BEST PRACTICE PAPER

MICRONUTRIENT SUPPLEMENTS FOR CHILD SURVIVAL (VITAMIN A AND ZINC)

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EXECUTIVE SUMMARY

The 2008 Copenhagen Consensus ranked micronutrient supplements as the top development priority out of more than 40 interventions considered. Specifically, vitamin A supplementation for children (every 4-6 months, from age 6 months to 5 years) and therapeutic zinc supplementation for diarrhea (10-14 days of supplementation, up to the age of 5) were considered. Vitamin A supplementation can reduce all-cause mortality for children 6-59 months by 23%, and several studies suggest that therapeutic zinc supplements for diarrhea can reduce diarrheal mortality below the age of five by 50%.

Up to 219 million children worldwide are susceptible to vitamin A deficiency, and over 1 billion people to zinc deficiency, with South Asia and sub-Saharan Africa the highest priority regions.

Large-scale vitamin A supplementation programs have been underway for a decade, and currently reach just over 70% of under-fives with two doses per year in South Asia and sub-Saharan Africa. The challenge ahead is to ensure that the remaining countries achieve the required minimum delivery of two doses per year on a regular basis, and to extend coverage in all countries to the "hard-to-reach", raising coverage overall to 90% and above. Aiming for universal coverage is a key step towards meeting the Millennium Development Goal of child survival.

Long-term sustainability of these programs requires combining the use of routine primary health care systems with outreach. Outreach can be particularly cost-effective when vitamin A supplementation is combined with the delivery of other services such as deworming, distribution of bednets, etc. Long-term financial sustainability is enhanced when developing countries take over the domestic distribution and administration costs, even if they continue to rely on external support for capsule procurement.

International recommendations for the use of therapeutic zinc supplements for diarrhea date from 2004. Although much work is in progress in several countries, only Bangladesh so far is in process of a national scale-up. International support is needed for strong advocacy, technical assistance and start-up costs, as well as to subsidize the initial procurement of supplements for low-income countries.

Therapeutic zinc supplementation has good potential for becoming self-sustaining. Technology allows for local production of supplements. Pilot studies suggest that households who currently make inappropriate use of medications which are ineffective against diarrhea, can see the benefits of switching to zinc supplements combined with oral rehydration salts.

The first phase of intervention with therapeutic zinc would likely involve reaching those children already reached by oral rehydration therapy (38% of children in the target 60 countries, largely in South and Southeast Asia and sub-Saharan Africa). The second phase would involve extending both zinc and low osmolarity oral rehydration therapies to children currently not reached, as the benefits of zinc supplementation will increase the attractiveness of oral rehydration.

Costs per child of supplementation vary by region, by degree of existing coverage, and can be reduced by combining supplementation with other programs. Our estimates for vitamin A are for a total delivery cost of $1.20 per child per year for South Asia and sub-Saharan Africa for up to 80% coverage in-country (including people's time for distribution). The estimated cost would be similar for East Asia, about 35% higher for Central Asia, and about 120% higher in Latin America. Incremental costs per child in a given country would potentially double in order to reach the "hard-to-reach" and therefore to move from 80% to 90% coverage in-country.

Benefit:cost ratios for vitamin A supplementation (using $60/DALY saved) are estimated as 17:1 (3% discount rate; DALY valued at $1000, which is reasonable for the low income regions). The benefit:cost ratio is correspondingly lower in higher-cost regions; it may or may not go down when extending coverage to the "hard-to-reach" since this group may also obtain greater benefits.

There are no national programs for therapeutic zinc supplementation from which to obtain cost data. Likely $1 per child per year would cover 2-3 episodes of diarrhea in the South Asia and sub-Saharan Africa, with cost premia in other regions similar to those for vitamin A. This would allow for coverage of up to 38% (the current coverage of oral rehydration therapy). Additional program experience is needed before costs for further expansion beyond 38% of children are known.

These two interventions are therefore inexpensive on a per-child basis, highly beneficial, operationally feasible, and have the potential to assist significantly with the child survival Millennium Development Goal.

INTRODUCTION

In the Copenhagen Consensus, 2008, a group of world-renowned economists ranked micronutrient supplements (specifically high-dose vitamin A, and therapeutic zinc supplements for children with diarrhea) as the top international development priority. The criteria used included the benefit:cost ratio, as well as feasibility and sustainability of the interventions (http://www.copenhagenconsensus.com).

Undernutrition remains a major issue in developing countries, being an underlying cause of 3.5 million deaths each year (Black et al, 2008). It is estimated that up to 219 million children are deficient in vitamin A (Mason et al, 2005) and over 1 billion people are susceptible to zinc deficiency (Black et al, 2008). Children with these deficiencies are significantly more likely to experience morbidity and mortality. Vitamin A deficiency in newborn babies, infants, and children accounts for about 6% of under-5 deaths, 5% of under-5 DALYs (disability-adjusted life-years), and 1·7% of total DALYs lost. Zinc deficiency accounts for about 4% of under-5 deaths and DALYs and 1% of total DALYs lost (Black et al, 2008).

Studies have shown that vitamin A supplementation (VAS) of children under five at risk of deficiency can reduce all-cause mortality by 23% (Beaton et al, 1993). This has been further supported by the recent Lancet journal series on child survival that identified vitamin A supplementation as one of the key proven interventions to reduce child mortality (Jones et al, 2003). It is no surprise therefore that in countries where vitamin A deficiency is considered a public health problem, and/or where the under-five mortality rates exceed 70/1000 live births, high-dose supplementation of all children with vitamin A every four to six months between the age of six months and five years has been an international recommendation for more than a decade. Almost all programs currently are every six months, for logistical reasons.

