GAP ANALYSIS

Defining the Issues for Vitamin A

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BACKGROUND

Vitamin A deficiency remains a widespread public health problem among women and children in the developing world. Over 20 percent of all preschool age children (~130 million) and nearly six percent of all pregnant women (~7 million) in developing regions suffer from vitamin A deficiency and its adverse health consequences (West, 2002). Deficiency of vitamin A remains the leading cause of preventable childhood blindness in the world, and a leading cause of morbidity and mortality among preschool aged children (Sommer and West, 1996; Rice et al., 2004). Guidelines for preventing vitamin A deficiency in the preschool years have long been in force (WHO, 1982), practiced, (West and Sommer, 1987) and periodically reaffirmed and updated to take into account new scientific information and programming experiences (Sommer and Davidson, 2002; Sommer, 2005). Recent studies in Southern Asia suggest that vitamin A may reduce infant mortality by 20 percent or more when given shortly after birth (Humphrey et al., 1996; Rahmathullah et al., 2003). This provides new opportunities for vitamin A deficiency control to lower mortality during this high-risk period of life. Vitamin A deficiency appears to extend through the pre-adolescent years, although both its extent and health consequences during this period of life remain uncertain (Singh and West, 2004).

Night blindness appears to reflect a stage of vitamin A deficiency that can have serious health consequence to women, including increased risks of maternal morbidity (Christian et al., 1998) and mortality (West et al., 1999; Christian et al., 2000) as well as an increased risk of infant mortality (Christian et al., 2001). During the reproductive years, vitamin A deficiency can occur, with the most prevalent symptom of night blindness often affecting 10 percent or more of pregnant women in undernourished populations (Christian, 2002). Such evidence raises the importance of preventing vitamin A deficiency during multiple, vulnerable periods of life.

The strength of existing evidence continues to inform and justify global policies and programs to prevent vitamin A deficiency during the preschool child years. Secondly, evidence continues to accumulate to reinforce, adjust, and improve efforts to reduce vitamin A deficiency in women of reproductive age, especially during pregnancy and lactation. Lastly, there is building evidence across South Asia to support developing a strategy to dose infants early in neonatal life.

INTERVENTIONS

Supplementation of Infants and Children

Pre-school Age Children

The scientific basis for providing twice-annual, high-dose vitamin A supplementation for children 6-59 months to reduce risks of mortality and nutritional blindness is unequivocal. This practice remains the most widely used intervention for preventing vitamin A deficiency in the world (Dalmiya et al., 2006). Typically, a high-potency dose of vitamin A (200,000 IU for children 12 months to 5 years, or 100,000 IU to infants 6 to 11 months of age) is distributed universally; that is, to all children in the community, every six months.

Universal distribution is usually operated on a national basis, though it can focus on sub-national population groups or regions. Globally, 58 percent of countries practicing vitamin A distribution do so on a semi-annual basis (Dalmiya et al., 2006). Vitamin A supplements can also be distributed through health outreach programs (e.g., under five growth monitoring) or limited to high-risk children presenting to clinics for treatment (i.e., children with xerophthalmia, measles, or other severe infections). Both of these approaches depend on high coverage of defined target groups, which is often not the case. Further, risk of deficiency, morbidity, and mortality often concentrates in those not reached through any of these programs (Klemm et al., 1993).

Giving a high dose of vitamin A twice a year is based on the principle that a single large dose of vitamin A is highly absorbed, stored in the liver and mobilized, as needed, over an extended period of time (West and Sommer, 1987). Guidelines have long been available for the distribution of vitamin A supplements in prevention programs (WHO/UNICEF/IVACG, 1997). Knowledge about the impact of vitamin A given to preschool children has extended to populations with HIV-positive children, who show reductions, or delays, in AIDS-related signs and symptoms as well as prolonged survival without apparent harmful effects (Semba et al., 2005). Therefore, existing guidelines for the use of vitamin A supplements in children six months to five years of age (Sommer and Davidson, 2002) appear to be robust and appropriate in virtually all vitamin A deficient preschool-aged populations.

