Vitamin A Deficiency and Child Health, Survival and Vision

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Bloomberg School of Public Health
Johns Hopkins University
Major dietary sources of preformed VA; 1 ug retinol = 1 retinol activity equivalent (RAE), previously retinol equivalent (RE)

Photo: V. Sheffield
Previously 6:1 bioconversion ratio for B-carotene;
Now ratio = 12:1 for B-carotene; 24:1 for others
Functions of Vitamin A

Regulates cellular differentiation:

- Embryonic
- Epithelial (e.g., conjunctival, tracts)
- Immune stem cells
- Hematopoietic
- Osteoid (osteoblasts, -clasts)

Participates in rod cell visual cycle
Vitamin A

**Adequacy**
- Bone growth
- Reproduction
- Embryogenesis
- Rod vision
- Cell differentiation
- Immunity

**Deficiency**
- Growth retardation
- Dysfunction (M&F)
- Teratogenesis
- Night blindness
- Epithelial metaplasia
- Impaired innate & acquired defenses
A 1913 “McCollum experiment” showing normal rate growth and growth of rat while becoming VA-depleted, followed by adding a small amount of butter fat to the diet.
Early mortality and xerophthalmia histogram of rats during progressive vitamin A depletion (Stephenson, 1920)
Health Consequences of VAD

- Xerophthalmia: Mild to severe
- Corneal blindness and disability
- Anemia
- Stunted growth
- Impaired immunity
- Increased severity of infection (e.g., measles, diarrhea, or malaria)
- Mortality
VADD Reflect a Gradient of Health Consequences

- Corneal Blindness
- Xerophthalmia
- Systemic Effects: Metaplasia, Impaired immunity, Morbidity, Anemia, Poor growth
- Tissue and plasma depletion
- Chronic dietary deficit

Adapted from: KP West Jr J Nutr 2002;132:2857S
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>XN</td>
<td>Nightblindness</td>
</tr>
<tr>
<td>X1A</td>
<td>Conjunctival xerosis</td>
</tr>
<tr>
<td>X1B</td>
<td>Bitot’s spots</td>
</tr>
<tr>
<td>X2</td>
<td>Corneal xerosis</td>
</tr>
<tr>
<td>X3</td>
<td>Corneal ulceration</td>
</tr>
<tr>
<td>XS</td>
<td>Corneal scarring</td>
</tr>
<tr>
<td>XF</td>
<td>Xerophthalmic fundus</td>
</tr>
</tbody>
</table>
KAKULANGAN SA BITAMINA A
Vitamin A Deficiency

Hindi nakakakita sa gabi
Nightblindness

Courtesy of Helen Keller International
Examine eyes for conjunctival xerosis with handlight shown from side

Photo: K. West
Conjunctival xerosis (X1A)
Photo: A Sommer

Bitot’s spot (X1B)
Night blindness or Bitot’s spots may occur in wasted or non-wasted children; typical prevalence of 1 to 5%
Corneal ulcer (X3A)
Corneal necrosis - Keratomalacia (X3B)  

Photo: A Sommer
Corneal scar: Adherent leukoma (XS)

Photo: A Sommer
Corneal necrosis – keratomalacia (X3B)

Photo: Alfred Sommer
Keratomalacia

- Nutritional blindness
- Corneal necrosis
- Associated with severe wasting
- Severe illness (e.g., measles)
- Chronic, severe vitamin A deficiency
<table>
<thead>
<tr>
<th>Xerophthalmia</th>
<th>Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>200,000 IU</td>
</tr>
<tr>
<td>Day 2</td>
<td>200,000 IU</td>
</tr>
<tr>
<td>Day 14</td>
<td>200,000 IU</td>
</tr>
</tbody>
</table>

**High Risk Conditions**

Severe PEM
Severe diarrhea (single 200,000 IU)
Severe ALRI
Severe Measles 200,000 IU on days 1 & 2

D Ross J Nutr 2002
<table>
<thead>
<tr>
<th>Condition</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nightblindness</td>
<td>1 day</td>
</tr>
<tr>
<td>Conjunctival Xerosis/ Bitot’s Spots</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Corneal Ulcers</td>
<td>2-4 days</td>
</tr>
</tbody>
</table>

Sommer, 1982
Bilateral corneal scars (XS):