Good progress has been made, such that approximately 70% of children in developing countries are being covered with the necessary two preventative, protective doses a year as shown in Figure 1. However, in any given country the challenge remains in ensuring and sustaining high coverage with both doses each year: in 2006 in West and Central Africa for example, less than 50% of the countries were able to maintain coverage above 80% for both distributions (Aguayo et al, 2007).

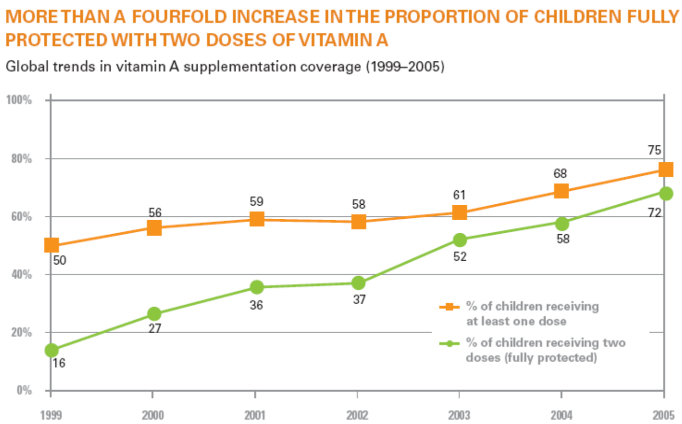

Figure 1 Progress in Vitamin A Supplementation

Source: UNICEF. A World Fit for Children Statistical Review – Number 6, December 2007

Despite progress being made, this highly beneficial, life-saving supplement needs to be extended to those children still not covered in order to succeed in reducing under-five mortality rates to meet the Millennium Development Goals (MDG's). While 70-80% and higher is considered good coverage, universal coverage is the goal. The millions of children who are still not being reached twice yearly are often the poorest and most vulnerable. Reaching them would therefore have an even greater impact on under-five mortality rates. Therapeutic supplementation with vitamin A of children who present with severe malnutrition, clinical signs of vitamin A deficiency, measles, or persistent diarrhea is also recommended and practiced in most countries.

Post-partum vitamin A supplementation for breastfeeding mothers, which is recommended to ensure that all infants receive the immune-boosting protection of vitamin A in the first six months of life, lags behind supplementation for children 6-59 months of age (UNICEF, 2007). Programs exist in only two thirds of priority countries, and most are limited in scope. In addition, a review of recent research suggests that supplementing newborns within a couple of days of birth reduces neonatal mortality (Haider and Bhutta, 2008), however it has not yet resulted in an international recommendation by WHO. If supplementing newborns was to be recommended by WHO, the recommendation for supplementation of the breastfeeding mother during the first six to eight weeks post-partum period as the best way to protect children in the first six months may be revised. International recommendations also allow for low-dose supplementation of pregnant women with xeropthalmia, but coverage is not widespread.

Recent research has demonstrated the effectiveness of zinc in treating acute, persistent and dysenteric diarrhea (see details in Section 2.2). The sample sizes are not large enough yet for definitive mortality results, but Bhutta et al (2000) estimate the mortality reduction associated with therapeutic zinc at 42% for persistent diarrhea, and Robberstad et al (2004) model the effect of a 50% reduction. Currently 1.9 million children die annually due to diarrhea (Bryce et al, 2005), hence there is the potential for saving a considerable number of lives. The recommendation for this life-saving intervention of zinc supplementation is more recent than that for vitamin A. WHO-UNICEF issued a joint statement in 2004 recommending use of zinc for 10-14 days for all episodes of diarrhea among children under 5. However, this highly beneficial intervention has not yet been widely adopted. Sustained support in the form of policy advocacy, technical assistance, capacity building, demand creation, product registration and supplies are needed to support the scale-up of zinc supplementation and low osmolarity ORS (oral rehydration salts) for the treatment of diarrhea in order to have an impact on MDG-4 on reducing child mortality in developing countries.

Supplementation with vitamin A and zinc are both key factors for child survival and have high benefit: cost ratios. This paper aims to provide a cost-benefit analysis of the specific solutions and provide decision-makers with more in-depth recommendations on project implementation at national level. Section 1 below briefly discusses the challenge of eliminating micronutrient deficiencies; section 2 describes best practices in implementing supplementation of children with vitamin A and zinc; section 3 contains some economic analysis; and section 4 briefly discusses the implications of the analysis.

1 THE CHALLENGE

The diets of poor households in developing countries are lacking in many of the key vitamins and minerals (micronutrients) which are essential to keep people strong, healthy and productive. Dietary diversification, including consumption of animal products or more fruits and vegetables, can help satisfy human vitamin and mineral requirements. Animal products are good sources of the most bioavailable forms of vitamin A and iron and of absorbable zinc; they are also higher cost items. Most poor people cannot therefore afford them and have limited opportunities to diversify their meals. In addition, during periods of increased needs or acute vulnerability, bulky everyday foods simply do not offer the necessary density of nutrients, including vitamins and minerals. Children are particularly vulnerable because of their physiological needs and vulnerability to infections.

In regions where vitamin A deficiency (VAD) is a public health problem and the under-five mortality rate is high, children under the age of five are at particular risk of further increased morbidity and mortality. They are born with negligible vitamin A stores, are exposed to frequent infections, and do not receive much vitamin A through breast milk in the first six months (particularly if their mother is malnourished). As they get older, even if some vitamin A-rich foods are available in the household, young children cannot eat enough to prevent the effects of deficiency without being supplemented. To overcome deficiency in these children by eating fruits and vegetables alone, they would have to increase their intake 10-fold (Miller et al 2002). High dose vitamin A supplementation every four to six months therefore helps to protect the child during this period of increased vulnerability.

