**Institution:** London School of Hygiene & Tropical Medicine (LSHTM)

**Unit of Assessment:** UoA2 – Public Health, Health Services & Primary Care

**Title of case study:** Informing policy and decision-making on vitamin A supplementation for mothers and children

## 1. Summary of the impact

Vitamin A deficiency (VAD) is a major public health problem in low- and middle-income countries with young children and pregnant women particularly at risk. Over the last 20+ years LSHTM researchers have carried out a series of definitive trials in collaboration with the Ghana Health Service to evaluate the impact of different vitamin A supplementation (VAS) strategies on maternal and/or child survival. Findings have had major impacts on national and global VAS programmes and influenced WHO guidelines on VAS in: infants and children 6–59 months of age; infants 1–5 months of age; postpartum women; and pregnant women.

## 2. Underpinning research

VAD is a widespread public health problem in low- and middle-income countries; it is the most common cause of blindness and in the 1980s was also shown to be associated with increased child mortality. LSHTM has been at the forefront of research since then, leading a series of definitive randomised controlled trials in collaboration with the Ghana Health Service to evaluate the impact of different VAS strategies on child survival.

The Ghana VAST Survival and Health trials[3.1] in the early 1990s were led by Professors David Ross (LSHTM since 1983, then Research Fellow) and Betty Kirkwood (LSHTM since 1979, then Lecturer) respectively. The survival trial was cluster randomised and involved 21,906 children aged 6 to 59 months, while the health study was individually randomised and involved 1,455 children followed weekly for one year. The trials were unique in including a detailed assessment of VAS on morbidity alongside mortality. They demonstrated that VAS reduces occurrence of severe (but not mild) episodes of illness, clinic attendances and hospitalisations, as well as reducing mortality by 19% (95% CI 2–32%, P = 0.03), suggesting that VAS protects children by reducing the severity of illness, rather than by increasing resistance to initial infection. The trials also allowed examination of impacts on the main causes of death (diarrhoea, pneumonia, measles, malaria)[3.2] and on growth.[3.3] They confirmed that four- to six-monthly VAS of children aged 6 to 59 months could save lives in a malaria-endemic sub-Saharan setting.

Three other large-scale trials followed under the leadership of Betty Kirkwood. The EPI-Plus trial was a multi-centre individually randomised trial in Ghana, India and Peru involving a total of 9,424 mother-infant pairs. It tackled VAD in the first six months of life and tested the safety and benefits of giving a postpartum dose to the mother together with VAS to the infant alongside the polio and DPT (diphtheria-pertussis-tetanus) vaccines at 6, 10 and 14 weeks of age, since combining VAS with the successful expanded programme of immunisation (EPI) would achieve coverage at scale. It confirmed the safety of this approach, but showed no impact on infant mortality up to nine months of age[3.4] (RR 0·96; 95% CI 0·73–1·27) and no sustained benefits in terms of vitamin A status beyond six months.[3.5]

The ObaapaVitA trial[3.6] was cluster randomised, evaluating the effect of weekly VAS to women of reproductive age (including during pregnancy and the postpartum period) on their survival and that of their babies. Analyses based on a total 207,781 women, 581,870 woman-years, 78,835 pregnancies and 73,752 livebirths yielded the following relative risks/rates (95% CIs) comparing weekly VAS with placebo: 0.92 (0.73, 1.17) for pregnancy-related mortality; 0.98 (0.89, 1.09) for severe pregnancy-related morbidity; 1.01 (0.93, 1.09) for all cause adult female mortality; 1.04 (0.96, 1.13) for stillbirths; and 0.98 (0.91, 1.05) for infant mortality. This body of evidence does not support inclusion of VAS for women in either safe motherhood or child survival strategies.

## 3. References to the research

3.1 Ghana VAST Study Team (Ross, DA, Dollimore, N, Smith, PG, Kirkwood, BR, Arthur, PR, Morris, SS, Addy, HA, Binka FN, Arthur P, Gyapong, JO and Tomkins, AM) (1993) Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality, *Lancet*, 342(8862): 7–12, doi: 10.1016/0140-6736(93)91879-Q. Citation count: 83

3.2 Binka, FN, Ross, DA, Morris, SS, Kirkwood, BR, Arthur, P, Dollimore, N, Gyapong, JO and Smith PG (1995) Vitamin A supplementation and childhood malaria in northern Ghana, *American Journal of Clinical Nutrition,* 61(4): 853–859, http://ajcn.nutrition.org/content/61/4/853.abstract (accessed 16 October 2013). Citation count: 55