In the late nineties, vitamin A supplementation gained a "boost" in once-annual coverage of children by being "piggy backed" onto the National (Polio) Immunization Day programs (NIDs) (Ramakrishnan and Darnton-Hill, 2002). In some countries, alternate (non-NIDs) six-monthly coverage began to be achieved through special vitamin A days or weeks (Pedro et al., 2004). With the end of NID activities over the past few years, an increasing number of countries, such as Bangladesh, Tanzania, and the Philippines, have adopted biannual special Child Health Days or weekly activities for achieving post-NID nationwide distribution. Many countries have now developed strategies for packaging other health services with vitamin A delivery, including growth monitoring, nutrition education, and other child health services. In some countries, such as the Philippines, these programs have been in effect for over ten years (Pedro et al., 2004), showing that such strategies can be sustained. However, sustainable programs of this nature depend on continued political commitment and financial resources, which may wane as other, more visible and politically sensitive health needs gain higher priority.

Achieving sustainability remains a major goal for vitamin A supplementation, as this is a donor driven intervention. The procurement of nearly five billion vitamin A supplements distributed globally over the past ten years has been supported by the Canadian Government, through the Canadian International Development Agency and the Micronutrient Initiative. While this has been a massive contribution, amounting to around $US 100 million, this program has undoubtedly provided the "nutritional vehicle" for reducing the numbers of preschool child deaths attributable to vitamin A deficiency. An estimated 1.7 million deaths (mid-range point estimate in 1991) (Humphrey et al., 1992) have been reduced to a current estimate of ~650,000 per year, leading to approximately ~1 million lives being saved per year. That makes the donor cost (excluding actual delivery costs) of $10 per death averted. Thus vitamin A supplementation continues to remain a highly cost-effective intervention, as concluded by the World Bank in 1993 (World Bank, 1993).

Still, there is a need to distribute the costs of vitamin A prevention across stakeholders, including host governments. Establishing the ability and willingness of countries currently relying on vitamin A supplementation to finance part or all of their supplement procurement costs, in the event of donor withdrawal or reduction in support, is a critical step toward achieving sustainability. In addition to the supplement costs, sustaining regular high coverage among target groups will require countries to strengthen their health delivery systems, improve capacity for community outreach and mobilization, and generate community awareness of the benefits of continued vitamin A supplementation.

Early Infancy

Early infancy represents the period of highest risk to nutritional vulnerability and death. Despite evidence that infants are born with small liver and total body stores of vitamin A (West, 2003), and show improved vitamin A status through breastfeeding (Stolzfus et al., 1993; Rice et al., 1999), there appear to be differences in how infant survival responds to vitamin A supplementation according to age at dosing, route of administration, disease status, and other nutritional factors. These differences are reflected in birth size, anthropometric status, and level of pre-maturity at birth (West, 2003). Although no formal programs currently exist to supplement infants under six months of age with vitamin A, research and programming initiatives have been directed to three approaches: a) supplementing the newborn infant; b) periodically supplementing infants from two weeks to five months of age; and c) targeting the six-month old infant for vitamin A supplementation. Except for efforts to incorporate vitamin A with DPT immunization visits (part of approach b), each represents an attempt to provide early infant care crafted around meeting a specific nutritional need. The following address these approaches in greater detail.

(a) Newborn Dosing: Four randomized, double-masked, placebo-controlled trials have evaluated the impact of dosing infants with ~50,000 IU of vitamin A within a few days after birth. Two trials carried out in Indonesia (Humphrey et al., 1996) and Southern India (Rahmathullah et al., 2003) reported reductions in infant mortality by 64 percent and 23 percent, respectively. If a third South Asian trial, in its final stages of completion in Bangladesh, finds there is a reduction in six-month infant mortality, the body of evidence may provide a "tipping point" for discussing newborn vitamin A dosing strategies for reducing infant mortality in Southern Asia.

The fourth trial, carried out in an urban clinic population of infants born to HIV- and HIV+ mothers in Harare, Zimbabwe, represents the sole newborn dosing trial completed in Africa. Among infants born to HIV- women with normal-to-marginal vitamin A status, newborn vitamin A supplementation failed to reduce infant mortality (Malaba et al., 2005). Among infants born to HIV+ women, vitamin A reduced mortality by

28 percent for those infants who were likely to have become infected with HIV in perinatal life, but increased mortality by almost two-fold for these infants who presumably became infected postnatally (Humphrey et al., 2006). These mixed findings leave the effect of newborn vitamin A supplementation in need of further research in Africa. However, among HIV+ preschool-age children (6 months to 5 years of age), as previously mentioned, the evidence suggests that periodic high-dose vitamin A supplementation (200,000 IU) is effective in decreasing mortality risk.