Photo: A. Sommer
Four-year old Indonesian child with leukoma (RE) and staphyloma (LE)

Photo: K West, Jr.
VADD in Preschool Children: Morbidity and Mortality
Xerophthalmia and Risk of Child Mortality in Preschool Indonesian Children over 18-Month Period

Sommer et al, Lancet 1983
The Aceh Trial
Northern Sumatra
1982-84: 2 cents of vitamin A cut child by 34%

Photo: K West, Jr.
Eight Major Trials Over a Decade Revealed: 25-35% Reduction in Preschool Child Mortality

Over 165,000 children participated in these 8 trials
Est in 1991: 1.1 to 2.4 m deaths avoidable each year

Adapted from Sommer & West, 1996
VA deficiency Increases Measles Fatality; VA Treatment Reduced CFR by 50% to 80%

OR = 0.40 0.49 0.19 0.34

Control
VA treated

London 1932
Tanzania 1988
Capetown 1990
Durban 1991
Vitamin A and Malaria

- VAD exacerbates *falciparum* malaria
- In Papua New Guinea, VA supplementation lowered...
  - Clinic attack rates by 30%
  - Parasite density
  - Enlarged spleen rates

Shankar et al, Lancet 1999;354:203
<table>
<thead>
<tr>
<th></th>
<th>RR (VA/Control)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic attendances</td>
<td>0.88</td>
<td>(0.81-0.95)</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>0.62</td>
<td>(0.42-0.93)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.81</td>
<td>(0.68-0.98)</td>
</tr>
</tbody>
</table>

Fever-related Mortality
= >6 Months of Age, Sarlahi, Nepal (NNIPS-1)

Days of Morbidity Past Week

4-Month MR/1000 Child Visits

RR=0.82
RR=0.56*
RR=0.49

* p <0.05
### Effect of Vitamin A on Diarrhea

**Serrinha, Bahia, Brazil**

<table>
<thead>
<tr>
<th>Stools/Day</th>
<th>Control n=620</th>
<th>Vit A n=620</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3</td>
<td>51.7</td>
<td>47.8</td>
<td>0.92</td>
<td>0.07</td>
</tr>
<tr>
<td>≥ 4</td>
<td>25.9</td>
<td>23.2</td>
<td>0.90</td>
<td>0.05</td>
</tr>
<tr>
<td>≥ 5</td>
<td>12.3</td>
<td>9.9</td>
<td>0.80</td>
<td>0.005</td>
</tr>
<tr>
<td>≥ 6</td>
<td>5.6</td>
<td>4.3</td>
<td>0.77</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Barreto et al, Lancet 1994
Can infant health and survival be improved by direct supplementation with VA any time during the first 6 months of life?
Bangladeshi infant < 6 months of age receiving 50,000 IU vitamin A by expressing 3-4 drops of oil from capsule into mouth

Photo: K West, Jr.
Vitamin A in the First Six Months of Life and Mortality

In Nepal: 50,000 and 100,000 IU given to infants < 6 months of age, recruited during six 4-monthly home visits over a 2-year period. Vitamin A failed to reduce mortality (NNIPS-1)

Based on K West et al AJCN 1995;62:143
In Ghana, Peru and India: Vitamin A (25,000) given at each EPI visit at 6, 10 & 14 weeks of age failed to reduce infant mortality.
## Biologically Plausible Mechanisms

- **Immunopotentiation**
  - Cell mediated (T-cell)
  - Humoral (Antibody-mediated)
- **Innate Immune mechanisms**
  - Neutrophils, Macrophages, NK cells
  - Epithelial cell differentiation
Epidemiology of VA Deficiency
Guide to Prevention

Xerophthalmia
- Location
- Age, Sex
- Season

Risk Factors
- Diet
- Morbidity
- SES, Care
Magnitude of Preschool Problem in Developing (Low Income) Countries

- Xerophthalmia: 4.4 million (0.9%)
- VA deficient (< 20 ug/dl): 127 million (25%)

versus in 1980s/early 1990s…

- 2.8 to 13 million with xerophthalmia
- 118 to 190 million with vitamin A deficiency

Humphrey, West & Sommer BWHO 1992;70:225
WHO MDIS: Geneva 1995
Emerging Indications of a Major Impact of VA Interventions on Child Mortality…

