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Should universal distribution of high dose vitamin A to children cease?

Up to $500m a year could be put to better use by stopping ineffective and potentially harmful supplementation programmes in poorer countries, say **JB Mason**, **CS Benn**, and **HPS Sachdev**; but **Keith P West Jr**, **Amanda C Palmer,** and **Alfred Sommer** disagree, saying that such programmes have been proved to save millions of lives and should be withdrawn only when robust evidence permits

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Yes—JB Mason, CS Benn, HPS Sachdev

Some 270 million children aged 6 to 59 months, in 60 to 80 low and middle income countries, receive high dose vitamin A capsules (200 000 IU, about 100 times the daily recommended intake) twice a year, according to reports from Unicef[1] and Nutrition International.[2]

These programmes, intended to reduce child mortality, are no longer effective, are wasteful, and are of doubtful safety. But this is disputed. Two key questions emphasise the main disagreements.

Programmes don't reduce deaths

The first key question is: what impact do these programmes have on child mortality today? Deaths prevented by intermittent high dose vitamin A supplements in the 1980s and 90s were primarily from measles and diarrhoea[3]; measles now has low incidence, with high vaccination coverage, and diarrhoea is better managed.[4] Re-analysis of a Ghanaian study showed that only unvaccinated children benefited.[5]

Even if programmes did have the same impact today, with as much as a 23% reduction in mortality among 6 to 59 month old children, we could expect only a 2% reduction in the 0 to 59 month mortality rate.[6-8]

In addition, the two studies reported since 2000[9 10] showed these programmes had no impact on mortality. Meta-analyses of data in systematic reviews are being misinterpreted when assessing current impact on mortality. Results of trials done after 2000 are pooled with those from before 2000, which make up around 80% of the analytical weight; crucially, they do not consider changes over time, such as vaccination coverage.[6]

The argument that meta-analyses still show reduction in child mortality is correct only in that recent meta-analyses give similar results to those from 20 years ago—which is unsurprising with the weight given to older studies.

The largest recent study, of two million Indian children,[9] assessed effectiveness (real world impact) using the existing distribution structure. Under field conditions, it found no effect on mortality, which may indeed be because of implementation. Our opponents' criticisms of the study as if it were an efficacy trial (impact in ideal circumstances) miss the point: no reduction in mortality is likely with similar programmatic conditions.

New understanding about how high dose vitamin A reduces deaths helps to explain field results, and inform expectations from changes in immunisation and disease patterns in the past 20 to 30 years.[11] Further, evidence indicates that high dose vitamin A distribution could put some groups at risk of harm—for instance, girls who also get vaccines containing diphtheria-tetanus-pertussis.[11]

Importantly, high dose supplements do not reduce child mortality by reducing vitamin A deficiency. Initially, the

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estimated impact of distribution was found to be unrelated to the prevalence of deficiency.[3 11] More recently, it has been shown that distribution of high dose supplements has little effect on deficiency.[4 6 12] Therefore, making programmes contingent on a population's vitamin A deficiency makes little sense, and the suggestion by our opponents to wait for prevalence of deficiency to drop to 5% before abandoning programmes is absurd, especially because programmes do not contribute to reducing deficiency.

Costs and opportunity costs

The second key question is: what is the cost and opportunity cost in relation to child mortality of current programmes? There are direct costs, which at $1 per child per six months could amount to more than $500m (£351m; €402m) a year.[13 14] And opportunity costs include using health workers for distribution.[15]

These costs should be compared with those for other interventions to reduce child mortality. For example, BCG vaccination at birth may reduce neonatal mortality by at least 30%.[16] Programmes with broader impact on child welfare—community based programmes, for example—might also be better justified.

Prevalence of vitamin A deficiency remains around 30%.[6 7] Several low dose interventions of well established effectiveness, such as fortification, exist[17] and should replace high dose supplementation. High dose vitamin A distribution is the only intervention that does not reduce prevalence of deficiency.[6]

Such programmes, started as a stop-gap measure in an era of extensive and severe deficiency, have become permanent, notwithstanding contemporary evidence. Despite opposition,[18] blanket supplementation continues across all Indian states, including those such as Kerala where under 5 mortality is comparable with that of richer countries.