(b) Dosing Infants Two Weeks to Five Months of Age: Several trials of varied design have assessed the impact of dosing infants. One study periodically dosed infants in the community with 50,000 IU in the first month and 100,000 IU once more before five months of age (West et al., 1995). A second study, conducted in three countries (Ghana, Peru, and India), added vitamin A to immunization visits at 6, 10, and 14 weeks of age (WHO/CHD, 1998). Findings from these trials indicate that vitamin A supplementation was safe but not efficacious in reducing morbidity or mortality, leaving only the possibility of improving vitamin A status as the main outcome when infants are dosed in the first half of their infancy.

(c) Dosing Infants at Six Months of Age: Evidence from mortality intervention trials suggests that vitamin A can reduce mortality risk from age six months onwards (Sommer and West, 1996), motivating interest to design home-based programs to reach infants around their sixth month of life. However, there has been no program to date with this design; rather, infants are dosed during periodic delivery programs in the community at any time beyond six months of age.

Supplementation of Women of Reproductive Age

Where maternal biochemical vitamin A deficiency or night blindness exceeds tentative cutoffs of 15 percent and 5 percent, respectively, prophylactic supplementation of up to 10,000 IU daily or 25,000 IU weekly has been recommended during pregnancy (Christian, 2002). In a chronically undernourished and vitamin A-deficient population in Nepal, routine, weekly maternal supplementation with vitamin A (23,300 IU), either preformed or as beta-carotene, reduced pregnancy-related mortality by more than 40 percent (West et al., 1999). This is the first trial to link vitamin A supplementation to improved maternal survival and reductions in morbidity (Christian et al., 2001). Additional efficacy trials are currently underway in Bangladesh and Ghana and are expected to generate evidence to guide the development of future maternal vitamin A supplementation recommendations.

The specific operational feasibility of routine maternal vitamin A supplementation during pregnancy has not been established. However, such challenges are expected to be similar as those that have been well documented for iron + folic acid. In addition, a decision to include vitamin A as an antenatal supplement can lead to the consideration of combining these nutrients into single supplements, as indicated by population needs. Such combining of nutrient supplements would also remove concerns expressed by some public health clinicians about potential confusion among peripheral health workers who could mistakenly give out high-potency vitamin A supplements (100,000 or 200,000 IU) to pregnant women that are intended for periodic use among children (P. Harvey, unpublished observations, 2006).

High-dose vitamin A supplementation is recommended for mothers within six weeks of delivery during a period when the chance of pregnancy remains remote and as a means to replete maternal stores following pregnancy and during lactation (IVACG, 1998). This policy is based on studies demonstrating that large-dose postpartum vitamin A supplementation can modestly improve maternal vitamin A status and/or breast milk vitamin A concentrations, as well as infant vitamin A status (Stolzfus et al., 1993; Rice et al., 1999). However, a postpartum dose of 200,000 IU appears to be insufficient to correct underlying sub-clinical vitamin A deficiency in women and their infants (Sommer and Davidson, 2002). The provisional recommendation of the International Vitamin A Consultative Group (IVACG) is to give two doses of 200,000 IU at least 24 hours apart to women living in endemic areas of vitamin A deficiency. This should be done as soon as possible after delivery in order to maximize the benefits of maternal vitamin A status, breast milk vitamin A content, and the vitamin A status of a breast-fed infant. Spacing the two doses by at least one day minimizes the risk of raising breast milk retinoic acid concentrations (a short-lived metabolite of vitamin A) to hypothetically toxic levels.

The evidence suggests that postpartum vitamin A dosing can improve infant and maternal vitamin A status. But unlike child supplementation, there remains no evidence that population-based, postpartum vitamin A supplementation reduces infant or maternal morbidity or mortality. Thus, in developing policy, the evidence that the intervention can improve vitamin A status in women and their infants needs to be balanced against several criteria, such as: delivery program costs, lack of efficacy in correcting severe deficiency, little evidence of improved functional outcomes, and recent evidence that, in HIV-positive populations, vitamin A supplementation may increase some health risks (Humphrey et al., 2006). Scientific and policy-making groups have issued inconsistent statements about the benefits of postpartum vitamin A supplementation programs over the past few years and at present, there is no donor supporting major procurement of vitamin A for this intervention. Reaching a consensus on the value of providing vitamin A supplements to women immediately after delivery as a strategy for improving maternal and child health is a priority at this time.