3.3 Kirkwood, BR, Ross, DA, Arthur, P, Morris, SS, Dollimore, N, Binka, FN, Shier, RP, Gyapong, JO, Addy, HA and Smith, PG (1996) Effect of vitamin A supplementation on the growth of young children in Northern Ghana, *American Journal of Clinical Nutrition,* 63(5): 773–781, http://ajcn.nutrition.org/content/63/5/773.abstract (accessed 16 October 2013). Citation count: 32

3.4 WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group (Martines, J, Underwood, B, Bahl, R, Bhan, MK, Kirkwood, BR, Moulton, LH, Panny, ME, Ram, M, Kjolhede, CL, Propper, L, Arthur, P, Morris, S, Etego, SA, Zandoh, C, Boahen, O, Wahed, MA, Lanata, CF, Butrón, B, Huapaya, AR and Rivera, KB (1998) Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy, *Lancet,* 352(9136):1257–1263, doi:10.1016/S0140-6736(98)02487-8. Citation count: 112

3.5 Bahl, R, Bhandari, N, Wahed, MA, Kumar, GT, Bhan, MK and the WHO/CHD Immunisation-Linked Vitamin A Group (Arthur, P, Kirkwood, BR, Morris, S, Etego, SA, Zandoh C, Boahen O, Penny, ME, Lanata, CF, Butron, B, Huapaya, AR, Rivera, KB, Bhandari, N, Bahl, R, Bhan, MK, Wahed, MA, Moulton, LH, Ram, M, Kjolhede, CL, Propper, L, Martines J and Underwood B) (2002) Vitamin A supplementation of women postpartum and of their infants at immunisation alters breast milk retinol and infant vitamin A status, *Journal of Nutrition*, 132(11): 3243–3248, http://jn.nutrition.org/content/132/11/3243.abstract (accessed 16 October 2013). Citation count: 35

3.6 Kirkwood, BR, Hurt, L, Amenga-Etego, S, Tawiah, C, Zandoh, C, Danso, S, Hurt, C, Edmond, K, Hill, Z, ten Asbroek, G, Fenty, J, Owusu-Agyei, S, Campbell, O and Arthur P, for the ObaapaVitA Trial Team (2010) Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial, *Lancet*, 375(9726):1640–1649, doi: 10.1016/S0140-6736(10)60311-X. Citation count: 35

**Key grants**

Kirkwood, Evaluating the Impact of Vitamin A Supplementation on Maternal Mortality in Ghana, DFID, 1999–2009, £6,493,282.
Kirkwood, NEOVITA: Efficacy of Newborn Vitamin A Supplementation in Improving Child Survival in Rural Ghana: Generation of Evidence Necessary for Informing Global policy, WHO (through a grant from the Bill & Melinda Gates Foundation), 2009–2013, £3,146,510.

## 4. Details of the impact

The Ghana trials have substantially influenced global policy on VAS as well as having a major influence on the development and content of the national vitamin A programme in Ghana.

In 2011 WHO published four revised VAS guidelines relating to VAS in: infants and children 6–59 months of age;[5.1] infants 1–5 months of age;[5.3] postpartum women;[5.5] and pregnant women.[5.7] These were based on updated Cochrane reviews[5.2, 5.4, 5.6. 5.8] commissioned by WHO and, in some cases, additional analyses carried out by WHO. They replaced the previous recommendations published by WHO, UNICEF and IVACG Task Force in 1997. Evidence from the trials in Ghana made substantial contributions to all the new guidelines:

- The Ghana VAST trials constituted 28.9% of the total evidence concerning the impact of VAS

on all-cause mortality in children aged 6–59 months and the continued recommendation that this is a key child survival intervention.[5.1, 5.2]

- The latest Countdown to 2015 (maternal, newborn and child survival) report[5.9] estimated a median coverage of 80% for children aged 6–59 months receiving VAS in low- and middle-income countries; the 2013 *Lancet* nutrition review series highlights the importance of continuing to improve this coverage, estimating that this could prevent an additional 145,000 deaths each year at a cost of $159 per life saved. This estimate was derived using the Lives Saved Tool (LiST) which models the number of child deaths that could be saved with different interventions. The cause-specific findings from the Ghana VAST trials make a major contribution to the evidence base on effect sizes for VAS used in LiST.
- The EPI-Plus trial provided 11.3% of the mortality evidence behind the recommendation not to recommend VAS in infants 1–5 months of age.[5.3, 5.4] This is a reversal of the previous policy recommending supplementation in this age group and which was not evidence based.
- Both the EPI-Plus trial and the ObaapaVitA trial contributed evidence behind the recommendation not to recommend VAS in postpartum women.[5.5, 5.6] This is also a reversal of previous policy which recommended postpartum supplementation.
- The ObaapaVitA trial contributed 61.9% of the evidence concerning no overall impact of VAS to pregnant women on maternal mortality and 61.9% of the evidence concerning no overall impact on neonatal mortality.[5.7, 5.8] Supplementation of pregnant women is not recommended.