Zinc occurs in a wide variety of food sources, but is found in highest concentrations in animal-source foods. Zinc content is also relatively high in nuts, seeds, legumes, and whole-grain cereals, and is lower in tubers, refined cereals, fruits, and vegetables. The absorption of zinc is inhibited by phytates and dietary calcium, and enhanced by protein. Thus predominantly plant-based diets with high phytate content and low consumption of animal-source foods contribute to low zinc consumption and limited absorption (Brown, 2007).

Zinc deficiency may also occur due to loss of zinc in food processing, and poor soil deprived of zinc, which can reduce the zinc content in agricultural products. Zinc deficiency is also caused due to infections that decrease appetite and food intake (e.g. respiratory infections and diarrhea), and increase zinc loss (e.g. diarrhea).

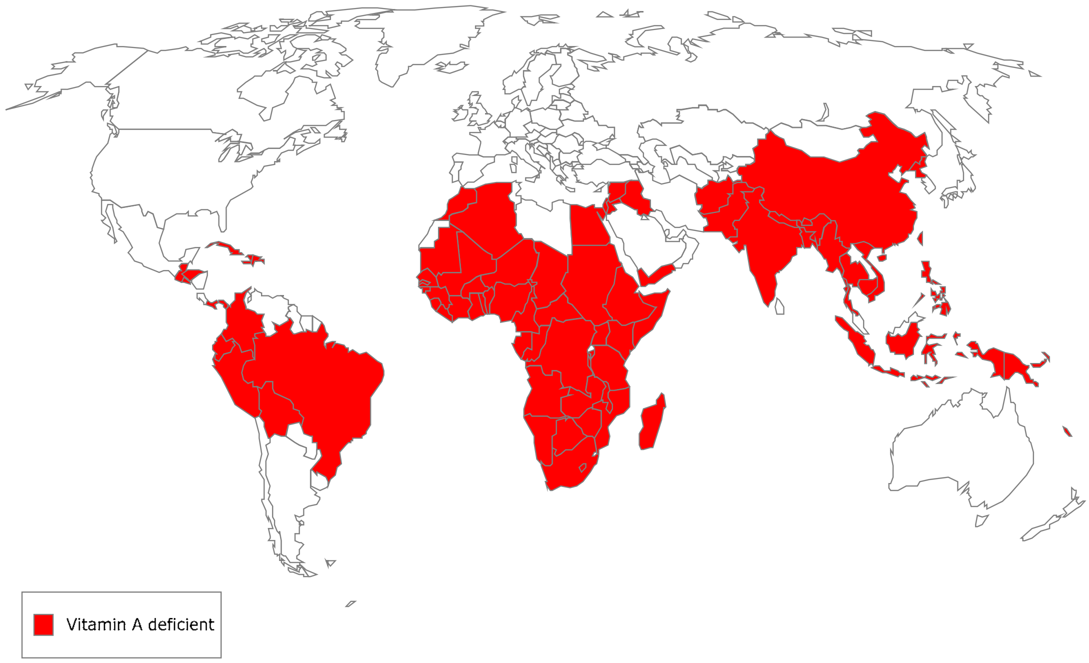

Figure 2 Prevalence of vitamin A deficiency in children under 5 years.

Source: WHO Vitamin and Mineral Nutrition Information System (VMNIS), 2008.
http://www.who.int/vmnis/vitamina/data/database/countries/en/index.html

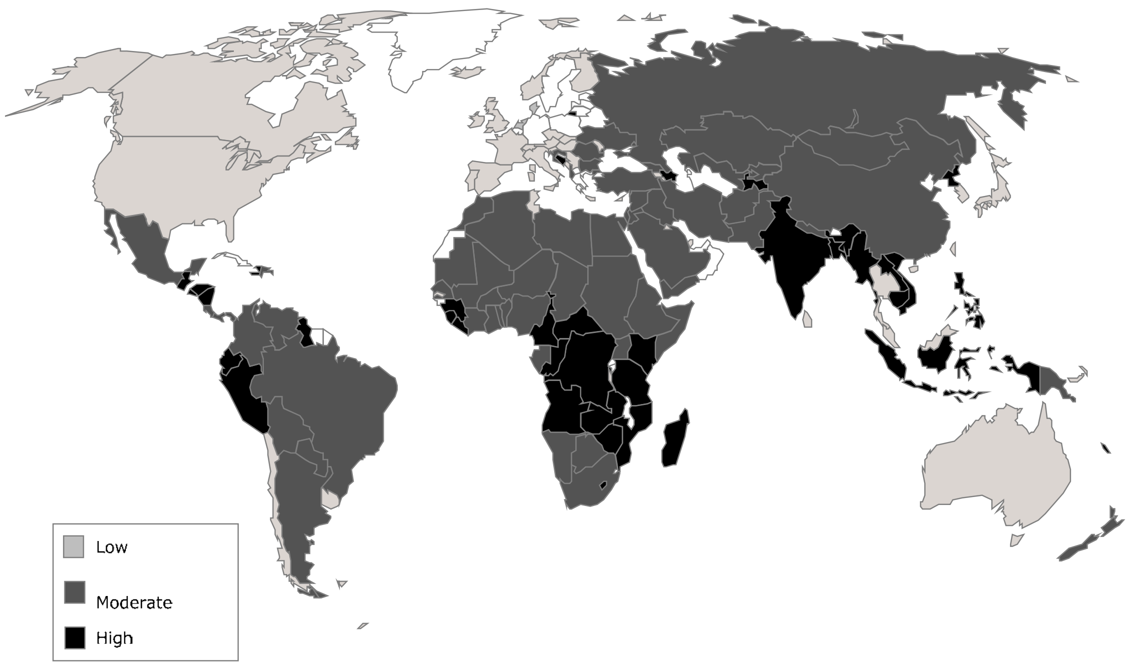

Figure 3 National risk of zinc deficiency in children under 5 years.

