine use of placebo control in infant vaccine trials reflects historical convention more than methodological necessity.

In this population, the absence of expectation-driven placebo effects and the objective nature of primary endpoints fundamentally limit the role of placebo in establishing efficacy. While caregiver-mediated biases are relevant, they are endpoint-specific and can be addressed through alternative approaches.

We therefore propose a shift from a placebo-default paradigm to an endpoint-driven framework, in which placebo use is justified only when it addresses a clearly defined methodological need. Such a transition would better align trial design with biological plausibility, ethical responsibility, and the evolving landscape of vaccine science.

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