Disparity between vitamin A-induced Th1-dependent oral tolerance in newborn mice and vitamin A-induced atopic sensitization in Guinean girls

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To the Editor: Turfkruyer *et al.*¹ elegantly demonstrate that inefficient oral tolerance in the newborn period is caused by impaired T_H1 activation

secondary to physiological vitamin A deficiency, effects that are restored by supplementation of the maternal diet with vitamin A. These findings highlight a gap between the sophisticated mechanistic understanding of vitamin A-induced tolerance and the real-world consequences of vitamin A supplementation (VAS). We have twice demonstrated that high-dose VAS given to newborn girls in Guinea-Bissau increases wheeze and atopic sensitization to aeroallergens later in childhood.^{2,3} Infants in Guinea-Bissau have a high level of vitamin A deficiency, and the mechanistic data generated by Turfkruyer *et al.* would suggest that these children should benefit most from VAS. The failure of VAS to protect against atopy and indeed to promote sensitization in Guinean girls leaves a disparity between the clinical and laboratory findings that needs to be resolved.

The difference may be between the single high-dose VAS used in Guinean children vs. the low-dose dietary supplement used in the laboratory animals, or there may be a factor unique to female humans not accounted for in the laboratory studies. In likening with many other animal studies, it was not clear whether male or female mice were used, or a mixture.¹ This lack of presentation by sex is unfortunate as numerous studies have documented major differences in male and female immune systems, and the way they respond to health interventions such as vaccines and VAS early in life.^{4,5} Alternatively, the different results may be due to interaction with other interventions to which the Guinean children were exposed, as only girls who concurrently received bacille Calmette-Guérin vaccination (BCG) had atopy potentiated by VAS.² There is also evidence for

interactions between VAS, vaccines and sex in relation to susceptibility to infectious diseases: VAS impairs the innate immune training enabled by BCG; and for females, it interacts with subsequent diphtheria-tetanus-pertussis vaccine in a harmful way, and with subsequent doses of VAS or measles vaccine in a beneficial way.⁴

In most high-income countries, children do not receive BCG or high-dose VAS at birth, but they do receive many vaccines later in childhood. For the physiological vitamin A deficiency of the newborn period to become a target for oral tolerance and allergy prevention,¹ we need mechanistic studies to investigate the doses and circumstances when VAS is beneficial and when it is harmful, and we also need to study males and females separately.

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