Adapted from IZiNCG Technical Document no 1. Assessment of the risk of zinc deficiency in populations and options for its control. Hotz C. and Brown KH, eds. Food Nutr Bull 25, 2004.

Regions where vitamin A is deficient in the diet include South Asia, most of sub-Saharan Africa, some countries in Latin America, and parts of China (Figure 2). While biochemical indicators (currently serum retinol) are used to estimate the prevalence of sub-clinical VAD in populations, an internationally accepted proxy indicating a high risk of vitamin A deficiency among children under five is under-five mortality rate exceeding 70/1000 live births. WHO and UNICEF identified 103 countries in 2006 as priority countries for VAS, due to these indicators.

The prevalence of zinc deficiency has not been adequately investigated, partly due to lack of suitable biomarkers. The recommendation is to rely on the combination of observed stunting, and zinc deficiency in the diet as assessed by food balance sheets (IZiNCG, 2004). Regions with high risk of zinc deficiency include South Asia, sub-Saharan Africa and a few countries in Latin America (Figure 3).

Both vitamin A and zinc have important roles in the immune system. The role of clinical vitamin A deficiency in measles mortality has been well understood for some decades, and a series of meta-analyses of the role of vitamin A in the early 1990's led to the consensus that vitamin A deficiency is associated with increased risk of mortality in children (23% reduction in vitamin A in supplementation trials) (Beaton et al, 1993). Black et al's (2008) most recent summary of the evidence shows that in children 6-59 months, there is a relative risk of 1.47 for diarrhea mortality and 1.35 for measles mortality associated with vitamin A deficiency in unsupplemented children. There is also a relative risk of 1.25 for deaths due to infection and due to prematurity (excluding the one-third of deaths due to prematurity in the neonatal period) in children below six months. This evidence on the effects of neonatal doses of vitamin A on mortality in the first six months of life is fairly recent and limited to Asia.

The scientific evidence of the impact of zinc deficiency and those of zinc supplementation interventions are also quite recent and the meta-analyses mostly date after 2000. The relative risk of mortality associated with zinc deficiency is estimated to be 1.27 for diarrhea, 1.18 for pneumonia, and 1.11 for malaria, with similar effects for morbidity, in trials of preventive zinc supplements. Zinc deficiency is also associated with stunting, which has significant adverse effects on health and productivity (Black et al, 2008). Recent studies (Bhutta et al 2000, Bhandari et al, 2008) suggest that therapeutic zinc for diarrhea can decrease mortality by 50%, and there are other studies likely to be published soon.

2 SOLUTIONS

2.1 Vitamin A supplementation

Brief history of program: Vitamin A supplementation on a very large scale began in the late 1990's when WHO recommended delivering vitamin A supplements along with polio vaccination during immunization campaigns, called National Immunization Days (NIDs). The percent coverage achieved became a key indicator of progress towards improved child health and is reported annually in UNICEF's State of the World's Children and was later informally adopted as an indicator of progress toward the MDG of reducing child mortality (Wagstaff and Cleeson, 2004). The scope of these immunization campaigns provided an opportunity for countries to achieve very high coverage of children under five every 6 months, however the strategy of linking vitamin A supplementation with polio NIDs was always recognized as being time-limited. As polio NIDs continue to be phased out, countries are faced with the challenge of maintaining the necessary high coverage twice a year, without the well-funded, vertical program of polio NIDs.

Many countries are now working to institutionalize twice yearly distribution using the existing health system infrastructure without the risk of drop in coverage. A series of assessments of supplementation programs in 20 countries with high under five mortality rates revealed that in many countries, vitamin A supplements are being distributed successfully through the routine, primary health care system when combined with regular, twice-yearly outreach of services targeting all children under five, such as Child Health Days (Aguayo et al, 2004). In several countries, national guidelines now define routine for vitamin A supplementation as a mix of facility-based, outreach and community-based interventions.

Successes: Until routine health services can reach all targeted children on a regular basis, outreach and biannual events such as Child Health Days will be critical to ensure full protection of children 6-59 months of age, not just with vitamin A supplements, but with other essential, preventive health services. Outreach entails not only extending the reach of the health services to all children who are live far from the health facility, but also to those older than 12 months who no longer receive regular immunizations.

For example, in Bangladesh, the strategy for vitamin A supplementation is two-fold: for children 6-11 months of age it is through the routine health services (Expanded Program of Immunization, 9 months of age measles booster) contact points, and to for children 12-59 months the twice-yearly Child Health Day approach is relied on, often called the National Vitamin A Plus Campaign. Conversely, in Kenya, twice-yearly coverage of children 6-59 months of age with vitamin A was over 80% when linked with immunization campaigns. However, in 2007 when the country decided to stop using campaigns and instead support increased delivery of routine services using fixed health facilities only (with no outreach), coverage for the full 6-59 month old age group dropped to approximately 20%. This drastic drop in coverage was not due as much to the 6-11 month old age group, whose coverage remained above 65% due to regular immunization contact points, but mainly due to the 12-59 month old age group whose coverage was less than 14% (MI, unpublished report to the government, 2008). A similar problem is observed in India in those states that rely only on routine health services such as immunization contact points to deliver vitamin A supplementation, and which are only reaching children up to 18 months of age successfully (Micronutrient Initiative - UNICEF, 2004).

