Collateral damage in the battle against hypovitaminosis A?1,2

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Chinese diplomats killed in the embassy of the People’s Republic of China in Belgrade, Red Cross workers bombed in a warehouse in Kandahar, and Afghani women crushed by a crate of humanitarian rations are recent examples of collateral damage, which occurs when innocent people become casualties of missions of supreme urgency and high moral justification. It is the consequence of being caught in the path of “friendly fire.” Collateral damage has its reflection in medical and public health risk assessment as well. When we and other young house physicians were undergoing clinical training in the 1970s, we would often discuss the example of smallpox vaccination and comment among ourselves that more people were succumbing to vaccinia from the vaccinations than were then actually dying of smallpox itself. Shortly thereafter, of course, obligatory vaccinations were suspended, and the book was closed on the smallpox pandemic. When 3200 persons were killed in the attacks on the Pentagon and the World Trade Center towers, the specter of biological terrorism with the smallpox virus reopened that book, with a call for universal vaccination of the 280 million residents of the United States. According to calculations from the Centers for Disease Control and Prevention, 2000–3000 deaths would be attributable to any universal smallpox vaccination campaign, almost the number of deaths that occurred during the first strike of the new war. Such are the equations for collateral damage in the public health aspects of war and in public health battles.

For some of us involved in micronutrient deficiency issues in developing countries, it has been disconcerting to see the brouhaha arising in the medical press over something gone (fatally) awry in a recent mass distribution of high-dose oral vitamin A supplements by the United Nations Children’s Fund to 3 million children younger than 6 y in the Assam province of India. Despite the flurry of commentary that appeared on the pages (1) and web pages (2–7) of the British Medical Journal, the facts remain elusive, pending the filing of an official inquiry. What is clear, however, is that 1) the vitamin A preparation was a liquid, produced less expensively within India (rather than the more costly, imported gelatin capsules); 2) the possibility of giving more than the intended 2-mL dose was produced by shifting from 2-mL spoons to 5-mL medicine cups for dosing; and 3) it was widely claimed in the Indian press that numerous recipients of the vitamin A supplements were made ill and that the deaths of 14 recipients are attributable to the vitamin A distribution (1, 2, 4, 5). In belligerent tones from within India came the allegation that rates of vitamin A deficiency in the Assam province did not justify public health intervention and that vitamin A supplementation will not reduce child mortality (4, 5). In this latter respect, some historical factors are clear, and truth should not become the first casualty of this rhetorical skirmish.

As reviewed by Narasinga Rao (8), former director of the Indian Nutrition Institute, safety and efficacy trials of periodic supplementation were conducted in India with pulse doses of 90000 retinol equivalents (300000 IU) vitamin A (9, 10) in the context of reducing nutritional blindness; this dose was certified as safe and effective (11). Within the subsequent paradigm of hypovitaminosis A and mortality, analysis of data from field-level vitamin A intervention trials suggests that on average a 23% reduction in mortality from common childhood infection could result from public health campaigns (12, 13) such as those being undertaken in Assam. Moreover, trials in India (14) and Nepal (15, 16) provide some of the most powerful mortality-reduction effects, ranging from 26% to 50% of lives saved with supplementary vitamin A. Interestingly, low-dose weekly supplementation decreased mortality by the greatest amount (14).

