

1997 ALBERT LASKER AWARD FOR CLINICAL RESEARCH

Clinical research and the human condition: Moving from observation to practice

One is said to be the product of early experiences, perhaps stretching back to the womb. A more readily recalled encounter, considerably later in life, may have colored my personal approach to clinical research and the imperative for application.

During the first year of medical school, I visited with a brilliant visiting professor whose lectures on cell growth had captured my imagination. He generously spent several hours reviewing his reasoning and sharing his vision. As we left his darkened laboratory, I naively proclaimed my excitement with the potential his work must hold for control of cancer. He responded with astonishment and a hint of disdain. Dramatically dropping his briefcase, he declared, "Young man, if I thought my work had any practical application I would abandon it immediately." The reader can only imagine the impression this made on a young student who naively believed "medical" science was urgently seeking cures for our ills.

Fast forward a decade. The former medical student is settling into a three-year research project in Indonesia designed to "provide all the answers you need to know to control xerophthalmia" (then the best recognized manifestation of vitamin A deficiency and the only one of interest to clinicians and public health officials)¹. My stream of research reports on xerophthalmia effortlessly entered ophthalmic canon^{2,3}. They stretched, but fit within the prevailing paradigm. An unanticipated finding, that vitamin A status was a determinant of childhood mortality, fell outside the paradigm and suffered a far different fate. Pursuing that vision was almost as interesting a sociologic journey as it was a scientific one.

New insights, old paradigms

Over 100 years ago, Virchow declared that "science" absorbs a new discovery in three stages: it's initially ignored, then attacked, and once incontrovertible, recognized to have been "known all along." This sounds like the classical reaction to bad news: denial followed by anger, and finally — acceptance. When and why this response? One can only speculate.

The initial report associating vitamin A deficiency with increased mortality⁴ (Fig. 1) was received with deafening silence. It elicited a single letter to the editor, questioning a minor technical point. Despite our provocative suggestion that vitamin A supplementation might reduce overall childhood mortality by at least 16% (e.g. a million deaths every year), no one (but us) pursued the issue. Not long before, an NRC committee had advised against funding studies to investigate the systemic impact of improving vitamin A status on the basis that it rarely occurred in isolation and its correction was therefore unlikely to have a discernable impact.¹

Fortunately funding was obtained for a randomized trial that demonstrated vitamin A supplementation dramatically reduced preschool-age mortality⁵. Published (as a lead) in *Lancet* and accompanied by a supportive editorial, it elicited a "stage II" response. Letters to the editor poured in, challenging the methodology, ethics and conclusions. One particularly convo-

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luted missive, from a respected senior scientist, declared the entire hypothesis and results bunk, but maintained, nonetheless,

that the trial was unethical!

There was now interest, even if largely negative. A growing number of research teams began to pursue the issue, even if to discredit it (an entirely valid hypothesis). One researcher, expressing the prevailing opinion, was quoted in a published interview: "If only Al had claimed a 10% impact, we might have believed it." This was a new approach I'd never previously considered: diluting positive results to make them more palatable to the disbelieving.

Paradigms, policies and persistence

Persistent intellectual commitment facilitates the development of coherent new paradigms and the policies that emanate from them. While many scientists persistently stick to an area of inquiry, others, particularly epidemiologists and other clinical researchers, often do not. They seem to be detached from the underlying implications, conducting investigations yielding facile conclusions with little attempt to get to the heart of the matter or reconcile potential discrepancies. Seven major controlled trials followed ours¹. Most results were consistent with the original hypothesis and with one another, almost amazingly so considering the vast variation in populations, cultures, practices, study design and conduct⁶ (Fig. 2). But two of the eight failed to demonstrate a significant impact. Why? Careful, continued attention provided ready explanations¹. From an exchange of letters to the editor, it became clear that in one the potential impact of vitamin A supplementation was blunted by intensive surveillance and treatment of all enrolled children, dramatically reducing mortality in both arms of the trial and thereby eliminating the ability to detect any impact. Children in the other trial were considerably better off than the average third world child, suggesting a baseline vitamin A status better than average, precluding significant improvement by supplementation or a meaningful impact on mortality.

