Editorials

Universal Vitamin A Supplementation Programme in India: The need for a re-look

Vitamin A is an essential nutrient needed in small amounts for normal functioning of the visual system, growth and development, maintenance of epithelial cellular integrity, immune function and reproduction. Severe deficiency of vitamin A is known to produce corneal xerophthalmia or keratomalacia and blindness in children. Vitamin A deficiency is seen mainly in young children in developing countries. The main causes of childhood vitamin A deficiency in the developing world include maternal vitamin A deficiency resulting in low concentrations of vitamin A in breast milk, inadequate dietary intake of vitamin A during and after weaning, and repeated bouts of common infectious illnesses (diarrhoea, measles and acute respiratory infection), which further decrease vitamin A levels. This micronutrient gained public health importance in the mid-1960s because of its ability to prevent nutritional blindness. Subsequently, vitamin A supplementation became the centre of attention because of its reported child survival benefits.[1] Periodic vitamin A supplementation to children over 6 months of age is being implemented in over 70 countries and is considered by many international agencies to be one of the most effective public health interventions ever undertaken.[2] However, this view is being contested by international and Indian scientists who stress that these claims are exaggerated and misleading.[3–7]

GENESIS OF THE UNIVERSAL VITAMIN A SUPPLEMENTATION PROGRAMME IN INDIA

The National Prophylaxis Programme against Nutritional Blindness was initiated in 1970 as an urgent remedial measure to eliminate the unacceptably high magnitude of xerophthalmic blindness.[8] All 1–5-year-old children were to be administered 200 000 i.u. of vitamin A orally once in 6 months. During the early 1990s this intervention was restricted to children between 9 months and 3 years as clinical deficiency was almost exclusively restricted to this age range.[9] In 2005, an expert group chaired by the Director General, Indian Council of Medical Research endorsed 9 months to 3 years as the target age group for universal vitamin A supplementation (UVAS). However, digressing from this counsel, in 2006 the age group was broadened to include children between 6 months and 5 years after reconsidering recommendations of the WHO, UNICEF and Ministry of Women and Child Development.[10] The stated objective of the UVAS programme in India remains unaltered since inception; however, the current advocacy for intensification and increase in age range primarily pertains to child survival benefit.

SECULAR TREND IN CLINICAL VITAMIN A DEFICIENCY: SIGNAL FOR POLICY MODIFICATION

In under-5 children, clinical vitamin A deficiency including severe xerophthalmia was a major public health problem in the early 1960s. However, in the past 4 decades keratomalacia has almost disappeared and there is a sharp decline in the prevalence of Bitot's spots.[11,12] Recent surveys indicate that the prevalence of Bitot's spots is

>0.5% (conventional cut-off to define public health problem) in a few isolated geographical pockets, which are socio-economically backward with poor health infrastructure.[9,11,12]

This observed decline is largely due to the implementation of relevant developmental and health initiatives in the country. This has led to better food availability, immunization coverage, access to healthcare facilities and management of childhood diseases. The available evidence indicates that this decline cannot be attributed to the UVAS programme. The latest national survey revealed that only 18% of eligible children received vitamin A supplementation.[13] Further, the predominant decline in clinical VAD antedated a functioning UVAS programme.[11] Conversely, an increase in coverage with UVAS in recent years has not been associated with a disappearance or substantial decline of clinical deficiency.

There is no obvious justification for continuing the UVAS programme to eliminate nutritional blindness. The available evidence too does not support a predominant role for this intervention in reducing clinical vitamin A deficiency. The advocacy for continuation and intensification of UVAS is thus now centred upon concerns of rampant subclinical deficiency and the child survival benefits. Subclinical or biochemical vitamin A deficiency is overestimated in our setting because the serum retinol cut-offs are based on western population norms, which pertain to subjects consuming primarily non-vegetarian diets and having relatively lower infectious diseases. Further, in the backdrop of intensely competing health interventions, there can be no justification for a public health programme solely for elevating biochemical parameters; it should be mandatory to unequivocally demonstrate important health or human capital benefits. As there are no obvious benefits of preventive UVAS for common childhood diseases and human capital,[14] this intervention can be justified only for the claim of mortality reduction.

CHILD SURVIVAL BENEFIT: IS IT LIKELY IN THE CURRENT INDIAN CONTEXT?

