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ISSUES IN PUBLIC HEALTH

Is it time for South Africa to end the routine high-dose vitamin A supplementation programme?

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In accordance with World Health Organization guidelines, South Africa (SA) introduced routine periodic high-dose vitamin A supplementation (VAS) in 2002. These guidelines were developed after research in the 1980s and 1990s showed the efficacy of VAS in reducing childhood mortality. However, two recent studies in low- to middle-income countries (2013 and 2014) have shown no effect of high-dose VAS on mortality. Additionally, there is no clear research evidence that 6-monthly doses of vitamin A result in a sustained shift in serum retinol levels or reduce subclinical vitamin A deficiency. These two points should encourage SA to re-examine the validity of these guidelines. A long-term view of what is in the best interests of the majority of the people is needed. The short-term intervention of administering vitamin A capsules not only fails to improve serum retinol levels but may create dependence on a 'technical fix' to address the fundamental problem of poor nutrition, which is ultimately underpinned by poverty. It may also cause harm. Although there are those, some with vested interests, who will argue for continuation of the routine high-dose VAS programmes, SA policymakers and scientists need to evaluate the facts and be prepared to rethink this policy. There is cause for optimism: SA's health policymakers have previously taken bold stands on the basis of evidence. The examples of regulation of tobacco products and taxation of sugar-sweetened beverages, ending the free distribution of formula milk for HIV-positive mothers and legislating against the marketing of breastmilk substitutes provide precedents. Here is a time yet again for decision-makers to make bold choices in the interests of the people of SA. While the cleanest choice would be national discontinuation of the routine VAS programme, there may be other possibilities, such as first stopping the programme in Northern Cape Province (where there is clear evidence of hypervitaminosis A), followed by the other provinces in time.

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Reasons for routine vitamin A supplementation in South Africa

In 2002, South Africa (SA) introduced a national routine vitamin A supplementation (VAS) programme, which provides 6-monthly high-dose (200 000 IU) vitamin A (retinyl palmitate) capsules to children aged 12 - 59 months and 100 000 IU to children aged 6 - 11 months at all public health facilities.[1] This programme was introduced in accordance with the recommendations of the World Health Organization (WHO) for children living in areas where vitamin A deficiency (VAD) was a concern.[2] The first survey to examine vitamin A status in SA was conducted by the South African Vitamin A Consultative Group (SAVACG), which reported a 33.3% prevalence of low serum retinol concentrations (serum retinol <0.7 µmol/L) in children aged 6 - 71 months.[3] These findings influenced the decision to institute a VAS programme in order to address VAD, which was classified as being of extreme public health importance.

Subsequent to VAS implementation, public health nutrition researchers raised concerns about routine VAS in SA, and proposed reappraisal of the programme. Their disquiet centred around the right to information (mothers not being informed about VAS or VAD), safety issues, the need for monitoring and evaluation, the programme absorbing a lot of resources, including human resources, and the inappropriate targeting of under-5s, while infectious morbidity and mortality are more prevalent in early infancy.[4,5] Implementation of VAS in areas where it is not needed incurs undue costs, when the money could be better utilised.[6]

There were two main reasons why routine VAS was recommended by the WHO and the international community: as a child survival strategy and to reverse VAD.

The role of high-dose vitamin A capsules in reduction of mortality in children aged <5 years

The WHO recommendation was based on a meta-analysis of data from the 1980s and 1990s that showed that high-dose VAS reduced overall mortality by 23%.[7] However, more recent studies have not supported this positive effect on mortality.[8,9] A 2013 Indian study, a large-scale programme evaluation with over a million children, reported no positive impact of high-dose vitamin A capsules (HDVACs) on mortality.[8] Another study, conducted in Guinea-Bissau (2014), which was the first individually randomised trial of HDVACs provided during immunisation contacts, similarly showed no effect of HDVACs on mortality.[9]

Andersen *et al.*[10] assessed the impact of HDVACs administered during public health campaigns with and without vaccination. They reported that although administration of oral polio vaccine (OPV) was associated with reduced mortality (mortality rate ratio 0.81 (0.68 - 0.95)), surprisingly, HDVACs given either with OPV or alone had no impact on mortality, with mortality rate ratios of 1.10 (0.82 - 1.48) and 1.04 (0.80 - 1.35), respectively.