Child Health Days which are a combination of fixed-site, outreach and community-based health days, offer the opportunity to strengthen the existing health system and deliver a package of essential child survival interventions. An example is in Ghana where their Child Health Days provide a package of services twice a year to over 80% of children 6-59 months, including vitamin A supplementation, immunization, deworming, re-treatment of insecticide-treated bednets, issuing of child health cards and undertaking birth registration (Aguayo et al, 2007). Another example is in Chattisgarh, India where a child protection month is celebrated twice a year (April and October) and delivers a package of services to over 85% of children. The services include vitamin A supplementation, deworming, growth monitoring, immunization focused on children never or partially vaccinated, and salt testing for iodine content in households and community feeding centers.

In Indonesia, the months of February and August are designated "Vitamin A Months", where intensified communication and social mobilization encourages mothers to bring their children 6-59 months to their nearest health post for vitamin A supplementation, nutrition counseling, immunization and growth monitoring. In the Democratic Republic of Congo, the joint delivery of vitamin A and deworming is reported to boost the attendance of immunization and vitamin A supplementation programs (Aguayo et al, 2007). Although such events require a significant amount of planning, strong logistical support and coordination among different departments of the Ministry of Health (EPI, Nutrition, Maternal Health for instance), the stakeholders and donors, they are very efficient in increasing coverage of several services at once. In fact, some countries like Senegal and Burkina Faso, are starting to use vitamin A coverage as a performance indicator of the health system (Aguayo et al, 2007).

Universal vitamin A supplementation coverage for Millennium Development Goals: While significant progress in coverage of children 6-59 months has been made over the past decade, the efforts must remain on ensuring that all children are receiving a preventive dose every four to six months until the age of five to assure the provision of full and sustained protection. While 70% coverage was at one time considered a benchmark for supplementation it really should be considered the minimum, as it is only at this level of coverage will a country achieve an impact on under-five mortality rates similar to that observed in the large-scale supplementation trials. Universal supplementation with two doses a year for the purposes of reducing child mortality is the goal. Large variations in coverage – from high levels one year to no vitamin A supplementation the next year – or high coverage in the first half of the year, and low-to-no coverage in the second half of the year - are still quite common in the vast majority of countries (UNICEF, 2007), which illustrates the challenges ahead not only to achieve universal coverage with bi-annual doses but also to sustain it.

In addition, well monitored programs are necessary to track progress, improve program delivery, and ensure that those intended to be reached are in fact being reached. Most countries will need complementary strategies to reach all children: the mainstream strategy to reach perhaps the first 80%, then the specialized, hard-to-reach strategy for the last 20%. The cost per child reached will vary between these two strategies, the "last 20%" expected to be the most costly to reach, but expected to yield a higher benefit.

Reaching the hard to reach: Although there is a strong belief that children who are currently not reached by vitamin A supplementation program are the most vulnerable and those arguably most in need, there is yet no clear picture of who are the unreached. Two studies from Indonesia suggest that children who are not supplemented come from lower socioeconomic status households, with lower immunization rates and lower parental education than children receiving supplements (Pangaribuan et al; Berger et al. 2007). Although it is assumed that the unreached live in geographically inaccessible areas, weak urban health infrastructure in poor urban areas makes health services such as Vitamin A Supplementation a challenge. Therefore in many cases the unreached may also live in or around big cities such as Nairobi and Delhi. Ongoing operations research and pilot programs comparing alternative strategies to reach hard-to-reach populations will yield cost data and a better understanding of who are the unreached. Working with local and community-based organizations or using community extenders is one way to identify and reach the hard to reach.

A successful program in rural Bangladesh initiated in 2007 provides a good model for the rest of Asia, and the world, on how to reach the unreached. It was estimated that around 600,000 children in Bangladesh, primarily from socio-economically vulnerable households were not being reached with vitamin A supplementation. Building on an already successful two-district pilot project to reach hard-to reach children, local resource persons were trained and deployed as Vitamin A Extenders in more than 12 districts, who then coordinated with government health staff and trained special community volunteers. The volunteers collected data, conducted house-to-house visits, made follow-up visits and monitored distribution. Through this outreach, not only did 360,000 formerly unreached rural children receive vitamin A, but also essential information was collected about the needs of those children so they can receive additional health and social services. Key to this success was the use of active involvement of community groups and special volunteers, including women, active in the community in monitoring, collecting data and mobilizing families with previously unreached children (Micronutrient Initiative, 2007). It cost about three times as much to reach this group of children as compared to those reached by regular distribution in 2007, although it is hoped that the differential could be reduced such that the "hard-to-reach" group would only cost 50% more than the regular distribution in future.

Supplementing mothers –Missed opportunities: Supplementation of women during the post-partum period is also an important component of vitamin A supplementation programs. Opportunities exist to administer supplements to mothers at delivery in health facilities or more commonly at home. In Nepal, community health volunteers, many of them illiterate, administer vitamin A supplements to mothers soon after birth (MOHP et al, 2007). Alternatively, mothers can receive their post-partum dose at the time of the newborn's first immunization contact for BCG. While BCG coverage is quite high in most countries (approximately 80%), not many countries actually use this opportunity to supplement new mothers with vitamin A, which clearly represents a missed opportunity (UNICEF, 2007).