The basis for the oft-cited mortality benefits are systematic reviews,[15–17] which suggest a mortality benefit of 23%–30% in children between 6 months and 5 years of age. The data pertain to global trials conducted over 2 decades ago when the magnitude of vitamin A deficiency was much higher. Most of these studies were conducted in areas with rudimentary healthcare facilities and by the same group of investigators from the Johns Hopkins School of Public Health, USA with a documented conflict of interest. Robust external validations of these claims by other groups of independent scientists are scarce.

A systematic review of Indian trials concluded that for the prevention of mortality and morbidity, the findings of 'vitamin A trials are not consistent, and there is no evidence as yet in favour or against substantive benefit of universal vitamin A supplementation to children in India'.[18] The DEVTA trial, between 1999 and 2004, explored child survival benefits among 1 million children above 6 months of age in underprivileged, rural areas (72 blocks) of Uttar Pradesh, India with a relatively higher prevalence of clinical vitamin A deficiency. This trial with a sample size greater than all earlier global studies pooled in the meta-analyses, failed to document a child survival benefit of vitamin A supplementation.[19] However, allegedly due to pressure by the 'vitamin A lobby' the results have not been published even 6 years after completion of the study. Nonetheless, these data must be considered while formulating our national policy.

POTENTIAL HARMS IGNORED

Potentially important and serious safety concerns have been ignored while framing policy regarding intensification of UVAS. Overzealous efforts at intensification of vitamin A supplementation were associated with the death of over 30 children in Assam, probably due to micronutrient overdosage.[20] Vested interests labelled this episode as mass hysteria.[21] The explicit warning of this possibility by the Indian Academy of Pediatrics was not heeded to.[22]

Administration of a mega-dose of vitamin A is associated with an increased risk of bulging fontanelle in early infancy due to a transient rise in intracranial pressure (RR 1.53, 95% CI 1.03–2.27, Gogia S and Sachdev HPS, unpublished observations). This may occur in up to 16% of young children.[23] Infancy is a crucial period for development of the brain and the long term adverse consequences of bulging fontanel on human capital are unknown.

Systematic reviews show that vitamin A supplementation results in an increased risk of developing acute respiratory infection,[14,24] which violates the public health principle of causing no harm.

Vitamin A in large doses causes hypercalcaemia due to a direct effect on bone.[25] It intensifies the severity of bone demineralization and inhibits the ability of vitamin D to prevent such demineralization.[26] Excessive dietary intake of vitamin A in adults is associated with reduced bone mineral density and increased risk for hip fracture.[27,28] In the backdrop of high prevalence of adult osteoporosis, we need to unequivocally establish the long term safety of UVAS for bone health in young undernourished children subsisting on low calcium intakes.

Other latent but crucial implications for public health policy deserve greater attention. An intervention that was intended to be an interim 'fire fighting' exercise to control xerophthalmic blindness is now a permanent 'quick fix' due to several reasons including commercial, which have been recently commented upon.[3] Intensification and permanency of such 'quick fixes' is an important barrier to sustainable solutions, the development process and self-sufficiency in India, which is struggling to prioritize competing interventions within the available financial resources. Local evidence and the opinion of national scientists and professional organizations have been repeatedly ignored in preference to international experience and vested interests. These potential negative consequences alone provide enough rationale for discontinuing UVAS.

THE WAY FORWARD

The current evidence suggests that UVAS cannot be justified as a public health intervention for prevention of xerophthalmic blindness or childhood mortality in India. The continuation and intensification of UVAS despite consistent opposition from Indian scientists is proving detrimental for our public health needs. We suggest a dispassionate, national evidence-based process to examine an appropriate shift in the vitamin A supplementation policy.

COMPETING INTERESTS

None

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Emerging carbapenem resistance in the context of a new metallo-β-lactamase (NDM-1)

Multidrug-resistant bacteria are an emerging problem that infection control practitioners, researchers, hospital epidemiologists and clinicians are struggling to overcome. In the battle between bacteria and mankind, bacteria are constantly evolving newer mechanisms of resistance, which makes the latest group of antibiotics ineffective. The strategy to win this battle would be to use a holistic approach of awareness, surveillance, research, implementation of appropriate policies and the realization that antibiotics may not be the only answer to bacterial resistance.

