

Commentary: Challenging public health orthodoxies—prophesy or heresy?[†]

Andrew M Prentice,^{1,2*} Mathilde Savy,^{1,2} Momodou K Darboe^{1,2} and Sophie E Moore^{1,2}

Accepted 9 December 2008

In 1633, after many years of skirmishing with the Catholic Church over his support for Copernicus' heliocentric theory of the universe, Galileo was finally sentenced by the inquisition to prison and religious penances. In a formal ceremony at the church of Santa Maria Sofia Minerva, he was forced to abjure his errors, and spent the rest of his life under house arrest in Sienna. The prophet had been convicted as a heretic.

Without, yet, wishing to confer the status of prophet on Peter Aaby and his disciples based in Guinea Bissau, there are significant parallels in their persistent challenges to some of the deepest rooted public health orthodoxies of the present day. Aaby has a long history of interrogating datasets in a way that others have failed to do and coming up with some uncomfortable findings. For many years he has been in conflict with WHO and many vaccinologists concerning his beliefs that childhood vaccines can have non-specific downstream effects on mortality (sometimes positive, but often negative) that have been ignored by mainstream research.^{1–4} More recently his team have even challenged, on the basis of a randomized trial, the value of WHO's recommendation that exclusive breastfeeding should continue to 6 months.⁵ Some may consider that house arrest is too lenient, even in Guinea Bissau instead of Sienna.

Christine Stabell Benn, working within Aaby's group, has for several years been pursuing another line of heresy, namely that it may be beneficial to withhold vitamin A supplementation (VAS) from infant girls in developing countries, at least until they

have had their first measles vaccination.^{6–8} In this issue of *IJE*,⁹ the Bissau team summarize the evidence in support of their belief that co-administration of vitamin A with diphtheria–tetanus–pertussis vaccine (DTP) results in negative interactions that lead to higher subsequent mortality; an effect confined to girls. They then take this a step further by drawing on data from two very large trials of zinc and iron-plus-folic-acid supplementation from Nepal^{10,11} and Zanzibar (Pemba).^{12,13} Using these data they argue that these trials also reveal important sex and age-differential effects of preventive treatment with micronutrients with a 'tendency' for detrimental effects in infants especially among girls.⁹ They conclude that micronutrient supplementation policies might have to differ for boys and girls, and that in their view 'all evidence suggests that currently infant girls have little to gain from micronutrients'.⁹

Could it really be true that in populations such as rural West Africa (where anaemia rates can exceed 90% and where >70% of young children can have plasma retinol levels <0.7 µmol/l¹⁴), we can advocate that micronutrients should be withheld from girls? Is it really possible that marginal nutrient deficiencies might be protective where infections are highly prevalent, as recently postulated for iron?¹⁵ Only a few years ago such a view, which is in direct conflict with policy recommendations from WHO,^{16,17} the International Vitamin A Consultative Group (IVACG)¹⁸ and the International Nutritional Anemias Consultative Group (INACG),¹⁹ would have been condemned as heresy. However, the recent findings from the Pemba trial¹² that supplementation with iron-plus-folic-acid caused a significant increase in serious adverse events and mortality leading to the trial's termination by its Data and Safety Monitoring Board have brought a renewed humility, and a recognition that there can be complex interactions between micronutrients, pathogens and immunity.²⁰ The state of our collective ignorance has been made painfully apparent.²¹

¹ MRC International Nutrition Group, London School of Hygiene & Tropical Medicine, London.

² MRC Keneba, The Gambia.

* Corresponding author. MRC International Nutrition Group, London School of Hygiene & Tropical Medicine, London. E-mail: andrew.prentice@lshtm.ac.uk

[†] A Commentary on: 'Should infant girls receive micronutrient supplements?' By Stabell Benn *et al.* (2008)

The evidence garnered by Benn and colleagues in support of their central contention that there are negative interactions between VAS and DTP vaccination in girls is somewhat fragmentary and often based on non-significant trends. Some of it is vulnerable to possible ascertainment biases related both to records of deaths and of vaccination status; criticisms of which the Guinea Bissau group are well aware,^{22,23} and which they endeavour to incorporate into their analyses. The evidence is complex and has been recently considered by a group of experts (including Benn and Aaby) convened at the London School of Hygiene & Tropical Medicine (LSHTM). It would be presumptive of us to offer a definite adjudication on the Benn thesis, or to pre-empt any report that may emerge from the LSHTM group. However, we offer the following recommendations:

- (i) There is sufficient circumstantial evidence for the Benn/Aaby thesis to be taken seriously; as has recently occurred at the LSHTM meeting. Those public health nutritionists or vaccinologists who tend towards the evangelical would be wise to leave room for scepticism and open debate.
 - (ii) One of the major aims of the London meeting was to gather together additional existing datasets that may be able to contribute further evidence for or against the Benn/Aaby hypothesis. Such datasets need to be very large given the welcome fact that infant and child mortality rates are declining in most countries and we may be searching for relatively rare endpoints and modest effect sizes. Impartial third-party re-analysis of such datasets should be expedited and, in view of the latest suggestion that the negative interactions may extend to supplementation with zinc and iron-plus-folic-acid, it is hoped that the Johns' Hopkins group have already been asked to contribute the data from their Nepal and Zanzibar trials¹⁰⁻¹³ so that the appropriate re-analysis can be done.
 - (iii) It would be unethical to conduct a prospective 4-arm trial in which infants were randomized with and without vitamin A and with and without DTP, but it might still be ethically acceptable to conduct a trial in which the vitamin A treatment was randomized (depending on the ethics committee's level of conviction concerning the Benn/Aaby hypothesis). However, much of the evidence accrued so far has come from areas with very high mortality and any research team initiating a new trial would have a moral responsibility to put in place better health surveillance and care, which, by reducing the number of serious adverse events, would probably require any such trial to be so large as to be prohibitively costly irrespective of any ethical arguments.
- Therefore the prospects of obtaining RCT standard evidence are remote.
- (iv) Aaby's contention that vaccines can have potent and long-lasting unintended effects has important implications for the design and analysis of vaccine trials. Since post-marketing (Phase 4) data surveillance is not currently practicable in most developing country settings, there is a responsibility to try and assess such outcomes at the Phase 3 stage with long-term follow-up and assessment of multiple outcomes, not just those related to the target disease.
 - (v) There is an urgent need to introduce a greater sophistication and more modern immunological techniques in order to understand the complex interactions between micronutrients and vaccines. Although community-wide VAS has been repeatedly proven to reduce all cause mortality in children, we know virtually nothing about the mechanism by which it saves lives.^{21,24} It is striking that Benn and colleagues are able to muster very little in the way of supportive mechanistic theories as to why there may be negative interactions and why these might be sex-specific. Even if large trials with mortality outcomes are not possible, it should be feasible to learn more about the putative interactions by means of very detailed investigations into how DTP and vitamin A status interact to modulate the downstream effects of the vaccine (for instance in relation to suggestions that it may exaggerate sex-specific T-helper cell biases).
 - (vi) Contrary to the frequently cited statement that 'it would be unethical' to perform trials in which vitamin A (or iron) were withheld in a control group, we believe that recent findings have re-established an ethical equipoise and that it is now essential to conduct such trials.
 - (vii) In the light of the concerns about vitamin A and DTP, and in view of the fact that at least two studies have shown that high doses of vitamin A can be associated with poorer clinical outcomes,^{8,25} and that measles vaccination appears to cancel out any adverse consequences of VAS + DTP,^{9,26} it may be wise to modify the current WHO advice concerning the timing of first VAS in infants. Currently the recommendation is 'after 6 months'.¹⁷ A prudent approach might be to recommend 'with, or soon after, measles vaccination'.
 - (viii) Public health nutritionists have generally moved on from single micronutrient interventions (vitamin A, iron, zinc and iodine) and are busily exploring the efficacy of multiple micronutrients in the form of Sprinkles[®] or lipid-based nutrient supplements (LNS). The inclusion of long-chain polyunsaturated fatty acids, which are already known to have

potentially significant immunomodulatory properties,²⁷ is being considered in LNS formulation. What effects might these other micronutrients have on vaccine responses? These should also be studied using, in the first instance, careful assays of their proximal effects on immune function.

Conflict of interest: None declared.