Emerging research –Neonatal supplementation: While evidence has shown that vitamin A supplementation of children 1-5 months of age has no effect on child morbidity or mortality rates (WHO, 1998), recent research has shown that providing a vitamin A supplement to newborns in South Asia in the first 48 hours can reduce the risk of infant death by approximately 20% (Bhutta et al, 2008; Klemm et al, 2008). It can be expected that the cost to reach newborns with vitamin A on a large-scale in countries with low rates of assisted births will be very high, but because death rates in infants (particularly in the first month of life) are much higher proportionally than the overall under-five mortality rates, the potential impact by supplementing neonates may be significant. WHO is currently reviewing the evidence, and until that is completed and consensus attained, this age group is not yet included in the international recommendations for vitamin A supplementation.

*Ensuring supplies**:*** Globally, with Canadian (CIDA) funding, the MI donates approximately 500 million capsules per year to UNICEF for onward donation to over 70 countries to meet virtually 80% of the supply needs for children 6-59 months. Several countries however, are beginning to transition to procuring their own, which is considered progress toward program sustainability even though the cost of the supplements remains quite low compared to the total cost of the program. Other countries already cover the distribution costs themselves, or are transitioning towards this.

Financial Sustainability: Twice-yearly vitamin A supplementation of children 6-59 months through Child Health Days is considered a well-established intervention that now needs concerted efforts to progress it to a more sustained intervention in countries that have traditionally been reliant on external donor support. Even if countries continue to rely on external finance for the capsules, the ability of a country to mobilize, and provide domestic resources to cover the local distribution costs is an important step towards sustainability. A number of countries already cover these costs themselves, and a few are even moving to finance procurement of capsules.

Governments can also ensure sustainability by, for example, including vitamin A and the correlation of deficiency with mortality and poverty, in poverty reduction strategy papers and health sector development plans. This in turn may ensure that activities to reduce vitamin A deficiency for child survival are prioritized and funded. The inclusion of a budget line for child survival activities that include vitamin A supplementation in annual operational plans at all levels is an indication of commitment and progress toward sustainability. As donors increasingly give direct budget support to countries, and monitor their performance against key indicators, vitamin A coverage could be used as is currently done in a few countries.

2.2 Therapeutic Zinc supplementation for childhood diarrhea

Pairing with ORS to ensure success: Diarrhea remains a leading cause of death among infants and young children, accounting for 18% of deaths among children under 5 years of age (Bryce et al, 2005). The success of Oral Rehydration Salt (ORS) has helped to reduce the number of deaths annually from diarrhea, from 4.5 million in the early 1980's, to 1.8 million by 2002. However median coverage rates for oral rehydration therapy have hovered around 38% of episodes (Bryce et al, 2006) among the 60 UNICEF priority countries and coverage has improved little over the last few years (Bryce et al, 2008). Although many now know that oral rehydration solution could replace lost fluids, its inability to stop diarrhea makes parents seek other medicines including antibiotics (Ellis et al, 2007).

A series of large-scale trials of zinc supplementation among children suffering from diarrhea revealed that zinc-supplemented children had a significantly lower probability of continuing diarrhea (acute and persistent). In addition, zinc supplemented children had 16% faster recovery (The *Zinc Investigators' Collaborative Group,* 2000). In another large trial in Bangladesh, mortality rates (excluding deaths from injury) were 51% lower in the cluster with therapeutic zinc supplementation for diarrhea, than the control (Baqui et al, 2002).

The weight of compelling scientific evidence regarding the benefits of therapeutic zinc and its complementarities with ORS, built scientific consensus supporting low osmolarity oral rehydration salts and zinc for diarrhea management. This led to the joint WHO/UNICEF recommendation in 2004, of administering10-14 days of therapeutic zinc for children under 5 years of age. Zinc supplementation paired with low osmolarity ORS were recognized as important approaches to tackle childhood diarrhea which would be critical for achieving the Millennium Development Goal 4 on child mortality.

Moving from efficacy to effectiveness to full scale programs: need for traction:
In order to assist countries in including zinc supplementation in the management of diarrhea, three introduction studies were conducted in India, Mali and Pakistan. The aims were to assess potential constraints when implementing this new recommendation together with the administration of lower osmolarity ORS solution, as well as to determine the best possible delivery channels for zinc supplements. The preliminary results from these three large effectiveness studies clearly show that zinc encourages greater uptake of ORS and reduces inappropriate drug use. One study showed that an intervention that included caregiver education on the use of zinc and ORS during childhood diarrhea, and provision of both zinc and ORS by public and private health care providers to caregivers, was associated with reduction in the prevalence of diarrhea and pneumonia, and in all-cause, diarrhea, and pneumonia hospitalizations. The intervention also resulted in reduction in the use of unwarranted oral and injectable drugs during diarrhea, reduction in the out-of-pocket costs for care of diarrhea to the family, and substantial increase in the ORS use rates (Bhandari et al., 2008)

Nevertheless, delays in moving from knowledge to action are being currently experienced. Policy initiatives, such as the joint WHO/UNICEF statement, have not yet acquired enough momentum to ensure widespread introduction of low osmolarity ORS and zinc across the world. Only about 53 countries have included therapeutic zinc in the diarrhea management policy, and fewer than 30 countries have initiated pilot programs so far. Bangladesh is the only country to attempt a national scale-up, and Nepal is the first country to engage in large-scale social marketing, which now covers half its population (Fischer Walker and Black 2008, cited in Dary et al, 2008). Several other countries such as India, Guatemala and Bolivia are in the process of rolling out their programs.

Addressing key issues to scale up: As for any interventions that are ready to scale up, there are key elements that need to be in place to ensure its success including adapting national policy, advocacy, coordination among stakeholders, comprehensive training, ensuring supply, creating demand in country, monitoring and evaluation, and financing. In the case of therapeutic zinc supplements, the following steps are considered particularly critical in order to increase the number of countries that will effectively implement zinc supplementation programs.

