A conversation with Evan Mayo-Wilson, June 10th 2013

Participants

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Note: This set of notes was compiled by GiveWell and summarizes the major topics covered by Dr. Mayo-Wilson.

Summary

GiveWell spoke with Dr. Mayo-Wilson as part of its investigation of the efficacy of vitamin A capsule supplementation to reduce childhood mortality. The major topics included interpretation of the DEVTA trial results, scientific debate surrounding DEVTA, and population changes over time relevant to vitamin A supplementation.

Bottom line

Taking into account all the evidence including DEVTA, there is a strong consensus that providing vitamin A supplementation in areas with high rates of vitamin A deficiency is an effective program that saves lives, and this is consistent with the WHO's current recommendations. This means that no more trials of efficacy should be conducted, although there are a few ongoing.

Population changes over time – particularly falling rates of child mortality due to diarrhea and measles and likely reductions in vitamin A deficiency – indicate that programs aiming to provide vitamin A supplements should explicitly target areas likely to have substantial rates of vitamin A deficiency and high childhood mortality as opposed to providing this program in all locations.

Comparing DEVTA with earlier vitamin A trials

Vitamin A meta-analyses
The Cochrane meta-analysis on the effects of early childhood vitamin A supplementation looked at children in areas of high vitamin A deficiency who received Vitamin A capsules. The studies included in the meta-analysis were large and showed similar results, indicating a low likelihood of publication bias. The meta-analysis finds an estimated 24% reduction in all-cause mortality among supplemented children between the ages of six months and five years.

Deworming and Vitamin A (DEVTA) trial
The DEVTA trial was conducted in India with over a million children, more than all of the other studies combined. Essentially it was testing a program, rather than the clinical efficacy of vitamin A supplementation (VAS). Several issues with DEVTA suggest this perspective:

- The **program was delivered very inexpensively compared with previous programs** and it used existing centers and care providers. Limited investment in the implementation of the intervention (e.g. training and monitoring) may help explain the relatively poor result.
- At such a large scale, it is **harder to target deficient populations**. At lower deficiency levels,

you would expect to find a smaller effect (such as the DEVTA point estimate). DEVTA occurred significantly later (mid-2000s) than many of the smaller trials (late '80s-early '90s). During this period, there was a worldwide reduction in vitamin A deficiency as a result of population-level interventions to reduce it; however, vitamin A deficiency remains common, and many children are at high risk of deficiency because they receive too little vitamin A through diet alone.
- Even though DEVTA's authors surveyed recipients to measure uptake, with such a large trial, there are **great complexities, especially in monitoring uptake**, and measures of uptake and delivery may be overstated.

A similar study would likely find similar results, but targeting high risk children and ensuring that they receive an adequate dose of the intervention would likely produce effects that are consistent with previous trials.

Population changes over time

The biggest specific cause of death that VAS reduces is diarrhea. Deaths from diarrhea are falling but still a leading cause of childhood mortality globally. While the global burden of diarrhea is declining, there are still many places where VAS would be helpful. Also, since vitamin A is necessary for general functioning of the immune system and for normal vision, one would expect VAS to reduce morbidity in addition to mortality.

Measuring vitamin A deficiency
Serum is not an ideal measure of the effectiveness of vitamin A supplementation as there is a lot of heterogeneity in this measure in VAS trials. While megadoses of vitamin A do increase serum levels, there appears to be significant variation on the individual level with respect to how vitamin A is absorbed and what a normal level of vitamin A in the serum is. Symptoms such as Bitot's spots can be diagnosed without the need for blood tests, and these are a useful way to screen children and estimate the prevalence of deficiency in an area.

For data on vitamin A deficiency levels, see:
- World Health Organization
- The Lancet's series on nutrition (www.thelancet.com/series/maternal-and-child-nutrition)
- PLOS Medicine article on diarrhea prevalence (http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001385)

Other viewpoints

The best place to look for an alternative perspective is Harshpal Sachdev (http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60600-5/fulltext).

There have been some controversial articles about the effects of vitamin A supplementation, but these often cite only a subset of the available data (see “The Vitamin A Fiasco”), whilst the Cochrane meta-analysis followed a pre-defined plan for analyzing all studies.

Christine Benn has argued that vaccination and VAS may interact and cause harm, particularly in girls. This claim is based on a small number of events in subgroups from a few trials; looking at data across all available trials, there does not appear to be an effect of gender. Because VAS prevents morbidity

and mortality from both diseases that can be prevented through vaccination and diseases that cannot be prevented through vaccinations, VAS remains an important part of the global effort to reduce child mortality.

The way DEVTA compares to previous trials is highly sensitive to the statistical model used. Professor Richard Peto argues that a fixed-effect model should be used, which assumes that all trials are measuring the same true effect and gives most of the overall weight to the DEVTA trial. Dr. Mayo-Wilson argues that differences between DEVTA and previous trials suggest they may not be measuring the same true effect; a random-effects model gives DEVTA relatively less weight overall, and the average result is unaffected by DEVTA.

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