Carbapenems, till recently, were the last resort for the treatment of severe infections. However, the emergence of carbapenem resistance in *Enterobacteriaceae* worldwide has further limited the treatment options available.[1,2] Carbapenem resistance in *Enterobacteriaceae* can occur due to modifications of outer membrane permeability of these bacteria, along with production of extended spectrum beta-lactamases (ESBLs) or over-expression of AmpC type β-lactamases. This mechanism of permeability change and expression of ESBL/AmpC is generally weakly active against carbapenems. The other, more important, mechanism of resistance is production of carbapenemases. Carbapenemases are a family of β-lactamases with a spectrum of activity unrivalled by other β-lactam-hydrolysing enzymes.[2] Acquired carbapenemases can either be metallo-β-lactamases (MBLs) such as VIM and IMP, or non-metallo-β-lactamases such as IMI/NMC, SME, KPC or OXA. Both groups of enzymes hydrolyse carbapenems well. The major concern is the carbapenemases as they are present in mobile genetic elements and can be easily disseminated.

Recently, a new MBL, designated New Delhi metallo-β-lactamase-1 (NDM-1) has been detected in *Escherichia coli* and *Klebsiella pneumoniae* from various parts of the world, both developing and developed nations—UK, India, Pakistan and Bangladesh.[3,4] This new member to the already proliferating group of carbapenemases has caused added concern as infections due to such organisms are reported to be virtually impossible to treat. The concern is reasonable but the expression of that concern is not.

The article by Kumaraswamy *et al.* has triggered a reaction all over India.[4] There are two aspects of this: first, the presence of this gene in *Enterobacteriaceae* in India, and secondly the naming of this enzyme as New Delhi metallo-β-lactamase and connecting it to medical tourism. These two aspects need to be examined separately.

The article by Kumaraswamy *et al.* shows isolation of NDM-1 harbouring isolates from 9 locations in India, 8 cities in Pakistan and Dhaka, Bangladesh.[4] This indicates that the plasmid is widely distributed in the subcontinent. Our experience in a remote neonatal set up in India also showed that the presence of this gene is a reality. In November 2009, 4 neonates developed sepsis with carbapenem-resistant *E. coli* carrying NDM-1. While the emergence of this new mechanism is bad news, the good news is that simple measures such as handwashing and hand hygiene with antiseptic agents could prevent the spread of NDM-1 even in susceptible neonates. Enforcement of cleaning hands with chemical disinfectants apart from routine handwashing with soap and water controlled the spread of the infection. In the following 10 months, we closely monitored the situation and no more neonates with septicaemia due to $bla_{\text{NDM-1}}$ have been detected.

The other aspect is about the nomenclature of the enzyme. The naming of the enzyme has become a bigger controversy, particularly because the earlier authors in their conclusion linked this to avoiding medical treatment in India. This implication of NDM-1 and avoiding medical tourism is not appropriate. Just because this enzyme was found in a patient who had travelled to India does not necessarily mean that the NDM-1 gene originated in India. Extensive epidemiological investigations are needed to establish that it originated in India. Nevertheless, the naming of this enzyme would not have been objectionable if it had not been linked aggressively with medical tourism. It should be noted that carbapenem resistance due to other enzymes, also on mobile genetic elements, such as the KPC (*Klebsiella pneumoniae* carbapenemase)

has been reported from many parts of the world.[1] The National (UK) Resistance Alert of the Health Protection Report specifically mentioning $bla_{\text{NDM-1,}}$ issued on 3 July 2009, mentions the importation of carbapenemase (other than NDM-1) carrying organisms into UK from a number of sites in the Eastern Mediterranean.[5]

One has to accept that prescription policies, over-the-counter availability of drugs, use of antibiotics in animal fodder and infection control policies in India have compounded the problem of antibiotic resistance. However, antibiotic resistance is a global problem and numerous articles in reputed journals have documented this fact.[6–8] The essentials of better control of antibiotic resistance are known—enhanced surveillance, reduction in the consumption of antibiotics and improved hygiene. It is important to know the breadth of this problem in India so that corrective measures can be taken to combat this problem. Surveillance data even at the local level would help doctors choose appropriate antibiotics. To reduce antibiotic consumption what is needed is education of doctors to change their prescription policies and measures to improve public awareness on the risks and benefits of antibiotic use.[7,9] Improving hygiene can also have a remarkable impact on decreasing resistance in bacteria. Adherence to protocols in hospitals and continuous staff training can bring down resistance rates.

While the reaction in India to NDM-1 is understandable, this should not deter microbiologists, infection control practitioners and clinicians from conducting research and publishing their work as only research can show the path ahead. Our experience has shown that a simple meticulous handwash could go a long way in treating this problem even in susceptible neonates. The reduction in the chasm between what we know and what we do about it will go a long way towards solving this problem.

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