Advocates for high dose vitamin A programmes refer to 20 year old data; have not shown cost effectiveness; and ignore data that show these programmes do not prevent deficiency and could cause harm in subgroups. In the interest of the world's children, blanket programmes should be stopped now.

No—Keith P West Jr, Amanda C Palmer, Alfred Sommer

Periodically it is appropriate to re-evaluate public health interventions. Here, we revisit the continued public health impact and need for six monthly, large dose, oral vitamin A supplementation programmes in low income countries.[19] Existing since the early 1970s, universal supplementation has been expanded in recent decades for its proved ability to reduce preschool child mortality, by 23% to 34%, in undernourished populations.[19-21]

Today, vitamin A supplementation is estimated to reach around 70%, or up to 270 million, 6 to 59 month old children, twice each year, in 82 countries,[22] based on reports from countries with reliable reporting (Unicef, personal communication, 2017). Should this programme categorically cease, as Mason and colleagues argue in this debate, or continue, with a rational plan to phase out once safe and appropriate to do so?

Gather evidence, then shift policy

We have long argued that a policy shift away from vitamin A supplementation be guided by evidence of a low prevalence of deficiency and dietary adequacy in populations at risk.[19 23-25] Although regional estimates of deficiency are broadly informative,[26 27] they are of uncertain validity for within country estimation and limited value for decision making, as they are often modelled from sparse and often outdated surveys.[25-27] Further, vitamin A deficiency can vary markedly among countries within a region.[26 27] Thus, extant survey data should be consulted, or collected anew, to guide a country's decision of whether or not to phase out vitamin A supplementation.

Despite its efficacy in reducing mortality, xerophthalmia,[19] and hearing loss from severe otitis media,[28] the evidence available indicates that periodic vitamin A supplementation raises serum retinol in an undernourished population only for a few months, even though its clinical benefits last 6 months or longer.[19] On the other hand, adequate dietary vitamin A intake has a cumulative effect on stores, and therefore sustainably increases serum retinol concentrations to a normal range.[24] A serum retinol survey carried out 3 to 5 months after supplement dosing is therefore unlikely to reflect effects of supplementation, but will reveal the adequacy (or not) of children's underlying dietary intakes of vitamin A.

It would be dangerous and foolhardy to consider discontinuing supplementation before documenting dietary adequacy, demonstrated by a stable, low prevalence of vitamin A deficiency (serum retinol <0.70 μmol/L)[26] in the targeted child population, not exceeding 5%.[24] To add assurance, the upper 95% confidence limit should be <10%, the minimum WHO recommended prevalence for vitamin A deficiency to be classified as a moderate to severe problem.[26]

Mason and colleagues call for the immediate cessation of vitamin A supplementation, declaring it expensive, ineffective, harmful, and wasteful. We are unsure of the sources of their information. The evidence supporting the value of vitamin A supplementation in safely reducing child mortality has no parallel in the field of nutrition.

Vitamin A still reduces mortality

Based on eight large and diverse trials in the 1980s and 90s,[19-21] the World Bank in 1993 declared vitamin A supplementation as one of the most cost effective of all health interventions in reducing child mortality.[29] Fifteen years later, in 2008, the independent Copenhagen Consensus ranked vitamin A supplementation highest among 40 carefully evaluated health interventions globally for reducing child mortality, citing a cost-benefit ratio of 17:3 and recommending greater integration with other primary healthcare programmes to improve coverage.[30]

Has the evidence suddenly changed in the past several years to now warrant global cessation of vitamin A supplementation? The answer is no. The most recent Cochrane systematic review, in 2017, has added dozens of more recent vitamin A interventions that were not designed, powered, or implemented to determine impact on child mortality; nonetheless, it still projects that vitamin A supplementation can reduce all cause mortality by 12% to 24%,[31] with the lower estimate entirely dependent on including the negative results of a vastly under-resourced programme evaluation in India[32] that failed to meet even minimal criteria of a randomised, controlled clinical trial.[25]

In summary, there are always good reasons to reconsider the continuing value of most public health interventions, including ones tackling vitamin A deficiency. But following the critical admonition, first do no harm, effective programmes should not be discarded until it is clearly shown that they are no longer needed, or that more efficient programmes can effectively replace them.[24]

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