Fortification

Food fortification offers a direct and potentially sustainable way to correct vitamin A deficiency. The aim is to add vitamin A to a regular dietary constituent (staple food or condiment) at a level (e.g. one-third the RDA) that would correct an existing dietary deficiency in target groups without posing significant risks of overdosing among those who habitually consume a large quantity of the fortified product (Dary and Mora, 2002). The issues in choosing an appropriate food vehicle are the same as for other nutrients and have been extensively reviewed elsewhere (Sommer and West, 1996; Dary and Mora, 2002).

To date, sugar has been the most successful vehicle with its public health effectiveness being well established in Central America (Arroyave et al., 1981). Fortification of monosodium glutamate (MSG) was nutritionally successful in improving vitamin A status and (Muhilal and Murdiana et al., 1988) reducing child mortality in Indonesia (Muhilal and Permeisih et al., 1988) but it failed to pass product stability and acceptability criteria, leading to its failure to be taken to scale. Oil is relatively easily fortified with vitamin A and several countries are establishing large-scale programs (Dary and Mora, 2002). Commercial margarine has been successfully fortified and marketed in the Philippines (Solon et al., 1996). Surprisingly, the effectiveness of vitamin A-fortified staple grain products has yet to be evaluated within the context of a large-scale national program, although experimental testing has shown favorable results on the vitamin A status of children in the Philippines (Solon et al., 2000).

In addition to demonstrating an impact on health and overcoming industrial and political special interests, food fortification strategies must address many food technological challenges, economic and costing constraints, and effectively work within an often burdensome regulatory system. In the end, the effectiveness of fortification relies on penetrating markets of the poor at nutritionally effective levels, while posing no apparent risk to subgroups of product over-consumers. In developing countries, public health impact relies largely on mandatory fortification of staples or condiments and this requires a regulatory environment that encourages food industry to participate willingly—i.e. the creation of an effective public-private partnership. Unless the fortification process adds little to the final retail cost of the food and the processed food producers are provided an "even playing field" in which to compete, then food industries are unlikely to participate in this intervention.

Dietary Approaches to Increase Vitamin A Intake

It is likely that food-based approaches can improve vitamin A status in some situations, particularly where sources of vitamin A are available but underutilized. Improving the consumption of vitamin A-rich foods where such foods are available but not consumed in adequate amounts by vulnerable groups requires effective behavioral change strategies. Numerous communications projects and behavior change interventions have been implemented during the last 15 years, but there have been few strong evaluations of the effects of these interventions on vitamin A status, and virtually none have been scaled to sub-national or national level. The difficulty in accurately measuring consumption may partially explain the dearth of evaluations. More attention and resources should be applied to strengthening evaluation designs, measuring consumption effects, and creating better assessment techniques that are appropriate for this particular type of intervention. It is likely that rigorous evaluation of well-designed trials would stimulate more support for dietary approaches.

VITAMIN A STATUS ASSESSMENT METHODS

The ability to accurately, but feasibly, assess vitamin A status in individuals and communities using responsive indicators is fundamental to quantifying the prevalence and severity of vitamin A deficiency, maintaining surveillance of a population over time, and evaluating programs. Although valid methods exist for research, there is an ongoing and urgent need to refine, simplify, and lower the cost and processing times required to assess population vitamin A status. Examples of recent developments that hold the potential for meeting program needs with further refinements in the future include the measurement of retinol-binding protein as a means to assess vitamin A status (Hix et al., 2006), collection and analysis of blood spots to determine the status of vitamin A and other micronutrients (Erhardt et al., 2004), and dark adaptometry (Congdon and West, 2002) which is presently undergoing further refinements to advance portability and reduce costs (Labrique A et al, personal communication, 2006). In terms of evaluating the impact of programs, it is likely that indicators for supplementation and fortification programs will be different, as the former can reduce mortality and xerophthalmia but often have minimal effects on concentrations of serum retinol (West, 2002). The latter can be expected to shift distributions of serum retinol over time (Arroyave, 1981). For example, assessing coverage alone may be adequate for evaluating vitamin A supplementation programs, while food fortification may require periodic assessments of a continuous status variable such as serum retinol concentration. In the future, it will be important to reach consensus on suitable and practical methods to assess the impact of different vitamin A intervention strategies.

