

A conversation with Helen Keller International, June 1, 2017

Participants

- Dr. Rolf Klemm – Vice President of Nutrition, Helen Keller International (HKI)
- David Doledéc – Regional VAS Program Manager, Kenya, HKI
- Frederick Grant – Regional Nutrition Advisor, Senegal, HKI
- Andrew Martin – Research Analyst, GiveWell

Note: These notes were compiled by GiveWell and give an overview of the major points made by Dr. Klemm, Mr. Doledéc, and Mr. Grant.

Summary

GiveWell spoke with Dr. Klemm, Mr. Doledéc, and Mr. Grant of Helen Keller International (HKI) as part of GiveWell's review of HKI's work on vitamin A supplementation (VAS) in sub-Saharan Africa programs. Conversation topics included: evidence for and data on the prevalence of vitamin A deficiency (VAD) and the impact of VAS in HKI's regions; the decision-making framework HKI is helping the Global Alliance for Vitamin A (GAVA) to develop for scaling back VAS; changes in child mortality rates in HKI's sub-Saharan Africa countries; HKI's areas of expertise and role in the field; and HKI's funding situation and funding for VAS in general.

Uncertainty in estimates of the impact of VAS on under-5 mortality

There are roughly 40 relevant trials examining the impact of VAS on under-5 mortality, of which about 10 or 12 are large, randomized controlled trials. These trials took place in several different countries, mostly in the 1980s and 1990s.

Although the trials were all conducted in areas where VAD was present, the participants in the different trials were likely different from each other in substantial ways (e.g., some groups had higher baseline prevalence rates of infectious diseases or VAD than others). The different trials found somewhat heterogeneous estimates of the impact of VAS on under-5 mortality, which makes it difficult to know what size mortality effect to expect for a given population participating in a VAS program.

There are a few options for estimating the size of the mortality effect of a VAS program for a given population given this uncertainty:

- **Use the overall effect estimate from a meta-analysis:** Meta-analyses combine the results of trials to increase statistical power and can make more precise estimates of the size of the average expected treatment effects than individual trials. A recently updated Cochrane Collaboration meta-analysis (Imdad et al. 2017: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008524.pub3/epdf>) finds a statistically significant overall reduction in child mortality when the results of all the relevant trials are combined.

- **Use sub-group analyses:** If the population characteristics of a country with respect to levels of VAD, child mortality, and infectious disease are similar to those of a particular study, the effects of that study may provide a better estimate of expected effects compared to the one derived from a meta-analysis which combines the results of studies from many different contexts.

Overall, even though the participants in the trials likely had somewhat different characteristics, the results of the meta-analysis still suggest that there is a reasonably strong "signal" of a mortality reduction effect across different settings, and that we should expect mortality rates for populations of children generally similar to children in the trials to be reduced due to VAS as well.

Threshold of VAD prevalence for impact

There is likely a threshold of VAD prevalence below which VAS is unlikely to have much impact on mortality. If there is high-quality data showing low VAD in a region, HKI thinks it is reasonable not to expect VAS to have a mortality impact there.

Organizations in the Global Alliance for Vitamin A (GAVA) currently use 10% VAD as the threshold at or above which VAS programs ought to be maintained in a region. The World Health Organization (WHO) classifies VAD rates of 20% or greater among preschool-aged children as a serious public health problem. VAD rates of less than 5% are accepted as not much of a concern.

Despite a lack of recent micronutrient analyses in many African countries, HKI is confident that VAD is prevalent enough in many places for VAS to remain an impactful intervention. For instance, while HKI is not aware of any recent micronutrient deficiency data in Mali, it would be surprising if VAD were not prevalent there, given Mali's child mortality and malnutrition rates.

HKI finds recent results showing very low VAD in Malawi surprising and would like to understand them better.

A threshold like this might not be observed if vitamin A had a pharmacological effect (i.e., if a large dose of vitamin A directly primed the immune system in some way, regardless of deficiency). However, Dr. Klemm thinks there is not any clear evidence to substantiate this hypothesis.