• 1991 estimated preschool child deaths per year due to VAD: 1.1 - 2.4 m (mid-point: 1.75 m)

• 2004 WHO GBD estimated preschool child deaths due to VAD: ~600,000  (Rice, West and Black, 2004)

• Difference: Roughly ~1 m deaths due to VA deficiency are currently being prevented each year

• 700,000 per year more to go!
## Village and Household Pairwise Odds Ratio for Xerophthalmia

<table>
<thead>
<tr>
<th>Village</th>
<th>Household</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi</td>
<td>1.2</td>
</tr>
<tr>
<td>Zambia</td>
<td>1.7</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1.7</td>
</tr>
<tr>
<td>Nepal</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Katz et al, Internat J Epidemiol 1992
Lessons from CLUSTERING?

- Treat child with xerophthalmia
- Dose siblings of a case with VA
- Counsel mother about family diet
- Target case’s village for program

IVACG Policy Statement, 1996
Prevalence of Bitot’s Spots by Gender and Age in Indonesia

Sommer, 1982
Percent of Rural Bangladeshi Children Still Being Breastfed by Age
Bangladesh Nutritional Blindness Survey, 1983

Helen Keller International, 1986
<table>
<thead>
<tr>
<th>Food</th>
<th>&lt;1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastmilk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow Fruit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark Green Leaves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggs/Dairy Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KP West, 2001
<table>
<thead>
<tr>
<th>Type of Food</th>
<th>Odds Ratio</th>
<th>Risk Decrease</th>
<th>“r” with Sib Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat w/liver</td>
<td>0.09</td>
<td>91%</td>
<td>0.38</td>
</tr>
<tr>
<td>Egg</td>
<td>0.11</td>
<td>89%</td>
<td>0.53</td>
</tr>
<tr>
<td>Fish w/liver</td>
<td>0.41</td>
<td>59%</td>
<td>0.39</td>
</tr>
<tr>
<td>Mango</td>
<td>0.28</td>
<td>62%</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Gittelsohn et al Eur J Clin Nutr 1997;51:484
Vitamin A deficiency appears to be a major health problem among women of reproductive age in many developing countries, suggesting that it is a chronic; that is, it persists throughout the “life cycle”.

Photo: Keith West
In developing countries

Increased evidence of VA deficiency among pregnant women; suggests that VAD persists throughout “life cycle”.

Low VA status: ~20 m
VA deficient: ~ 7 m
Night blind: ~ 6 m

K West J Nutr 2002

Photo: Keith West
Night blind, pregnant Nepalese woman

Photo: P Christian
Mortality of Women by Night Blind Status in Pregnancy, Sarlahi, Nepal

**Maternal Period**

- Pregnant 0-6 wk
- 7-12 wk
- 13-24 wk
- 25-36 wk
- 37-52 wk
- >52 wk

**Late Pregnancy-related Period**

- Night blind
- Not night blind

**Post-Late Pregnancy**

- Night blindness disappears shortly after birth

Christian et al., Am J Epidemiol 2000
Can intervening with VA improve maternal health and survival?
NNIPS-2 Design

270 Wards

Beta-carotene
7000 RE / wk
90 wards
14,536 women
7201 pregnancies

Vitamin A
7000 RE / wk
90 wards
15,305 women
7747 pregnancies

Placebo
0 RE / wk
90 wards
14,805 women
7241 pregnancies
Cumulative Pregnancy-related Mortality of Mothers NNIPS-2, Nepal

Deaths per 100,000 pregnancies

RR = 0.60 0.47 0.63 0.56 0.60 0.51

RR = Relative Risk; RR excludes 1.0

West et al, BMJ, 1999
VADD: Women of Reproductive Age

- Maternal XN/ with disability
- Other xerophthalmic eye signs
- Infection: Diarrhea, sepsis/fever
- Anemia
- Reproductive morbidity (?)
- Maternal mortality
- Infant risk: Mortality
JiVitA Bangladesh

A new 8-year research project in Bangladesh to confirm the impact of maternal vitamin A or beta-carotene supplementation on maternal mortality (n=68,000);

“Jivita”: Bengali word Meaning “alive”