REVIEW OF PROMISING STRATEGIES TO PREVENT AND CONTROL VITAMIN A DEFICIENCY

Newborn Infant Supplementation

The impact of newborn vitamin A supplementation is becoming increasingly clear in Southern Asia. Should the current community-based trial in Bangladesh reveal a reduction in infant mortality in newborns given vitamin A, these findings would corroborate those from two similar trials in Asia. Together, these would provide strong evidence for advocating this intervention as a low cost approach to reducing early infant mortality in Southern Asia.

There is a need to conduct similar studies in rural African sites where both infant mortality and vitamin A deficiency prevalence are high, and preferably in areas that vary in their degree of co-prevalent co-morbidities to determine the relevance of this intervention within these varied contexts. Specifically, there are theoretical arguments to suggest that newborn vitamin A could have a substantial impact on infant mortality due to malaria.

Newborn vitamin A supplementation, as a program, would require adapting local surveillance mechanisms for identifying childbirths coupled with non-campaign style, rapid-response delivery of vitamin A. These needs could be met, for example, by integrating vitamin A into safe birthing kits to be used by women themselves (obtained during pregnancy through antenatal care services), through home-based nurse midwife or trained traditional birth attendant delivery, and through clinic-hospital based obstetric care and delivery programs. Newborn vitamin A delivery could be combined with other emerging and effective neonatal care services, such as cord cleaning with chlorahexadine. Newborn vitamin A delivery would establish birth dates and identify the timing for an infant's "six-month" vitamin A dosing visit—a strategy that is presently gaining interest.

Finally, a newborn vitamin A dosing strategy could provide a new, highly motivated linkage to enable postpartum maternal vitamin A supplementation to gain coverage by combining these two deliveries at the same home or clinic visit.

Screening and Treating Night Blindness in Pregnancy

In Nepal, a study showed that women who became night blind during pregnancy had a higher risk of morbidity, anemia, malnutrition, and infant and self-mortality during pregnancy at the first one to two years postpartum than those who did not (Christian, 2002; Christian et al., 1998; Christian et al., 2000; Christian et al., 2001). However, the extended postpartum risk among night blind women during pregnancy is "latent"; that is, women carry their risk without remaining night blind typically beyond the first week postpartum, necessitating the history to relate to a woman's most recent pregnancy. Finding night blind women during pregnancy, typically through a simple but specific history, can identify high-risk women who are likely to suffer consequences of vitamin A deficiency. However, more work needs to be done to identify common, specific terms for the condition and to incorporate the assessment and treatment of night blindness into primary antenatal and postnatal care.

BARRIERS TO SCALING-UP SUSTAINABLE INTERVENTIONS OF KNOWN EFFICACY

Vitamin A Supplementation

Approximately 70 countries currently carry out vitamin A supplementation for children less than five years of age, of which 44 have surpassed 70 percent coverage with at least one annual dose (UNICEF, 2006). Far fewer countries are reaching children with the recommended second dose, and only 15 countries have sustained high semi-annual coverage for three years or more (UNICEF, 2006). The primary barrier to progress is a lack of dedicated delivery mechanism for vitamin A and other child health services. As mentioned previously, several countries have established biannual "special days" or "special weeks" that package other child health services with vitamin A supplementation. When combined with social marketing strategies that promote community awareness and participation, supplementation coverage has dramatically improved. However, since such mechanisms are absent, weak or sporadic, vitamin A coverage can fluctuate widely from round to round. Even where high coverage has been sustained, a significant proportion of children go unreached each year. Children missed by vitamin A supplementation are also likely to be those already at greatest risk for vitamin A deficiency and its consequences. Reaching those children will likely require special measures, such as intensifying outreach in geographic areas of low coverage. This will, in turn, require effective coverage monitoring and increased costs per child supplemented.

Vitamin A supplementation for women in the postpartum period remains very limited in scope because: programmatic linkages (e.g., with BCG vaccination) have not been well-established; there is little accountability for postpartum supplementation coverage, with no global monitoring; and no donors are currently supporting the procurement of supplements for this target group.