Mechanism of VAS impact

The impact of VAS on mortality appears to come through boosting immune response to infectious diseases. While there is little evidence that vitamin A prevents infections, there is evidence that it reduces the chance of death from infection, particularly for measles and febrile diarrhea. Infectious diseases are typically a major cause of death in high mortality countries.

Potential impacts on diseases other than measles and diarrhea

A common interpretation of the evidence is that VAS only impacts mortality from measles and diarrhea. Dr. Klemm thinks its impact may extend to other infectious diseases.

Because there are often numerous factors involved in a child's death, there is often uncertainty about the final cause of death, leading to imprecision in cause-specific mortality data. In the few settings where reliable cause-specific mortality data is available related to VAS impact, deaths have been largely measles-related. There is also good evidence for impact on diarrhea-related deaths, though the evidence around febrile deaths are more uncertain since there are many causes of fever (e.g. respiratory tract infections).

Because of this uncertainty, Dr. Klemm thinks it is helpful to consider what vitamin A is likely to operate on biologically, primarily via mechanisms related to mobilizing immune system resources to fight infectious diseases. Dr. Klemm would also expect vitamin A to have an impact on respiratory tract infections because of its effect on lung cells (though direct evidence for this effect is uncertain).

One trial showed an effect of vitamin A on malaria deaths (though another trial did not).

Framework for decision-making around VAS

Due to changes over time in child mortality rates, dietary diversity, and increased consumption of vitamin A-fortified foods, it may now be appropriate for some countries to scale back VAS programs that currently target all preschool-aged children. The GAVA partners are working on an operational framework to help countries make well-informed decisions about scaling back VAS. Because countries' situations are diverse and complex, this will be a set of general guidelines rather than a strict, linear decision-making system. The framework encourages countries to look at several factors, including:

1. VAS coverage and implementation
2. Food fortification (which is increasing in many African countries, especially in West Africa). Relevant factors include: coverage and utilization of vitamin A fortified food, b) which foods are being fortified, and c) the conversion factor of dietary beta-carotene into vitamin A, which varies significantly between foods. Data on fortification coverage so far is limited. Dr. Klemm would consider it a very positive sign if children were to get half of their recommended daily allowance of vitamin A per day via fortified food.
3. Infant breastfeeding rates (breast milk is a major source of vitamin A for infants). A substantial increase in exclusive breastfeeding would be a positive sign.
4. Dietary diversity. Dietary diversity is an imprecise indicator of vitamin A intake that lacks the resolution of, e.g., fortification data, but improvements in dietary diversity, particularly in young children, are a positive sign.

Secondary indicators that are useful as proxies for VAD include:

1. Malnutrition rates for children under five
2. Maternal mortality
3. Child mortality
4. Malnutrition among mothers (vitamin A deficiency in mothers lowers the concentration of vitamin A in breast milk)
5. Morbidity rates for infectious diseases
6. Types of supplementary foods used for children aged 6 to 24 months

HKI expects the availability of these data to vary significantly by country; lack of data in general is still a major issue. There is likely to be more district- and region-level data, largely collected by NGOs that are focused on specific problems in specific regions, and less national-level data. The GAVA framework will emphasize the importance of collecting more data and include a section with recommendations on how to do this.

HKI recommends that countries look at trends in the above factors (over, e.g., the last 10 years) rather than just the current situation. For instance, if food fortification coverage has increased significantly and malnutrition has decreased in a given country, this can helpfully inform decision-making even without providing direct information on VAD prevalence.

Potential data sources

The Demographic and Health Surveys program conducts surveys in many countries roughly every five years. These can provide some data on dietary diversity, and this data is standard and comparable. Household income and expenditures surveys, which are also typically available about every five years, can provide some data on food purchases and food quality at the household level. These data can be disaggregated sub-nationally to differing extents.

Other considerations

It is important to examine the extent to which health, nutrition, and food industry systems are functioning as intended. For instance, there may be a law that vegetable oil be fortified with vitamin A, but without data on coverage or industry compliance it is difficult to estimate children's actual intake of vitamin A from oil. Young children in particular are likely to have limited oil intake (vegetable oil is typically used in family meal preparation, so young children are likely to consume it roughly as often as the rest of the household but in smaller amounts). Additionally, the quality of fortified oil can degrade by the time it reaches a household (if, e.g., it has been repackaged or sat in the sun for an extended period). It would be ideal if oil quality data were collected at the point of sale or consumption, rather than at the factory.