While it is clear that historically HDVACs have played an important role in several low-income countries as a child survival strategy, it is worth investigating why this effect no longer seems to be evident. Mason, Greiner and Shrimpton were instrumental (together with others in the International Vitamin A Consultative Group) in encouraging VAS programmes in populations with evidence of VAD. However, these same scientists have been forced by evidence and observations to call for a re-think of vitamin A policies.[11] As they point out, the mortality effect after the 1980s and 1990s was minimal since there had been a positive change from the previous situation where there were fewer vaccines and more widespread diarrhoea and measles (the two infections against which VAS had most effect). When researchers re-analysed the data from one of the original vitamin A trials, the Ghana Vitamin A Supplementation Trial, surprisingly, only children who had not received any immunisations benefited from the vitamin A.[12] Since then, vaccination coverage has increased, and the availability of new vaccines against pneumonia and diarrhoea has contributed to a significant reduction in morbidity and mortality from these. In view of the above changes, it is therefore not surprising that VAS no longer results in the earlier large reductions of mortality.

The role of HDVACs in reducing subclinical VAD

Although it is plausible and a widely held belief,[11] there is, however, no clear research evidence to support the assumption that 6-monthly high-dose VAS will shift serum retinol levels or reduce subclinical VAD (serum retinol <0.7 μmol/L). Even West *et al.*,[13] strong defenders of HDVAC programmes, admit that HDVACs do not correct the root problem of VAD and that better interventions would be dietary diversification and food fortification. Studies have shown that serum retinol levels rise rapidly after high-dose vitamin A administration, but that these levels decline within 1 - 3 months.[14,15] Additionally, it has been shown that food-based interventions, e.g. red palm oil consumption, can reverse VAD,[16] and in SA beta-carotene-rich orange-fleshed sweet potato improved the vitamin A status of primary schoolchildren.[17] Food-based interventions have advantages over HDVACs because of the added nutritional benefit of the vitamin A food matrix. Indeed, in the 1990s international agencies always saw HDVACs as an interim emergency measure while encouraging dietary diversification and dietary education. However, even after two decades VAS is still being promoted and implemented by the international agencies.[18]

SA and many other low- to middle-income countries (LMICs) would benefit from food-based approaches, as these would result in general improvement in food intake with an added beneficial impact on malnutrition and survival.

What of the possibility of harm in HDVAC programmes?

As discussed above, the two tenets on which the recommendation for routine VAS were based (child mortality and VAD reduction) appear no longer to be valid. This has resulted in vigorous debate in the past few years,[5,11,13,19,20] with the new scientific evidence largely being ignored by the proponents of HDVAC. In our view, this is partly because many from both science and pharma have invested considerably in promoting HDVAC as a magic bullet against mortality.[21]

An additional important piece of information is that in the early years when high-dose VAS was introduced, there was little thought that these exceptionally high, non-physiological doses of vitamin A might actually cause harm, and that interactions with certain vaccines may cause harm.[22] Benn and colleagues[23,24] reported that HDVAC was associated with increased mortality in girls who also received diphtheria, pertussis and tetanus vaccine. Hypervitaminosis/excessive vitamin A intake has been linked to adverse health effects.[25] We are reminded of the basic foundation of public health policy – 'first do no harm'.

As more evidence emerges on the physiology and processing of vitamin A, it has become clear that the use of such high pharmacological doses of vitamin A, especially in a young child, can overload the liver, which may not be able to store such large quantities, resulting in excess vitamin A being unbound and potentially toxic to cells.

