In developing countries, vitamin A deficiency (VAD) in children and pregnant women is a serious public health problem. Vitamin A supplementation (VAS) has been used to prevent or treat VAD and to decrease mortality and morbidity in children. However, there are still controversial issues, especially in relation to VAS’s role in deaths or morbidity not related to measles in the pediatric population.

**Mortality Outcomes**

Several trials and meta-analyses have revealed that VAS in children > 6 months is associated with a decrease in all-cause and diarrhea-specific mortality (24–28%) \[1\]. These studies were performed mostly in countries with a high incidence of VAD and also in populations with not universal measles immunization. Latham \[2\] suggested that the statistical difference in deaths might disappear if measles mortality were excluded from some studies of VAS. This concern was based on the uncertainty regarding the real causes of death in these studies. One of the largest studies exploring whether massive-dose vitamin A administration is associated with a reduction in childhood mortality was taken up in India. Approximately 1 million children were followed. There was no significant difference in death rates between children who received the massive dose of vitamin A and those who did not \[3\]. These controversial results need to be carefully analyzed; unfortunately, this trial has not been published to date, and details that might explain the difference between this study and previous meta-analyses are not available so far.

VAS in infants between 1 and 5 months of age has not shown any positive effect on overall mortality \[4\] (table 1). Plausible explanations for these findings have focused on possible protection of breastfeeding against malnutrition and infection or on differences...
between the studied populations (e.g. different prevalence rates of infectious diseases among study sites may affect underlying mortality rates).

There are controversial results regarding the effect of VAS in newborns (see table 1). Most Asian studies show a benefit, while African studies do not. Overall, a meta-analysis by Gogia and Sachdev [5] suggests that there is insufficient evidence to support neonatal supplementation with vitamin A; however, in populations where the prevalence of VAD in pregnant women is high, it might be beneficial. Regional and biological factors need to be further studied to understand these contrasting results.

### Morbidity Results

VAS in children may decrease diarrheal disease; however, it is uncertain if this might be related to protection conferred by vitamin A against measles infection (may have a clinical presentation with diarrhea) or not. VAS (prophylactic or therapeutic) does not seem to have a protective effect on lower respiratory tract infection, except perhaps in malnourished children. In addition, VAS in children may even be detrimental, as revealed in some studies [6]. It has been speculated that these results may be related to the pathogen-specific and disease pathway-specific responses associated with VAS.

#### Table 1. Main controversies related to periodical VAS in children (mortality outcomes)

<table>
<thead>
<tr>
<th>Age at intervention</th>
<th>Results</th>
<th>Controversial issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 months [1, 3]</td>
<td>Decrease all-cause and diarrhea-specific mortality. No effect.</td>
<td>To what extent is this related to measles?</td>
</tr>
<tr>
<td>1–5 months [4]</td>
<td>No effect on mortality.</td>
<td>Are these results explained by breastfeeding practices? To what extent may vaccination at this age interfere with a positive response?</td>
</tr>
</tbody>
</table>
Measles

In measles infections, there is evidence of benefit with two mega doses (200,000 IU on consecutive days) of vitamin A (but not a single or smaller doses). This approach reduced the mortality in children aged < 2 years (0.21; 0.07, 0.66) and the risk of pneumonia-specific mortality (0.33; 0.08, 0.92) [7]. It is important to recognize that benefit was demonstrated in hospitalized children aged < 2 years given two doses of VA and in areas where the case fatality rate was > 10%. Controversy still remains as to whether these findings could be generalized to populations with high rates of measles immunization (low exposure) with low case fatality rates and in non-hospitalized children.

Vaccines

VAS may improve immune response to measles vaccination if there are low basal measles-specific antibodies. There is controversy regarding a potential harmful effect of VAS and DTP vaccination. More studies are needed to address this issue.

References