Drug degradation as a potential reason for differences in the effect of Vitamin A Supplementation on all-cause mortality among children.

Summary

A critical assumption in the cost effectiveness of programs such as the vitamin A supplementation (VAS) by Helen Keller International (HKI) is that the drugs and/or supplements provided are reliably effective as suggested by empirical evidence. In the case of VAS, the evidence of its effect on all-cause mortality has curiously been heterogenous. Some studies show no improvement[1], others vary between 4-86%[2] in terms of potential reductions in all-cause mortality. At the moment, GiveWell concedes that there is uncertainty around the size of impact of VAS, but uses estimates from a Cochrane review updated in 2017 which reported a random effects reduction of 24% and fixed effects reduction of 12%.[3] GiveWell contends that because of differences in settings, implementation and effect estimates found in the literature, a random effects model makes sense and also mention that they have evidence to support their decision that they have not published.[4]

I propose that drug degradation may in part be responsible for the differences in effects seen. There is evidence to suggest that degradation of drugs, particularly in countries targeted by HKI for VAS, may be a significant barrier to programs improving the health of populations they aim to serve. Estimates from the WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products estimate that as much as 10.5% of all drugs sampled in low- and middle-income countries are deemed either substandard or falsified.[5] Drugs can be substandard either through non-intentional errors during the manufacturing process, or due to degradation during transport and storage.[6]

Evidence on drug degradation in VAS interventions

A study comparing high dose VAS among mothers and infants found, when doing quality assurance on their vitamin A capsules, that about 14 months after the study started enrolment, some of the capsules used in the intervention arm had only 32% of the expected amount of vitamin A, the loss being attributed to degradation, as capsules from the same source was earlier shown to have >80% of the expected vitamin A dose.[7] Significantly, this study made use of vitamin A that was manufactured in high income settings and sponsored by the WHO, so I believe it is fair to assume that the drugs were not counterfeit nor of low quality to begin with. Additionally, the authors took steps to reduce the risk of degradation, such as transporting the supplements in light-proof boxes and storing the box in an airconditioned room at the trial site.

Since the HKI supports government-run vitamin A supplementation programs, and given the countries reported in the cost-effectiveness analysis may not have air-conditioned storage facilities to combat hot and humid weather, the possibility and degree of drug degradation should be included in cost-effectiveness analyses around VAS supported by Helen Keller International.

While no country is immune to this issue, the WHO states that health systems that are resource constrained with limited medicines regulation may be at higher risk for drug degradation.[8] A report by the African Union showed that out of 26 sub-Saharan African countries that had any medicine regulatory system in 2010, only 9 had quality control as part of their function.[9] Even when countries are able to regulate and ensure quality drugs are imported or manufactured, lack of sufficient cooling in transport and storage lead to degradation through exposure to heat and humidity.[10]

I could not find any literature describing patterns of degradation of drugs in the settings served by HKI. It likely differs substantially between countries and even between facilities, depending on climate, and temperature within pharmacies where the supplements are stored. It could be that shipments delivered during the winter are much more stable than those arriving in the heat of summer. One could suggest that bottles closest to a wall that is not well insulated are all degraded, or that most bottles are fine, with only the last couple of doses administered from it being affected. With the current evidence available, one can only speculate.

Recommendations:

The issue of drug degradation is global and will require significant systemic changes to address. This is outside the scope of what Givewell does. However, I think there is value in considering the potential impact of drug degradation as it relates to GiveWell's VAS cost effectiveness in the following ways:

1. **Effectiveness.** GiveWell currently estimates the relative reduction in risk of all-cause mortality for children between the ages of 6 and 59 months among children participating in VAS programs at 24%. As far as I could read, the studies that were included in the Cochrane review did not include any reporting on drug degradation, but this could at least in part explain the substantial differences in effect observed across different studies, particularly the differences between DEVTA and other smaller trials. The DEVTA trial was conducted in Uttar Pradesh, an area known for high heat and humidity that increases the likelihood of degradation. I do not think drug degradation can explain the total difference in relative risk reduction, but believe it should be considered as a contributing factor. As it stands, the effectiveness of the intervention may be overestimated due to unknown drug degradation. However, if GiveWell were to recommend additional funding to HKI that is earmarked for quality assurance, limiting the effect of unknown drug degradation, the potential impact of VAS could be larger than previously estimated.
2. **Coverage**. If a participant receives a drug that does not contain the minimum effective dose, they did not truly receive the intervention. Coverage can be significantly over estimated in settings where drug degradation is rampant.
3. **Supplement cost.** Accounting for drug degradation would increase the cost per supplement dose, as more doses that are purchased would need to be discarded. As part of the cost per vitamin A capsule, GiveWell assigns a "capsule wastage" cost. This estimate, currently at 10%, is based on GiveWell's judgement and is also used in their

SCI analysis. The capsule wastage is meant to capture the number of drugs that are paid for by the program, but do not end up treating the intended program population. This could be due to theft or drugs that reach their expiry date before they can be delivered to beneficiaries. However, this misses the potentially large cost of drug degradation – i.e. capsules that are paid for, but no longer have the potency to deliver the expected benefits, despite still being within its expiry date. If there are practices in place that limit the odds of giving degraded mediations to program recipients – an example being discarding supplements that were exposed to high heat – those costs should also be considered. Using the 10.5% estimate of the WHO, this would lead to a cost per capsule of $0.07. However, this does not translate in a 10% change in overall cost-effectiveness.

Conclusion:

Drug degradation may have significant impacts on the true effect of interventions recommended by GiveWell. Particularly in VAS, there has been evidence to suggest that drug degradation is present even when best practices that are not available to all facilities served by HKI are followed.

This issue may also have implications for CEA among other programs currently recommended by GiveWell. Malaria drugs in particular seems to be popular targets for counterfeiting. It is estimated that $38.5 million is spent on falsified and substandard antimalarials in sub-Saharan Africa, causing between 31,000 and 116,000 deaths.

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