Many countries have also introduced successful fortification programmes, including SA, which commenced fortification of wheat flour and maize meal with vitamin A in 2003 as part of the National Food Fortification Programme.[26]

With such ongoing parallel fortification programmes, as well as improved intake of vitamin A-rich foods, there is a real possibility that some members of the population will in fact be consuming abnormally high amounts of vitamin A. A recent review, using case studies in the USA, Guatemala, Zambia and SA, clearly illustrated the potential for excessive intakes in some groups.[27] The review reported that in SA there are sectors of the population that regularly consume liver,[28] a rich source of vitamin A, and that children who received VAS as well as eating liver had an increased risk of hypervitaminosis A based on elevated serum retinyl esters. Hypervitaminosis A was originally described in high-income countries, where it was linked to over-use of over-the-counter supplements. The review,[27] however, showed that even in LMICs with overlapping programmes providing vitamin A, hypervitaminosis A may affect some populations.

A recent SA study conducted in Northern Cape Province, where liver is frequently eaten, measured liver vitamin A stores (using retinol isotope dilution) before and after a high-dose supplement in preschool children who consumed liver regularly and were exposed to VAS and fortification.[29] It showed that 64% had hypervitaminosis A at baseline, which increased to 72% after VAS, while no children had vitamin A-deficient liver stores. Liver vitamin A concentrations correlated significantly with the number of vitamin A supplements received during the past year, as well as the total number of vitamin A supplements received since birth.[29]

Opportunity costs of VAS programmes

It is recommended that HDVACs are administered with vaccinations. While this occurs with routine immunisation, it is often supplemented by 'child health days' when a national campaign is conducted to rapidly boost coverage. Furthermore, many countries still rely solely on such campaigns to provide HDVACs. The opportunity cost of child health days is significant, especially in terms of health personnel who are withdrawn from their normal duties for these events, with consequent negative effects on other activities. These opportunity costs have been shown both in SA[30] and in other countries.[31,32] HDVAC campaigns may therefore indirectly cause harm by diverting attention and resources from other important activities such as breastfeeding promotion and food security programmes. The United

Nations Children's Fund (UNICEF) in its 2018 report *Coverage at a Crossroads: New Directions for Vitamin A Supplementation Programmes*[18] lamented that 'While Child Health and Nutrition Days are delivering vitamin A supplements in many places, in some countries these events have been co-financed using polio funding, which is now dwindling. The sustainability of VAS programmes is also tenuous.' The South African Health Review also noted the low coverage of 54.3% in SA in 2017 - 2018.[33] However, as argued by some, there may not be reason to lament.[22]

Conclusion and recommendations

In summary, there is no evidence from the past two decades, with changing disease profiles, increased use of vaccines and reduced morbidity from diarrhoea and pneumonia, that a high-dose VAS programme is nearly as effective today as it was in some countries 20 - 30 years ago. Furthermore, in spite of the current VAS coverage of 54.3%, diarrhoeal disease-related deaths showed a 70.1% decrease from 2005 to 2015.[33] These data imply that the deaths decreased in spite of stagnant and poor VAS coverage. According to the Global Burden of Disease 2013 estimates for SA, VAD accounted for only 0.17% of total disability-adjusted life years (DALYs), compared with wasting (2.96%) and non-exclusive breastfeeding (1.73%).[34]

SA implemented VAS in 2002 based on the SAVACG findings and WHO guidance and without, we believe, taking into account the prevailing morbidity and mortality patterns.

The proponents of continuation of HDVAC programmes argue that discontinuing HDVAC programmes should be considered only when countries can report a prevalence of <5% for low serum retinol.[35] However, this suggestion is not supported by current scientific evidence that shows that HDVAC programmes do not prevent VAD in terms of serum retinol.[13] Using such a prevalence level as a cut-off would imply that almost every country in the world should use HDVACs, as at any given time some people will fall below the serum retinol cut-off owing to natural variation or as a result of infection, which is known to temporarily lower serum retinol levels.

We believe that there is a role for disease-targeted vitamin A, such as in the treatment of measles cases, severe malnutrition and persistent diarrhoea.[36] We do not believe that there is sufficient evidence to justify the continuation of the routine VAS programme in SA. However, constant vigilance is key in order to identify areas where VAD may be prevalent in the population, e.g. among the poor or in poorly resourced informal settlements.

