Vitamin A and Epigenetic Modifications
1. Observations by Keith P West, Jr.

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Arts and Benn hypothesize that early-life supplemental vitamin A may affect nutritional programming of the immune system, an established concept[1] being tested for vitamin A in animals,[2] *in-vitro* systems,[3] and randomized cohorts.[4] While an important scientific quest, Arts and Benn make an untenable leap to justify their vaccine-exposure hypothesis as relevant to policy by over-interpreting imprecise risk ratios (RR) from existing trials, evident by wide 95% confidence intervals (CIs) that should give pause about uncertainty.

For example, in a trial in Guinea-Bissau that the authors cite as providing evidence of decline in the impact of vitamin A on preschool child survival, there was a 9% reduction in mortality among 6–23-month-old children. While not significant (95% CI: -41% to 41%),[5] the estimate remains compatible with a long-established 24%–34% reduction in preschool child mortality that has been estimated across different vitamin A interventions.[6,7] Associated with this weak overall effect, there was a significant interaction by sex that revealed a clear reduction, and suggestive increase, in mortality among girls and boys, respectively. Despite a need for caution when interpreting subgroup effects and imprecise confidence intervals, the authors claim their results are strikingly different from previous trials.

Caution is similarly ignored in inferring that newborn vitamin A supplementation may increase infant mortality, especially in girls. Studies cited by Arts and Benn to support their claim all reported RRs of 0.90 to 1.12, with none having 95% CIs excluding 1.00.[5,8–12] Some estimates were suggestive of a higher RR from vitamin A receipt in boys,[5,11] another in girls,[9] and some in neither sex,[10,12] while all sex-specific 95% CIs except one (for girls in Guinea-Bissau[9]) included unity. At present, the most tenable explanation for variation in risk observed by sex across trials, given the evidence, is chance.

The above inference should not detract from Arts and Benn's pursuit of a vaccine-exposure hypothesis, but it should guide one's stand on policy. Newborn vitamin A trials in Southern Asia have all reported protective main effects (RRs) against infant mortality of 0.36 to 0.90, each with a 95% CI <1.00,[12–15] while across Africa effects have ranged from 0.98 to 1.16, all with 95% CIs that include unity.[8–11,16] Reasons for this "continental divide" may relate to regional differences in maternal vitamin A deficiency.[17] Thus, a policy implication also consistent with existing evidence would be to supplement newborns with vitamin A in Southern Asia, averting >150,000 infant deaths annually,[18] but not in Africa where, for reasons to be understood, it has, to date, shown no effect.

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Vitamin A and Epigenetic Modifications
2. Observations by Charles B Stephensen

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Cells of the immune system undergo epigenetic, transcriptional programming during normal development. Perhaps the best characterized example is the development of memory T-cells which develop both "inflammatory" phenotypes, such as Th1 cells that protect against infections including tuberculosis, and "regulatory" phenotypes, such as Treg cells, that dampen inflammation during the resolution phase of an immune response.[1]

Interestingly, the vitamin A metabolite retinoic acid can enhance the development of either cell type depending on experimental conditions.[2] Looking at either effect in isolation might lead to a prediction that vitamin A supplementation would only promote or only dampen inflammation, while the actual effect is more complex. Innate immune cells such as monocytes and macrophages also undergo transcriptional programming.[3] Retinoic acid again has apparently contradictory effects on these cells, both enhancing killing of tuberculosis bacilli by monocytes[4] but also dampening the production of cytokines by monocytes transcriptionally programmed by BCG to produce high levels of cytokines upon activation.[5]

The vitamin D metabolite calcitriol has similar effects, enhancing killing of tuberculosis bacilli by macrophages[6] but also programming a mechanism to dampen IL-6 production longer term.[7] When vitamin D is used to treat tuberculosis as adjunct therapy it can, at least in some settings, both speed bacterial clearance and dampen inflammation,[8] with both effects likely benefitting the patient.

In this issue Arts and Benn suggest that the ability of vitamin A to dampen BCG programming of monocytes to produce high levels of inflammatory cytokines will be a "negative" under circumstances where this programming may have non-specific protective effects for infants. This is an interesting and important hypothesis but, as the preceding examples show, making predictions from isolated *in-vitro* treatment effects for vitamin A is risky. It would be useful to test this prediction in an animal model to see if there is an *in vivo* correlate of the *in-vitro* observation. Even then, it is difficult to make concrete predictions for nutrients such as vitamin A and vitamin D, which have such varied effects on the immune system. Continuing to examine these questions will help us understand the mechanisms of action of these nutrients. Such advances in knowledge will help in the formulation of public health nutrition policies. It is important to re-evaluate such policies in the light of new research findings. This is particularly true of vitamin A at the moment, as such a re-evaluation is currently being discussed by the scientific community.[9,10]

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