The emerging new paradigm was further strengthened by grow-

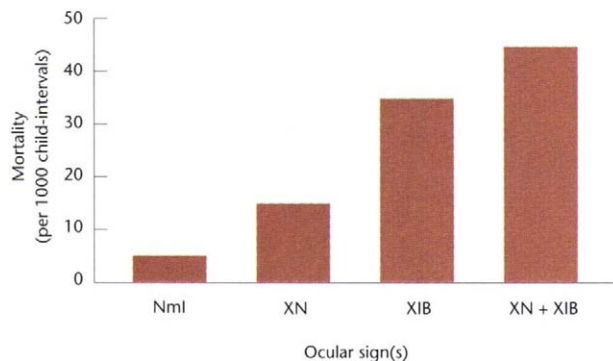
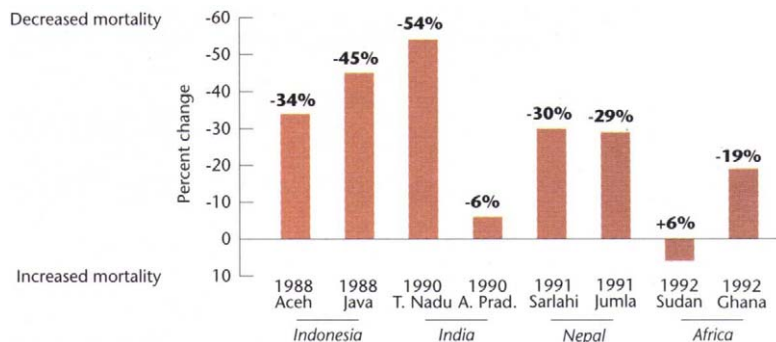


Fig. 1 Mortality associated with vitamin A deficiency (classified by stage of xerophthalmia).

COMMENTARY

Fig. 2 Impact of vitamin A supplementation on child mortality.

ing evidence that vitamin A status influenced case-fatality of hospitalized measles cases^{7,8} and, to the same degree, measles cause-specific mortality in the community-based prophylaxis trials¹. One “red herring” that threatened this coherent geometry was readily nipped in the bud. An otherwise meticulous community trial reporting an overall 54% reduction in preschool mortality maintained they were unable to detect a reduction in measles-related deaths. The authors, and an accompanying editorial⁹, offered a variety of hypotheses to explain this apparent discrepancy: our studies had used large doses of vitamin A while theirs had used small ones, the vitamin was administered (in the hospital treatment trials) shortly after, rather than weeks before the onset of measles infection, or perhaps the virus was a different strain. Fortunately the published paper contained the raw data explaining the apparent discrepancy; unfortunately, the authors of the paper and the editorial overlooked it. The control group contained 12 measles deaths, the vitamin A group 7, about as close as one could come to the average 50% reduction observed in the other trials! The authors had confused a lack of “statistical significance” (imposed by their small sample size) with the absence of clinical impact.

The collateral measles-vitamin A studies provide another, more generic lesson about the value of persistence. After publishing results of our initial randomized treatment trial of hospitalized measles cases⁷, we discovered, much to our chagrin, that an almost identical study had been published in the same journal 50 years earlier¹⁰! Why had that study not changed medical practice and health policy? Presumably isolated and unpursued reports are often insufficient to change behavior and existing paradigms. In contrast, our report, coming hard on the heels of the community trials, resulted in almost immediate recommendations from WHO and UNICEF that large-dose vitamin A be used in treating measles¹¹. What might have been the fate of the vitamin A/micronutrient initiative if we’d not followed up on our original observational study⁴ with our randomized trial⁷?

Persistence also has a more mundane but powerful long-term effect. By periodically spiking interest with “booster inoculations” of data, conferences, lectures and editorials, it keeps the issue alive and before the scientific and policy communities. To provide a useful insight and then sit back expecting someone else to exploit it leaves a lot to chance. The policy-engaged scientist abhors chance (though as Pasteur recommended, he or she seizes on whatever opportunities it presents).