Putting an end to routine high-dose VAS programmes may represent an inconvenient truth for many in the search for magic bullets to alleviate public health problems. However, Mason *et al.*[11] highlight the potential cost-benefit of ending ineffective and potentially harmful HDVAC programmes. Discontinuing the HDVAC programme in SA will free up resources, both human and financial, to concentrate on intervention programmes of known benefit with wider and more sustained impact, viz. timely BCG vaccine provision,[37] breastfeeding promotion, dietary diversification, mentoring of community caregivers and poverty alleviation.

We need to take a long-term view of what is in the best interests of the majority of the people we serve. Although it may seem easier to just 'pop a pill', this intended short-term intervention not only fails to maintain vitamin A health but also renders populations dependent on a 'technical fix' to address the fundamental problem of poor nutrition, ultimately underpinned by poverty – and it may cause harm.

Although there are those who will argue for continuation of the routine high-dose VAS programmes, SA policymakers and scientists need to evaluate the facts and be prepared to rethink this policy. We have cause to be optimistic: SA's health policymakers have previously taken bold stands on the basis of evidence. The examples of regulation of tobacco products and taxation of sugar-sweetened beverages, ending the free distribution of formula milk for HIV-positive mothers, and legislating against the marketing of breastmilk substitutes provide precedents. Further, when the WHO released new guidance in 2011[38] on postpartum, neonatal and young infant VAS based on new evidence, and concluded that providing HDVACs to these groups was not to be recommended owing to lack of any measurable effect, SA ended these programmes. These same guidelines called for a review of the guidelines for HDVAC to children aged >6 months to be undertaken in 2016. This has not yet taken place. We hereby call for an urgent review of the WHO policy guidelines for children aged >6 months.

However, SA does not need to wait for the WHO to review its guidelines: here is a time yet again for decision-makers to make bold choices in the interests of our people. While the logistically easiest choice would be national discontinuation of the routine VAS programme, there may be other possibilities, such as first stopping VAS in the Northern Cape (where there is clear evidence of hypervitaminosis A), followed by the other provinces in time. Whatever decision is taken regarding the VAS programme in SA, monitoring and evaluation of the consequences for both VAD and overall mortality are essential.

Dedication. This public health policy article is dedicated to Emeritus Professor David Sanders, who sadly passed on after it was accepted for publication. David spent his life campaigning for the rights of children, and especially their health and nutrition. He was bold in his stand against 'magic bullet' interventions that displaced more locally appropriate and sustainable actions. David was committed to ensuring that public health policies, such as routine HDVAC supplementation, would be regularly assessed and replaced when necessary. He will be sorely missed, but his legacy will continue through his writings and the many lives he has touched.

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1. National Department of Health, South Africa. Guidelines for the Implementation of Vitamin A Supplementation, 2004. Pretoria: Nutrition Directorate, NDoH, 2004.
2. World Health Organization/United Nations Children's Fund/International Vitamin A Consultative Group Task Force. Vitamin A Supplements: A Guide to their Use in the Treatment and Prevention of Vitamin A Deficiency and Xerophthalmia. Geneva: WHO, 1997. https://apps.who.int/iris/handle/10665/41947 (accessed 31 March 2019).
3. Coutsoudis A, Hussey G, IJsselmuiden C, et al.; for the South African Vitamin A Consultative Group. Anthropometric, vitamin A, iron and immunisation coverage status in children aged 6 - 71 months in South Africa, 1994. S Afr Med J 1996;86(4):354-357.
4. Dhansay MA. Vitamin A supplementation: A case of not seeing the wood for the trees? S Afr J Clin Nutr 2003;16(4):116-117.
5. Dhansay MA. Vitamin A supplementation in South Africa: Time for a reappraisal. S Afr J Clin Nutr 2007;20(4):123-124. https://doi.org/10.1080/16070658.2007.11734138
6. Schoeman S, van Stuijvenberg M, Lombard C, et al. Frequent Consumption of Liver Protects against Vitamin A Deficiency in a Socio-economically Deprived Community: Time to Reappraise the Vitamin A Supplementation Policy for South Africa's Diverse Population. MRC Technical Report, March 2012. Cape Town: South African Medical Research Council, 2012.