References

- ¹ Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000;**321**:1435–58.
- ² Aaby P, Samb B, Simondon F, Seck AM, Knudsen K, Whittle H. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *BMJ* 1995;**311**:481–85.
- ³ Aaby P, Biai S, Veirum JE *et al.* DTP with or after measles vaccination is associated with increased in-hospital mortality in Guinea-Bissau. *Vaccine* 2007;**25**:1265–59.
- ⁴ Roth AE, Stensballe LG, Garly ML, Aaby P. Beneficial non-targeted effects of BCG—ethical implications for the coming introduction of new TB vaccines. *Tuberculosis* 2006;**86**:397–403.
- ⁵ Jakobsen MS, Sodemann M, Biai S, Nielsen J, Aaby P. Promotion of exclusive breastfeeding is not likely to be cost effective in West Africa. A randomized intervention study from Guinea-Bissau. *Acta Paediatr* 2008;**97**:8–75.
- ⁶ Benn CS, Balé C, Sommerfelt H, Friis H, Aaby P. Hypothesis: vitamin A supplementation and childhood mortality: amplification of the non-specific effects of vaccines? *Int J Epidemiol* 2003;**32**:822–28.
- ⁷ Benn CS, Fisker AB, Jørgensen MJ, Aaby P. Why worry: vitamin A with DTP vaccine? *Vaccine* 2007;**25**:777–79.
- ⁸ Benn CS, Martins C, Rodrigues A, Jensen H, Lisse IM, Aaby P. Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. *BMJ* 2005;**331**:1428–32.
- ⁹ Benn CS, Lantz S, Fisker A, Jørgensen MJ, Aaby P. Should infant girls receive micronutrient supplements? *Int J Epidemiol* 2009;**38**:586–90.
- ¹⁰ Tielsch JM, Khattry SK, Stoltzfus RJ *et al.* Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial. *Lancet* 2006;**367**:144–52.
- ¹¹ Tielsch JM, Khattry SK, Stoltzfus RJ *et al.* Effect of daily zinc supplementation on child mortality in southern Nepal: a community-based, cluster randomised, placebo-controlled trial. *Lancet* 2007;**370**:1230–39.
- ¹² Sazawal S, Black RE, Ramsan M *et al.* Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006;**367**:133–43.
- ¹³ Sazawal S, Black RE, Ramsan M *et al.* Effect of zinc supplementation on mortality in children aged 1–48 months: a community-based randomised placebo-controlled trial. *Lancet* 2007;**369**:927–34.
- ¹⁴ Bah A, Semega-Janneh I, Prentice AM, Bates CJ. *National Survey on the Prevalence of Vitamin A and Iron Deficiency in Women and Children in The Gambia*. Banjul: National Nutrition Agency and MRC, 2001, pp. 1–56.
- ¹⁵ Denic S, Agarwal MM. Nutritional iron deficiency: an evolutionary perspective. *Nutrition* 2007;**23**:603–14.
- ¹⁶ WHO and UNICEF. *Focusing on Anaemia. Towards an Integrated Approach for Effective Anaemia Control*. Geneva: Joint WHO/UNICEF Statement, 2004.
- ¹⁷ WHO/UNICEF/IVACG. *Vitamin A Supplements: A Guide to Their Use in the Treatment and Prevention of Vitamin A Deficiency and Xerophthalmia*, 2nd edn. Geneva: World Health Organization, 1997.
- ¹⁸ Sommer A, Davidson FR. Assessment and control of vitamin A deficiency: the Anney Accords. *J Nutr* 2002;**132** (Suppl 9):2845S–50S.
- ¹⁹ Stoltzfus RJ, Dreyfuss ML. *Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia*. Washington, DC: International Life Sciences Press, 1998.
- ²⁰ Prentice AM, Ghattas H, Cox SE. Host-pathogen interactions: can micronutrients tip the balance? *J Nutr* 2007;**137**:1334–37.
- ²¹ Prentice AM, Gershwin ME, Schaible UE, Keusch GT, Victora CG, Gordon JI. New challenges in studying nutrition-disease interactions in the developing world. *J Clin Invest* 2008;**118**:1322–29.
- ²² Aaby P, Benn CS, Nielsen J, Lisse IM, Rodrigues A, Jensen H. DTP vaccination and child survival in observational studies with incomplete vaccination data. *Trop Med Int Health* 2007;**12**:15–24.
- ²³ Jensen H, Benn CS, Lisse IM, Rodrigues A, Andersen PK, Aaby P. Survival bias in observational studies of the impact of routine immunizations on childhood survival. *Trop Med Int Health* 2007;**12**:5–14.
- ²⁴ Keusch GT. Vitamin A supplements—too good not to be true. *N Engl J Med* 1990;**323**:985–87.
- ²⁵ Darboe MK, Thurnham DI, Morgan G *et al.* Effectiveness of an early supplementation scheme of high-dose vitamin A versus standard WHO protocol in Gambian mothers and infants: a randomised controlled trial. *Lancet* 2007;**369**:2088–96.
- ²⁶ Aaby P, Garly ML, Nielsen J *et al.* Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* 2007;**26**:247–52.
- ²⁷ Yaqoob P, Calder PC. Fatty acids and immune function: new insights into mechanisms. *Br J Nutr* 2007;**98** (Suppl 1):S41–45.