VACCIREVIEW

Low-dose yellow fever vaccination in infants: a randomized, double-blind, non-inferiority trial

Bibliography

Kimathi D, Juan-Giner A, Bob NS, et al. Low-dose yellow fever vaccination in infants: a randomised, double-blind, non-inferiority trial. Lancet. 2026; Published online January 13, 2026. doi:10.1016/S0140-6736(25)02069-0

Summary

This randomized, double-blind, non-inferiority trial evaluated whether a very low-dose yellow fever vaccine (500 IU) is sufficiently immunogenic in infants aged 9–12 months compared with the standard dose (>13 000 IU) of the 17D-204 vaccine from Institut Pasteur de Dakar. The trial was conducted at two centers in Kenya and Uganda and co-administered yellow fever vaccine with measles–rubella vaccine to mirror the routine WHO Expanded Program on Immunization schedule.

A total of 420 infants with no prior yellow fever vaccination or infection were enrolled between Oct 7, 2021, and June 14, 2023, and randomly assigned 1:1 to receive either standard dose or 500 IU. The primary endpoint was seroconversion at day 28, defined as a four-fold or greater rise in neutralizing antibodies measured by PRNT50, with a non-inferiority margin of −10 percentage points for the difference in seroconversion rates between groups. The safety population included all vaccinated infants, and serious adverse events (SAEs) were carefully monitored.

In the per-protocol population, seroconversion at day 28 reached 99% (177/179; 95% CI 96–100) in the standard-dose group and 93% (166/179; 95% CI 88–96) in the 500 IU group. The absolute difference was −6.15 percentage points (95% CI −10.27 to −2.02), crossing the predefined −10 percentage-point non-inferiority margin at the lower bound; consequently, non-inferiority of the 500 IU dose could not be concluded. Seroconversion rates at day 10 and at 1 year were also consistently lower in the 500 IU group than in the standard-dose group, reinforcing that the infant response to 500 IU is suboptimal.

Twelve SAEs occurred during the study (eight in the 500 IU group and four in the standard-dose group), including pneumonia, malaria, and other common pediatric conditions, but none were judged related to vaccination. No post-vaccination viraemia was detected in infants in either arm, in contrast to low-frequency viraemia observed in adults given similar doses in prior work, and no new safety signals emerged. Overall, both doses were well tolerated.

The authors place their findings in the context of previous fractional-dose studies. Adult trials in Brazil and in the same Kenyan and Ugandan communities had shown that doses around 500–600 IU were non-inferior to standard dose, with sustained immunogenicity up to several years. In children, earlier fractional-dose trials used much higher potencies (one-fifth of a very high-potency standard dose, still ≥13 000 IU) and found non-inferior immunogenicity compared with full dose, but these regimens remained well above the WHO minimum potency requirement of 1000 IU. This infant trial is the first to test a dose close to the minimum adult "effective" potency in children.

The study also reviews evidence that neutralizing antibody responses after full-dose infant yellow fever vaccination can wane substantially over time, with some cohorts dropping to 28–59% seropositivity within a few years. Against that backdrop, the authors argue that any deliberate reduction in infant dose needs to be judged not only on short-term seroconversion but also on durability, especially in routine EPI contexts where long-term protection is desirable. They acknowledge that, in severe outbreak scenarios with extreme supply constraints, a modestly lower seroconversion rate from low-dose regimens might be acceptable but emphasize that this trade-off is context-specific and not suitable for routine programs.

Limitations include the restriction to two east African sites, which may limit generalizability to other endemic regions, and potential influences of co-administered EPI vaccines and local flavivirus epidemiology (including dengue) on antibody patterns. Nonetheless, the main conclusion is clear: minimum effective-dose data derived from adults cannot simply be extrapolated to infants, and standard yellow fever doses should continue to be used for infants in routine immunization.

Comment

This trial is an important reminder of a fundamental principle in vaccine development: start by demonstrating solid safety and robust efficacy at a dose that clearly works, and only then explore whether you can safely economize on antigen. The 500 IU yellow fever dose looked attractive on paper, backed by strong adult data and real supply-pressure arguments, but in infants it fell just short of the non-inferiority bar—precisely the kind of marginal underdosing that can quietly erode program impact.

From a development and regulatory perspective, this is a cautionary tale: a phase 3 failure due to underdosing cannot be "rescued" later by post-hoc explanations or modest protocol tweaks. Once a key target population has been shown to respond suboptimally at a chosen dose, the label, the confidence of NITAGs, and the reputational capital of the product all suffer. The correct sequence is therefore: prove the vaccine at a clearly

effective dose, then consider dose-sparing, fractional schedules or lower-potency formulations in carefully designed follow-up trials. This paper does not argue against dose-sparing; it argues against skipping steps. In the rush to stretch supply, it quietly insists that nothing is gained if a vaccine program fails because the pivotal trial tried to do “more with less” and delivered less protection instead.

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