7. Beaton GH, Martorell R, McCabe G, et al. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries – Nutrition Policy Discussion Paper No. 13. In: Mason JB, ed. United Nations Administrative Committee on Coordination/Subcommittee on Nutrition State-of-the-Art Series. Toronto: University of Toronto, 1993. https://www.unscn.org/layout/modules/resources/files/Policy_paper_No_13.pdf (accessed 28 October 2019).
8. Awasthi S, Peto R, Read S, et al. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. Lancet 2013;381(9876):1469-1477. https://doi.org/10.1016/s0140-6736(12)62125-4
9. Fisker AB, Bale C, Rodrigues A, et al. High-dose vitamin A with vaccination after 6 months of age: A randomized trial. Pediatrics 2014;134(3):e739-e748. https://pediatrics.aappublications.org/content/134/3/e739
10. Andersen A, Fisker AB, Rodrigues A, et al. National immunization campaigns with oral polio vaccine reduce all-cause mortality: A natural experiment within seven randomized trials. Front Public Health 2018;6:13. https://doi.org/10.3389/fpubh.2018.00013
11. Mason J, Greiner R, Shrimpton R, et al. Vitamin A policies need rethinking. Int J Epidemiol 2015;44(1):283-292. https://doi.org/10.1093/ije/dyu194
12. Benn CS, Aaby P, Nielsen J, et al. Does vitamin A supplementation interact with routine vaccinations? An analysis of the Ghana Vitamin A Supplementation Trial. Am J Clin Nutr 2009; 90(3):629-639. https://doi.org/10.3945/ajcn.2009.27477
13. West KP Jr, Sommer A, Palmer A, et al. Commentary: Vitamin A policies need rethinking. Int J Epidemiol 2015; 44(1):292-294. https://doi.org/10.1093/ije/dyu275
14. Pedro MR, Madriaga JR, Barba CV, et al. The national Vitamin A Supplementation Program and subclinical vitamin A deficiency among preschool children in the Philippines. Food Nutr Bull 2004;25(4):319-329. https://doi.org/10.1177/156482650402500401
15. Mason JB, Ramirez MA, Fernandez CM, et al. Effects on vitamin A deficiency in children of periodic high-dose supplements and of fortified oil promotion in a deficient area of the Philippines. Int J Vitam Nutr Res 2011;81(5):295-305. https://doi.org/10.1024/0300-9831/a000077
16. Delisle H. Vitamin A distribution in danger: Should we worry? Lancet 2018;392(10148):631-632. https://doi.org/10.1016/s0140-6736(18)31667-2
17. Van Jaarsveld PJ, Faber M, Tanumihardjo SA, et al. Beta-carotene-rich orange-fleshed sweet potato improves the vitamin A status of primary school children assessed with the modified-relative-dose-response test. Am J Clin Nutr 2005;81(5):1080-1087. https://doi.org/10.1093/ajcn/81.5.1080
18. United Nations Children's Fund (UNICEF). Coverage at a Crossroads: New Directions for Vitamin A Supplementation Programmes. New York: UNICEF, 2018. https://reliefweb.int/sites/reliefweb.int/files/resources/Vitamin-a-report-web.pdf (accessed 23 April 2019).
19. Mason JB, Margetts BM. Magic bullets vs community action: The trade-offs are real. World Nutrition 2017;8(1):5-25. https://doi.org/10.26596/wn.2017815-25
20. Greiner T, Mason J, Benn CS, Sachdev HPS. Does India need a universal high-dose vitamin A supplementation program? Indian J Pediatr 2019;86(6):538-541. https://doi.org/10.1007/s12098-018-02851-x
21. Sommer A. Vitamin A, infectious disease, and childhood mortality: A 2c solution? J Infect Dis 1993;167(5):1003-1007. https://doi.org/10.1093/infdis/167.5.1003
22. Benn CA, Fisker AB, Wieringa FT, et al. Vitamin A distribution in danger: Should we worry? Lancet 2018;392(10148):631. https://doi.org/10.1016/s0140-6736(18)31547-2
23. Benn CS, Aaby P, Arts RJ, et al. An enigma: Why vitamin A supplementation does not always reduce mortality even though vitamin A deficiency is associated with increased mortality. Int J Epidemiol 2015;44(3):906-918. https://doi.org/10.1093/ije/dyv117