Persistence also helps change paradigms, a prerequisite for changing policy. Prevailing orthodoxy assumed xerophthalmology was the major manifestation of vitamin A deficiency, and that mild xerophthalmia (nightblindness, Bitot’s spots) represented mild vitamin A deficiency. However, while our original

observational study⁴ suggested that eliminating all xerophthalmia and the increased mortality associated with it would reduce preschool childhood mortality by 16%, intervention trials in the same population reduced mortality by 33% or more^{2,5,12}. Why the discrepancy? Because many of the non-xerophthalmic children suffered from milder but clinically significant vitamin A deficiency¹, resulting in their increased risk of death, anemia, and other protean, systemic consequences¹³. “Mild” xerophthalmia is no longer equated with “mild” vitamin A deficiency. Xerophthalmia represents moderate to severe deficiency; previously overlooked systemic consequences become manifest at much milder degrees of deficiency (Fig. 3)¹. This new vitamin A paradigm has had collateral effects, helping to spur research into potentially overlooked consequences of zinc, iron, iodine, folate and other micronutrient deficiencies.

Ethics and health policy

Producing adequate evidence to affect health policy may pose a particularly challenging ethical conundrum. The successful series of Indonesian studies resulted in a national commitment to controlling vitamin A deficiency that has achieved considerable success. However, the Philippines, Nepal and India, countries in the same region and rife with xerophthalmia, questioned the relevance of the Indonesian data to their own situation. Indeed, influential segments of the Philippine scientific community claimed Filipino children were uniquely sensitive to the side-effects of large-dose vitamin A supplements, necessitating a randomized safety trial before launching a larger prophylaxis study.

No country was willing to act without a local trial. As more data

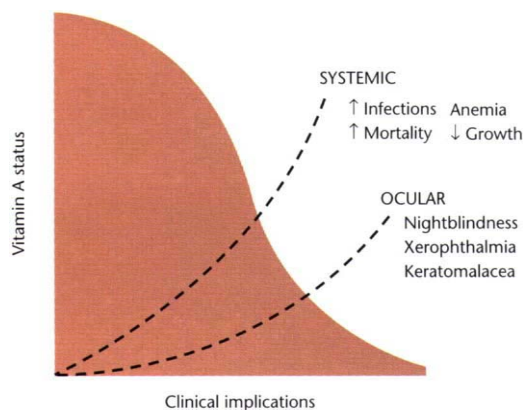
**Fig. 3** Schematic representation of temporal relationship between decline in vitamin A status and onset of systemic and ocular complications.

IMAGE
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Fig. 4 Countries categorized by degree of public health importance of vitamin A deficiency.

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became available from hospital and community trials, the ethical nature of further trials came into question. There is no "gold standard" for determining when a trial is ethical or not. I considered these ethical, and freely participated in them, on the basis that: 1) they were conducted in areas where vitamin A prophylaxis was not carried out — therefore no children would be denied vitamin A who might otherwise have received it; 2) if vitamin A were useful, then half the children in the study (those in the vitamin A arm) would benefit immediately; 3) if the trial were successful, all children would ultimately benefit from a change in national health policy; 4) in the absence of a trial, all children would be denied the benefits of a national control program.

This satisfied some critics, but not all. It soon ceased to satisfy even me. With successful trials from three Asian countries, was one justified in satisfying demands for replicative studies in Africa? Without them, it was clear no African government was likely to divert limited health resources to a national vitamin A control program. Once two trials were in, the issue became even more acute. Some ministries of health still held out; I, for one, could not in good conscience condone or participate in further studies that withheld vitamin A from preschool-age children. Did I have a simple standardized rule for making this decision? No, just a personal conviction that "enough was enough." Will professional ethicists be able to formulate one standardized algorithm, sufficiently flexible and pragmatic to move policy? I have no idea, but it is a fertile field for their endeavors. Policy is, after all, made in the public arena (for a lesson on how not to formulate policy, review recent events pertaining to the appropriate age for mammography screening).

Conclusions

Like basic research, successful clinical research requires commitment, luck and innovation. But because clinical research is closely connected with clinical practice, the committed researcher must

go beyond discovery and construction of new scientific paradigms to change practice and policy. In the vitamin A field a real change has taken place. In 1972 only a handful of countries were committed to controlling deficiency; today, the problem is considered a worldwide scourge (Fig. 4) and control programs, of varying maturation and intensity, are active in over 60 nations.

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