It is also important to look at differences across regions of a country (e.g. rural vs. urban, north vs. south, etc.), and to clarify assumptions about given regions with countries before recommending strategy changes, recognizing that particular strategies may or may not be appropriate in different regions.

Child mortality in HKI-supported countries

Child mortality rates have decreased overall over the past few decades, and there has been an epidemiological shift in some areas of Africa in which HKI works (though not in others). To maximize the impact of VAS going forward, it might be beneficial to adjust the targeting of VAS with respect to:

- *Age groups*: HKI has had discussions with UNICEF and others about potentially focusing VAS on children aged 6 months to 24 months (instead of 6 months to 5 years). In the context of lower overall mortality, the 6- to 24-month age group supports an increased proportion of the mortality burden.
- *Geographic regions*: Universal supplementation may not be the best approach in countries with lower deficiency and mortality rates (e.g. Kenya). It might be more effective to focus on the most vulnerable geographic regions (e.g., northern Cameroon still has a high rate of VAD while rates in the south are substantially lower).

While child mortality has decreased in all HKI's African countries, the lowest national averages are still around 50 per 1,000 live births; within countries, there are regions and/or age groups with higher or lower rates.

UNICEF has done analyses that find a correlation between mortality rates of 50 per 1,000 live births or higher and countries with high VAD rates, with high sensitivity and specificity (though some of the VAD data used in these analyses is old).

To evaluate the impact of VAS, it might be best to use mortality data only for 6-month to 5-year-olds (i.e., to remove deaths occurring just after birth) and potentially stratify age-specific data even further (since, e.g., if mortality rates have decreased significantly among 3 to 4 year olds, it might make sense to focus VAS efforts on younger children). There is currently a lack of specific data of this kind.

If a region has high VAD rates and relatively high overall mortality, HKI is confident that VAS will have an impact on child mortality rates, particularly if a high proportion of child mortality is due to infectious disease. The lower the mortality burden from infectious febrile diseases, the lower the likelihood of a large impact from VAS (though how much lower is unclear).

The initial RCTs on vitamin A supplementation were powered to look at all-cause mortality, rather than cause-specific mortality (though it would be straightforward to remove deaths from, e.g., accidents or other causes that vitamin A would not affect).

HKI's role

Assisting with the transition from door-to-door to routine services delivery

In the past, most VAS programs in Sub-Saharan Africa have delivered supplements to children in door-to-door mass campaigns tied to polio immunization campaigns,

but countries need to find alternative methods of delivering VAS, since many polio campaigns are ending due to progress in polio elimination. Transitioning to "routine delivery" (in which caregivers bring children to facilities combined with periodic outreach/delivery posts within communities to receive VAS at appropriate ages) appears to be the most sustainable long-term option.

HKI expects its capacity to assist governments to transition to routine service delivery to be particularly critical over the next five years or so. HKI's flexibility to send teams from one region to another to provide technical assistance and build capacity has been valuable, and HKI has a recognized expertise in this area.

Transitioning to routine delivery of VAS can be challenging. When Kenya transitioned from door-to-door to routine delivery without technical assistance, coverage fell from roughly 90% to 20% during one campaign, and it took several years to bring coverage rates back up. HKI hopes to help prevent this in other places, since it is more difficult and requires more resources to bring coverage rates back up than to prevent them from falling. UNICEF has asked HKI to provide transition assistance in Benin and Togo.

Monitoring, evaluation, and research

HKI has produced helpful research (e.g. on best practices for delivering VAS) and monitoring data to share with governments and other actors. HKI, along with government counterparts, has also planned data collection, worked to analyze data quickly, and organized teams to present results. In most of its countries, HKI has also organized workshops at the end of each campaign to convene the groups involved and discuss the results, what went well, and what could be improved.