The VAS trial findings have also had a major influence within Ghana. The establishment of the National Vitamin A Programme was in direct response to the Ghana VAST trials, and the content of the programme has been influenced and informed by the subsequent trials in Ghana. The 2012 Countdown report[5.9] gives 93% coverage of two doses per year of VAS to children aged 6–59 months. The national vitamin A programme no longer supports VAS given with vaccines in the first six months of life or supplementation of postpartum women, saving the programme considerable money and opportunity costs each year, and, following the ObaapaVitA trial, VAS for women of reproductive age will not be introduced. The definitive no impact findings of the ObaapaVitA trial emphasize that good research can make important contributions by showing that something doesn't work; Esi Amoaful, the National Vitamin A Programme Manager, Ghana Health Service[5.10] commented: 'Research does not just tell us what new things to do, it also tells us what not to do. The remarkable finding has made the case that had the Ghana Health Sector implemented this policy all over the country to women without the requisite information about its benefits, we might have spent millions of dollars each year to no avail."

Finally, the vitamin A trials in Ghana have made a major contribution to research capacity, building the initial infrastructures for the Navrongo and Kintampo Health Research Centres which are making substantial research contributions to global health. For example, the Kintampo Health Research Centre has a widespread malaria programme and was one of the seven African sites carrying out trials to assess the GlaxoSmithKline RTS,S malaria vaccine which has just been reported to almost halve the number of malaria cases in young children. The vitamin A trials have also trained staff who have gone on to senior research and policy positions in Ghana including two current university Vice-chancellors and Directors of two health research centres.

**5. Sources to corroborate the impact**

**WHO VAS guideline & related systematic review: Children 6–59 months**

5.1 WHO (2011) *Guideline: Vitamin A Supplementation in Infants and Children 6–59 Months of Age*. Geneva: WHO, http://whqlibdoc.who.int/publications/2011/9789241501767_eng.pdf (accessed 16 October 2013).

5.2 Imdad, A, Herzer, K, Mayo-Wilson, E, Yakoob, MY and Bhutta, ZA (2010) Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age, *Cochrane Database of Systematic Reviews*, 12, doi:10.1002/14651858.CD008524.pub2.

**WHO VAS guideline & related systematic review: Infants 1–5 months**

5.3 WHO (2011) *Guideline: Vitamin A Supplementation in Infants 1–5 Months of Age*. Geneva:

WHO, http://whqlibdoc.who.int/publications/2011/9789241501811_eng.pdf (accessed 16 October 2013).

5.4 Gogia, S and Sachdev, HS (2011) Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less, *Cochrane Database of Systematic Reviews*, 10, doi: 10.1002/14651858.CD007480.pub2.

**WHO VAS guideline & related systematic review: postpartum women**
5.5 WHO (2011) *Guideline: Vitamin A Supplementation in Postpartum Women*. Geneva: WHO, http://whqlibdoc.who.int/publications/2011/9789241501774_eng.pdf (accessed 16 October 2013).

5.6 Oliveira-Menegozzo, JM, Bergamaschi, DP, Middleton, P and East, CE (2010) Vitamin A supplementation for postpartum women, *Cochrane Database of Systematic Reviews*, 10, doi: 10.1002/14651858.CD005944.pub2.

**WHO VAS guideline & related systematic review: pregnant women**
5.7 WHO (2011) *Guideline: Vitamin A Supplementation in Pregnant Women*. Geneva: WHO, http://whqlibdoc.who.int/publications/2011/9789241501781_eng.pdf (accessed 16 October 2013).

5.8 van den Broek, N, Dou, L, Othman, M, Neilson, JP, Gates, S and Gülmezoglu, AM (2010) Vitamin A supplementation during pregnancy for maternal and newborn outcomes, *Cochrane Database of Systematic Reviews*, 11, doi:10.1002/14651858.CD008666.pub2.

**Coverage of VAS for children 6–59 months: 2012**
5.9 Countdown to 2015: Maternal, Newborn & Child Survival (2012) *Building a Future for Women and Children: the 2012 Report*. Geneva: WHO/UNICEF, http://www.countdown2015mnch.org/documents/2012Report/2012-Complete.pdf (accessed 16 October 2013).

**LSHTM contribution to policy in Ghana**
5.10 Deputy Chief Nutrition Officer & National Vitamin A Programme Manager, Ghana Health Service.