24. Benn CS, Aaby P, Fisker AB. Lessons learned from the testing of neonatal vitamin A supplementation. Nutrients 2019;11(2):449-459. https://doi.org/10.3390/nu11020449
25. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. Am J Clin Nutr 2006;83(2):191-201. https://doi.org/10.1093/ajcn/83.2.191
26. National Department of Health, South Africa. Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act No. 54 of 1972). Regulations relating to the fortification of certain foodstuffs, 2003. Government Notice No. R 2003. http://www.health.gov.za/index.php/2014-03-17-09-09-38/legislation/joomla-split-menu/category/123-reg2003=265:regulations-relationg-to-the-fortification-of-foodstuffs (accessed 28 October 2019).
27. Tanumihardjo SA, Kaliwile C, Boy E, et al. Overlapping vitamin A interventions in the United States, Guatemala, Zambia, and South Africa: Case studies. Ann N Y Acad Sci 2018;1446(1):102-116. https://doi.org/10.1111/nyas.13965
28. Nel J, van Stuijvenberg ME, Schoeman SE, et al. Liver intake in 24 - 59 month old children from an impoverished South African community provides enough vitamin A to meet requirements. Public Health Nutr 2014;17:2798-2805. https://doi.org/10.1017/S1368980013003212
29. Van Stuijvenberg ME, Dhansay MA, Nel J, et al. South African preschool children habitually consuming sheep liver and exposed to vitamin A supplementation and fortification have hypervitaminotic A liver stores: A cohort study. Am J Clin Nutr 2019;110(1):91-101. https://doi.org/10.1093/ajcn/nqy382
30. Verguet S, Jassat W, Bertram MY, et al. Impact of supplemental immunisation activity (SIA) campaigns on health systems: Findings from South Africa. J Epidemiol Community Health 2013;67(11):947-952. https://doi.org/10.1136/jech-2012-202216
31. Hanvoravongchai P, Mounier-Jack S, Oliveira Cruz V, et al. Impact of measles elimination activities on immunization services and health systems: Findings from six countries. J Infect Dis 2011;204(Suppl 1):S82-S89. https://doi.org/10.1093/infdis/jir091
32. Doherty T, Chopra M, Tomlinson M, et al. Moving from vertical to integrated child health programmes: Experiences from a multi-country assessment of the Child Health Days approach in Africa. Trop Med Int Health 2010;15(3):296-305. https://doi.org/10.1111/j.1365-3156.2009.02454.x
33. Gray A, Vawda Y. Health legislation and policy. In: Rispel LC, Padarath A, eds. South African Health Review 2018. Durban: Health Systems Trust, 2018. https://www.hst.org.za/publications/South%20African%20Health%20Reviews/SAHR%202018.pdf (accessed 21 May 2019).
34. GBD Compare | Viz Hub. Institute for Health Metrics and Evaluation (IHME), University of Washington, 2015. https://vizhub.healthdata.org/gbd-compare/ (accessed 10 June 2015).
35. Wirth JP, Petry N, Tanumihardjo SA, et al. Vitamin A supplementation programs and country-level evidence of vitamin A deficiency. Nutrients 2017;9(3):190. https://doi.org/10.3390/nu9030190
36. National Department of Health, South Africa. National Vitamin A Supplementation Policy Guidelines for South Africa: 2012. Pretoria: Nutrition Directorate, NDoH, 2012. http://www.adsa.org.za/Portals/14/Documents/DOH/Vit%20A%20policy%20guidelines%20OF%20S%20A%20-%20recent_1.pdf (accessed 11 May 2019).
37. Biering-Sørensen S, Aaby P, Lund N, et al. Early BCG in Denmark and neonatal mortality among infants weighing <2500 g: A randomized controlled trial. Clin Infect Dis 2017;65(7):1183-1190. https://doi.org/10.1093/cid/cix525
38. World Health Organization. Guideline: Vitamin A supplementation in infants and children 6 - 59 months of age, 2011. https://www.who.int/nutrition/publications/micronutrients/guidelines/vas_6to59_months/en/ (accessed 22 May 2019).

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