Collaboration with UNICEF

In sub-Saharan Africa, HKI and UNICEF collaborate effectively and play complementary roles in VAS. UNICEF, as a multinational organization involved with a broad spectrum of nutrition, health, and development issues, has superior capacity to convene national and international stakeholders, advocate for policies, and influence national-level programming and strategies. In contrast, HKI, as a non-governmental organization, can provide technical expertise at the national level but has the dexterity, flexibility, and field-based expertise to work at sub-national levels on implementation, monitoring, evaluation, and testing program innovations. Both UNICEF and HKI often coordinate their respective VAS activities and roles with each other resulting in a complementary partnership in many countries.

Funding

Changes in global funding levels for VAS

In a three-year period between 2013 and 2016, Global Affairs Canada (GAC) granted around \$30 million (CAD) to HKI and provided significant funding to UNICEF and the Canadian-based Nutrition International for VAS programs in sub-Saharan Africa. Going forward, GAC will be passing its VAS funding directly to UNICEF to ease the

administration burden of managing two separate grants with the expectation that UNICEF will use some of this funding to provide grants to other organizations supporting VAS programs, including HKI. Under the new arrangements between GAC and UNICEF, the amount of funding to support VAS appears to be considerably lower than in previous years because it covers four rather than three years of VAS activities, supports immunization activities in addition to VAS, and because the value of the Canadian dollar relative to the US dollar has decreased ~30% since 2013.

UNICEF, as a multi-national United Nations program, works in many more countries than HKI does, and has had to prioritize certain countries over others to receive GAC funding. Many UNICEF priority countries for VAS are not countries where HKI has a presence, which has meant fewer resources to continue HKI's VAS work in those countries not prioritized by UNICEF. There are several other global trends that cause concern for the future of funding VAS programs:

- HKI is concerned that over recent years, global attention to and funding for VAS has waned, most likely due to competition with other pressing priorities and interventions emerging to address broader maternal-newborn-child-adolescent health and nutrition needs.
- “Donor fatigue” may be contributing to declining interest in supporting VAS.
- Due to the changing political landscapes in the U.S., Europe, and the U.K., HKI anticipates major reductions in development aid for maternal and child health programs, including for nutrition and VAS. This may further threaten the long-term funding situation for child survival interventions such as VAS in countries where the need remains high, including many of those in which HKI has a presence.

Consequences of funding shortfalls

Many African countries are facing funding shortfalls around VAS, and some planned VAS mass campaigns have had to be cancelled. For instance, in Mali (which HKI does not currently have funds to support, but which received support from HKI for VAS programs in 2013-16), it is not clear whether VAS mass campaigns will occur at all without external technical assistance from HKI. HKI still expects vitamin A capsules to be provided to countries in sufficient numbers, but there is a risk of millions of capsules remaining undistributed if campaigns are underfunded.

HKI is also losing the capacity to run its end-of-campaign workshop in many countries due to lack of funding.

HKI's room for more funding

HKI operates in 22 countries—13 in Africa, 8 in Asia, and the U.S. HKI's VAS work in Asia in the 1980s and 1990s has contributed to many successful, nationally-owned and sustained programs in that region. Over the past decade, HKI has focused its attention to building country capacity for VAS programs in 13 African countries. Only half of these countries are UNICEF-priority countries for VAS funding through

GAC. To operate at full capacity in the thirteen countries in sub-Saharan Africa it operated in in 2013 to 2016, HKI would probably need less than the \$10 million per year that it previously used. Over the next five years or so, HKI expects that it would primarily be assisting countries in transitioning from door-to-door distribution of vitamin A to the use of routine systems for distribution. HKI estimates that a budget of between \$6 million and \$7 million per year (i.e. roughly \$500,000 per country per year) for the next five to eight years would be sufficient for this work.

Other potential funders

HKI has not received much interest in VAS from other potential funders, even when proposing embedding it in more comprehensive health system support programs. It does have support in some specific cases (e.g. Irish Aid is supporting HKI in Sierra Leone to cover a gap for scale-up to routine service delivery). HKI thinks potential funders may not recognize the importance of maintaining VAS as current platforms for it (e.g. polio programs) disappear.

All GiveWell conversations are available at <http://www.givewell.org/conversations/>