Overall, supplementation remains a push- rather than demand-driven intervention, both among policy makers and among consumers. An extraordinary exception to this usual pattern has been in the national vitamin A distribution program in Nepal where community demand for periodic vitamin A supplementation has been raised, leading to increased demand on the government to provide this service on a regular basis. Progress has been made in including supplementation in broader development and child survival policies, and greater than half of countries reporting vitamin A supplementation are contributing to operational costs. However, dedicated national budget lines and country-level procurement of supplements is still very limited. Commitment to vitamin A supplementation at the policy level will be needed to sustain supplementation while the underlying problems of infectious disease and inadequate diets are addressed.

It will be important to clear up confusion regarding how long vitamin A supplementation needs to be sustained, as questions regarding impact assessments and the phase-out of supplementation are common. Among consumers and health workers, past linkages with immunization campaigns did not require that the importance of vitamin A supplementation be effectively communicated; continued training and IEC will be needed to motivate health workers and inform caretakers so that demand for supplements will be generated at the community level.

Fortification

Actual coverage with vitamin A-fortified foods is not systematically monitored at the global level. Eight countries are currently fortifying foods such as sugar and oil with vitamin A, reaching at least 50 percent of the population. Twenty-nine countries have smaller scale fortification efforts and 19 countries report some progress towards fortification (e.g., feasibility studies, identification of food vehicles, etc.). Successful fortification requires a strong political commitment over the life of the program. Adequate technical capacity, one or more centrally processed and widely distributed foods, and public-private partnerships are generally required for effective food fortification. In most cases, this strategy can take several years to initiate and longer still to penetrate poor markets and reach sufficient proportions of those at risk. Major barriers include: a) coverage monitoring of vitamin A-fortified foods, particularly access and utilization among population groups at high risk for vitamin A deficiency; b) ongoing assessment of the impact of food fortification on vitamin A status (effectiveness); and c) quality assurance of the vitamin A content of fortified foods. These data will be needed to inform effective targeted of interventions, i.e., such that vitamin A intake can be ensured through a combination of interventions.

Dietary Approaches

There has not been any systematic collection of information on national policies or programs focused on dietary approaches to increase vitamin A intake. However, multiple experiences have been documented in the gray literature on the promotion of home gardening to increase the production of foods rich in vitamin A, behavior-change communication, social marketing of vitamin A-rich foods, or some combination of these strategies. Experiences have primarily been small-scale – with the exception of nutrition education linked with vitamin A supplementation campaigns – and have often been driven by non-governmental organizations. Research is also lacking in terms of clearly documenting the impact of dietary approaches on health outcomes, reflecting the difficulties in design, scale, and costs in conducting health impact research related to dietary strategies. Scale-up of dietary interventions is limited by a lack of well-designed assessments to attest to their efficacy and effectiveness in reducing the burden of vitamin A deficiency.

Monitoring Intervention Impact and Outcome

There is a growing interest in measuring the impact of vitamin A programs in countries that have implemented national scale programs for several years. The lack of a change in serum retinol distribution over time in several countries that have sustained >70 percent vitamin A supplementation coverage for several years has raised the concern about the appropriate impact indicator for vitamin A supplementation. Clear guidelines are needed to assist countries to select, use, and interpret appropriate impact indicators.

The selection and use of indicators in the monitoring of vitamin A interventions will differ depending on the intervention objective. For example, vitamin A supplementation programs may aim to improve coverage of recipients of vitamin A supplements; fortification programs may aim to ensure that a vitamin A-fortified food meets quality-assurance standards or is selected for consumption by target groups; and programs that aim to increase vitamin A intake may need to use indicators able to measure a change in food-consumption behavior. The appropriate intervention-specific impact indicator(s) for each of these objectives will differ; in some cases process indicators will be used, in others, biological indicators are appropriate.

The indicators and tools that are likely to be useful for program impact evaluations should be selected based on a consideration of a) the purpose of the evaluation, b) the type of vitamin A program/intervention, c) the target group intended for the vitamin A program/intervention, d) the indicator's validity, reliability, and potential responsiveness relative to the vitamin A program/intervention, and e) feasibility within the cultural context and evaluation setting.

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Maternal postpartum vitamin A supplementation may also be combined with newborn vitamin A dosing.

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