- *Adapting national policy*: strong advocacy is needed to encourage Ministries of Health to include zinc and low osmolarity ORS in their diarrhea management policy as most often this prevents countries to initiate any activities. For those countries that do not procure zinc locally, the drug and regulatory authorities in countries need to be involved in these policy decisions. In some countries, support from medical and pediatric associations who have a strong influence may help to get the policy adapted, implemented and disseminated to all levels including states/provinces and districts.

- *Ensuring supply:* In March 2005, zinc was included on the WHO Essential Medicines List to enable countries to add zinc to national medicines lists and include zinc as part of their national health budgets. In order to promote production of appropriate formulations, WHO and US Pharmacopeia Drug Quality Information Program have completed a guideline to the specifications for producing zinc tablets and syrup. There are currently two products that have been registered by UNICEF for international procurement, and it is expected that another half a dozen will be approved by early 2009.

- Most countries will need initial support in the form of supplies or technical assistance for setting up local production before they are able to cater to the needs of their populations. Locally produced zinc products are now available in at least Bangladesh, Egypt, El Salvador, India, Indonesia, Nepal, Pakistan and Tanzania (Fischer-Walker and Black, unpublished document, 2008). Other local companies need to be supported to enable them to attain quality standards and production capacities to meet in country/ regional demands. In the meantime, it is critical to increase the number of manufacturers for both international and national markets as competition will reduce prices and ensure an adequate supply as demand increases.

- *Creating demand in country*: as clearly outlined in the unpublished paper by the Zinc Task Force (Fischer Walker and Black, 2008) creating demand for zinc should be coupled with that for ORS. For example, in countries where there is great demand for ORS from caregivers and health providers, the case for zinc is much easier. Where ORS uptake is not as high, additional efforts involving private sector, social marketing through mass media and local channels and community-based behaviour changes will be required.

- *Providing adequate financing for start-up*: because zinc supplementation is a new intervention, additional financing is required for all program elements such as initial procurement, policy adaptation and dissemination of guidelines, demand creation and initial training of health workers. In contrast to vitamin A programs, no major donor has yet committed to support large-scale procurement of zinc tablets, or to cover initial implementation costs. This may be a key factor which has limited the scaling-up of zinc supplementation globally.

3 ECONOMIC ANALYSIS

3.1 Vitamin A

Supplementation with vitamin A is inexpensive on a per-child basis. Costs vary widely by region, tend to be lower in large-scale government programs than smaller non-government-organization programs, and are lower when vitamin A delivery is combined with other health interventions. Reported costs are often substantially underestimated if personnel time is not included: capsule costs may be only 5-10% of costs. The authors' estimates incorporate information from Fiedler et al (2008) not available at the time of the 2008 Copenhagen Consensus (Horton et al, 2008).

Drawing on the Bangladesh pilot program to extend coverage to the hard-to-reach discussed in section 2.1, it is estimated that within countries it is possible to increase coverage from 80% to 90% at a cost per child about double the cost per child in getting to 80%. The estimates are that the total cost per child is $1.20 per year in South Asia and sub-Saharan Africa to reach 80%, the incremental cost goes up to $2.40 per child to go from 80% to 90%, and that costs in other regions are higher (Table 1).

Cost-effectiveness estimates per death-averted are $64-294 for a range of countries (Ching et al 2000): $289-489 for Nepal, using community health workers (Fiedler, 2000); $100-$500 for eight low-income Asian countries (Horton, 1999, using PROFILES models and a cost of $0.20 per child per year); and $228 for Child Health Days in Ethiopia, which corresponds to $9 per DALY saved (Fiedler and Chuko, 2008). In Ethiopia, the cost per child per year was $1.12 (based on two rounds of supplementation, also combined with deworming and nutrition screening).

Table 1 Estimates of total cost of supplementation per child per year, by region and level of coverage.[a]

Region(s)	Vitamin A coverage 20-80%	Vitamin A coverage 80-90%	Zinc coverage 0-40%
South Asia, Sub-Saharan Africa, East Asia	$1.20	$2.40	$1.00
Central Asia	$1.60	$3.20	$1.35
Latin America and the Caribbean	$2.60	$5.20	$2.20

[a] Cost estimates for vitamin A are based on Neidecker-Gonzalez et al (2007), Fiedler et al (2008) and estimates from Micronutrient Initiative (Mark Fryars pers. comm.), for South Asia and sub-Saharan Africa. These represent costs of programs involving outreach, assuming that 20% coverage can be achieved through the routine health services. Costs are higher in other regions, due to higher personnel costs. Cost increase factors of 35% for Central Asia, and 120% for Latin America are based on Mulligan et al (2003, revised 2005), tables 5 and 6 for costs per health centre visit, and personnel costs. It is likely that some of the expansion to 80% coverage, specifically in India, can be achieved at a lower cost of $0.60/child.
Costs for zinc are authors' estimates only, based on estimated cost of supplement and a similar ratio of supplement/personnel cost as for vitamin A. No national programs currently exist. Estimates for other regions are not included, since there are no priority countries elsewhere for supplementation with vitamin A and zinc.

Table 2 Possible regional variations in benefit:cost ratios, supplements.[a]

Region(s)	Vitamin A coverage 0-80%	Vitamin A coverage 80-90%	Zinc coverage 0-40%
South Asia, Sub-Saharan Africa, East Asia	17:1	9:1	13.7:1
Central Asia	< 13:1	< 6:1	< 10:1
Latin America and the Caribbean	< 8:1	< 5:1	< 6:1

[a] DALY value of $1000 is used throughout. If DALY value of $5000 were used in particular regions, benefit:cost ratio would be correspondingly higher. See text for explanation as to how authors generated estimates.