Supported by USAID & Gates
Additional Maternal VA Trials

- **Ghana**: Maternal mortality; underway
- **Tanzania**: No survival benefit for infants born to HIV+ mothers; possible increased risk of MCT of HIV (W Fawzi et al)
- **Zimbabwe**: postpartum dosing on infant mortality, HIV transmission, other outcomes, unaffected by VA (J Humphrey et al)
Improving VA Intake: Complementary Approaches

- Supplementation
- Food fortification
- Dietary diversification
- Novel approaches: genetic modification, plant breeding
Diet
Fortification
Supplements
Deficient Population
Vitamin A Supplementation

- Centerpiece for prevention
- Proven, low-cost, sustainable, rapid
- Highly effective
- Low risk (in both extent and severity)
- ~600 m capsules distributed by UNICEF each year
## Target Groups and Vitamin A Prophylaxis Guidelines

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosage (IU)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 mo</td>
<td>50,000</td>
<td>6, 10, 14 wk</td>
</tr>
<tr>
<td>6-12 mo</td>
<td>100,000</td>
<td>Every 4-6 mo</td>
</tr>
<tr>
<td>≥ 12 mo</td>
<td>200,000</td>
<td>Every 4-6 mo</td>
</tr>
<tr>
<td><strong>Mothers</strong></td>
<td>400,000</td>
<td>≤ 6-8 wks postpartum</td>
</tr>
</tbody>
</table>

*(IVACG, J Nutr 2002)*
• Medical: Therapeutic
• Saturated: All health contacts with target groups
• Universal: Stand-alone, NIDS, semi-annual campaign
Vitamin A Coverage Increases with “Campaigns”

Bangladesh starts semi-annual 2-day campaign

Helen Keller International, 1996
Large Dose Vitamin A

.2¢ per 200,000 IU dose in oil

encapsulate

2¢ per 200,000 IU capsule

delivery system

20¢ per delivered dose

Sugar Fortification in Guatemala
GOURMET POWDER
PURE MONOSODIUM GLUTAMATE

P.T. SASA INTI, JATIM

Terdaftar
Dep. Kehakiman No. 102622
Dep. Agama No. B.VI/02/2444/1976

Photo: Keith West
Impact of MSG + A in Indonesia

Based on Muhilal et al, Am J Clin Nutr 1988;48:1265
Fortify multiple foods with vitamin A
Food Fortification

Passive Delivery

“Centrally” Processed

Widely Consumed

Technically Fortifiable

Innovative Financing
PAGPAPLANO NG PAGKAIN

Meal Planning

Ano ang uulamin?

Ano ang isasahog?

Ano ang panghimagas?

Magplano ng pagkain nang maaga.

Plan meals ahead of time.

Helen Keller International
Promotion of Home Gardening Through Training
A DAE NGO Collaboration

Helen Keller International Bangladesh

Monitoring of Activities in Block Nurseries
and Household Gardens

Round 1
Vitamin A and Child Mortality Prevention
Evidence-based Global Advocacy

- UN-ACC/SCN Statement (1986)
- IVACG Statement (1989)
- World Summit for Children (1990)
- Lusaka Convention (1990)
- Ending Hidden Hunger (1991)
- Internat’l Conference on Nutrition (1992)
- Bellagio Brief (1992)
- 25th Session of UN-ACC/SCN (1993)
- UNICEF/WHO Mid-Decade Goals (1994)
- 2002 UNGA Special Session to follow-up of World Summit and Millenium Dev. Summit
NNIPS-2 Studies in Nepal: Key Findings

### Impact of Maternal Vitamin A or Beta-carotene Supplementation on Pregnancy-related Mortality (Through 12 Weeks Post-partum)

<table>
<thead>
<tr>
<th></th>
<th>PL (7241)</th>
<th>VA or BC (14948)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. deaths</td>
<td>51</td>
<td>59</td>
</tr>
<tr>
<td>MR/100,000</td>
<td>704</td>
<td>395</td>
</tr>
<tr>
<td>RR</td>
<td>1.00</td>
<td>0.56</td>
</tr>
<tr>
<td>(95% CL)</td>
<td>-</td>
<td>(0.37, 0.85)</td>
</tr>
</tbody>
</table>

44% reduction (p ≤ 0.005)

West et al, BMJ 1999