In the Copenhagen Consensus 2008 exercise, benefit:cost calculations were made, using a 3% and a 6% discount rate, and attaching the value of $1000/DALY and $5000/DALY. The appropriate value for the DALY in low-income countries in South Asia and sub-Saharan Africa, the priority regions for vitamin A supplements, is likely to be closer to $1000. The DALY value of $5000 is more appropriate in middle-income countries. However, these are not the priority regions for vitamin A supplementation.

Combining the cost-effectiveness results with the assumption that a DALY is valued at $1000, yields a benefit:cost ratio for vitamin A supplements as high as 100:1 (using the data from the Ethiopian program), or 17:1 (using the Horton, 1999, estimates for Asia and a cost of $1.20). The ratio of 17:1 is appropriately conservative for a range of countries (the 100:1 ratio is likely to apply only to the highest-mortality countries). This ratio applies in South Asia and sub-Saharan Africa, for coverage rates up to 80% of the population. The ratio is perhaps half of this to reach the next 10% of children (where costs approximately double as shown in Table 1). The benefit:cost ratio is lower (possibly substantially lower) in other regions of the world, where program costs are higher, and prevalence of vitamin A deficiency is lower (see Table 2).

Costs of distribution to women post-partum and to neonates are not yet available.

3.2 <u>Zinc</u>

For zinc, there are no current programs at scale. Operational research is needed to develop and test varying delivery mechanisms in the public and private sectors (formal and informal), including comparative cost analysis. Estimates of cost-effectiveness by Robberstad et al. (2004) suggest that the incremental cost of zinc as part of case management is $0.47 per course of treatment, leading to an average cost of $73 per DALY gained, and $2,100 per death-averted. The cost of tablets are about $0.02 each, hence a course of the tablets costs about $0.19, with the additional costs representing distribution and administration. A broad cost analysis for a micronutrient investment plan for India in 2005-06 estimated that it would cost US $ 0.35 per child per episode, including programmatic costs (Micronutrient Initiative, 2006) for a scale up of therapeutic zinc for childhood diarrhea.

Preliminary results from the economic evaluations performed in India and Pakistan (WHO/CAH et al, 2008), based on the large-scale effectiveness trials have shown that:

- Zinc is cost effective in treating diarrhea in patients under 5 years as compared to ORS alone in this setting
- The introduction of zinc led to a decrease in out of pocket payments for medicine/ consultation fees of over USD$1.00 per patient per episode in both India and Pakistan;
- In Pakistan, the addition of zinc to the treatment of diarrhea makes it approximately twice as expensive as with oral rehydration salts alone, but it reduces deaths by one third.
- Incremental Government staff time costs are negligible.

If coverage were extended to 40% of children under 5 in sub-Saharan Africa and South Asia (including also Southeast Asia) this would be 40% of 300 million children, which (at $1 per child per year) would come to $120 million. The international commitment could be lower if richer households in these countries switched from buying antibiotics which are ineffective except against dysentery, and instead purchased zinc tablets, and if national governments co-shared the costs. The Zinc Task Force (2006: unpublished) has developed estimates of needs for international assistance, assuming that the middle income developing countries purchase the zinc tablets themselves, and the poorer countries receive an initial subsidy.

4 IMPLICATIONS AND CONCLUSIONS

Vitamin A supplementation for young children and therapeutic zinc supplements for management of diarrhea in young children were ranked as the top international development priority by a group of world-renowned economists. Twice yearly vitamin A supplementation is now occurring in many countries as part of a minimum package of health services. However, the challenge is to ensure that the remaining 30% of children, who are not covered, are being reached to ensure and sustain universal supplementation for child survival. This requires additional resources to "do that last mile" and commitment from governments to mobilize and efficiently use supplementary resources. Countries which are lagging behind need to adopt best practices including twice yearly events like CHDs to extend the outreach of the primary health care system, identifying those who are regularly unreached, and using of vitamin A coverage as a health performance indicator.

International financial support still covers the majority of the cost of the vitamin A supplements, although a few countries are now purchasing their own. The high-dose vitamin A capsules are produced by a very small number of suppliers internationally because they are a highly specialized low-cost commodity that does not have a market outside of public health programs for child survival. Local production of high quality capsules is limited, and so international support for procurement and facilitating access to a global supply is likely to continue to be needed, particularly for poorer countries with limited supplies of foreign exchange and for countries with small populations whose annual supply needs are not large enough to procure independently.

Experience with zinc supplementation as an adjunct treatment for diarrhea is more recent. Zinc supplementation programs have been very slow to roll out at national scale in spite of strong evidence of efficacy and more recently, effectiveness. The few countries that have shown encouraging progress have adapted their management diarrhea policy to include zinc, registered the product in the case of local production, ensured sufficient supply, and created demand through social mobilization and marketing.

Therapeutic zinc supplementation has to begin from the outset integrated into the primary health care system, unlike many other initiatives which began as vertical programs. Zinc supplements can work synergistically with ORS and help increase use of ORS. Since the zinc supplements can be produced locally in many countries, this also will help the transition to sustainability. Richer households (who already purchase antibiotics for their children with diarrhea) may be encouraged to switch to purchasing zinc, which can help alleviate the burden on the government health budget. The most urgent issue for therapeutic zinc supplements is to build momentum to initiate national programs. International financial support for start-up, and technical support, is an urgent priority.

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