If the human ecology of Assam is anything like that of the nearby Orissa province, hypovitaminosis A probably affects more than 50% of the population targeted for vitamin A intervention (17). India’s National Foundation for Health Statistics reports a mortality rate of 89.5% in children younger than 5 y. Hence, at least 135000 of the 3 million children aged 2–5 y in 2001 living in the Assam province would be expected to die before reaching their 6th birthday. This means that, across the province, 185 Assam children in this age range would die in accidents or of natural causes on any given day, with or without a vitamin A distribution campaign. Moreover, if the overall projected death rate were reduced by one-fifth as a result of a sustained and universal vitamin A intervention policy, 27000 lives saved could be attributed to the measure. If one extended the smallpox vaccination collateral damage argument to the hypovitaminosis A situation in India, one could even accept the validity of the claim that 14 deaths are attributable to the high-dose vitamin A pulse campaign. With this premise, one might even rate the favorable equation of 642 lives saved for every vitamin A-related death as well. Pending an official inquiry, this example is not the best equation of 642 lives saved for every vitamin A-related death as well. Pending an official inquiry, this example is not the best equation of 642 lives saved for every vitamin A-related death as well.
mortality over a 3-y period in this cohort of vitamin A recipients in the Assam province as an acceptable tradeoff.

Trained in the clinical practice of medicine, we two physicians have a professional discomfort with the calculus of collateral damage, whether applied in military war or in public health battles. Calculations of collateral damage involve ethical dilemmas and converging and diverging ethical standards. As a discipline, ethics has developed an orderly set of principles. Among them are principles of autonomy, utility, and nonmaleficence (18). The first principle relates to a respect for the free will of individuals, which in the present context would mean that they were suitably informed of the risks and benefits and participated voluntarily. The second principle relates to effecting policies that provide the greatest good for the greatest number. The third principle maintains that the proponents of a measure should do no harm to their clients.

As physicians sworn to the Hippocratic primus non nocere (first do no harm) dictum, we must point out the ethical dilemma raised by the nonmaleficence principle that is entailed in any acceptance of the concept of an acceptable attributable mortality risk from a public health intervention. We must point out that retinyl palmitate is both a nutrient and a drug, depending on the dosages involved. Indeed, just having a large amount of the compound in a vial poses a risk of accidental poisoning. Retinyl esters can be sight-saving and life-saving drugs. The standard unit dose of vitamin A for a therapeutic application, as in acute xerophthalmia or complicated measles, is 200000 IU or 60000 retinol equivalents, and this dose is to be repeated on the next day (19). No human food, except for morsels of shark or polar bear liver, could ever deliver this amount of preformed vitamin A in a single sitting. From this logic, it is reasonable to propose that administering any amount of a potentially toxic nutrient that cannot commonly be consumed with a meal should be subject to the requirement of “medicalization” of its use. A confirmed diagnosis of deficiency and medical supervision would be the minimal criteria for administration of high-dose vitamin A. These procedures would clearly raise the ante on safety considerations and reduce the chances of doing any harm. In the public health battle against hypovitaminosis A, however, these criteria would raise the cost of programs and reduce the efficiency of covering a population’s risk. With this approach, we will have reduced collateral damage from high-dose vitamin A at the probable expense of greater net mortality, ie, that associated with hypovitaminosis A itself.

Even constrained under a safety-first, Hippocratic resolution of the ethical dilemma, public health authorities still have options to reduce child mortality in hypovitaminosis A–endemic populations with campaigns of vitamin A promotion that involve no pharmacologic agents and only minimal risk. This solution would rely on foods. What separates industrialized societies from the risk of hypovitaminosis A is the preformed vitamin A used to enrich and fortify processed foods (20). Eventually, periodic supplementation could be replaced by fortification of staple items (21) or a variety of processed foods (22). Meanwhile, the high-dose supplementation scheme could move from medicinal preparations of potentially toxic preformed vitamin A to virtually equally potent (23)—but innocuous and nontoxic (24)—provitamin A carotenoids in an oily matrix. A protective benefit comparable with that for high-dose vitamin A supplements can be claimed for periodic administration of red palm oil (8, 17, 25). Moreover, the autonomy of informed choice is certainly maximized in food-based interventions, because the public at large understands matters of food better than they do those of chemical prophylaxis.

The greatest ethical transgression that can occur is that of the big lie. Misinformation and disinformation are the greatest dangers to public health efforts at all levels, because they rob the populace of the autonomy to make an informed choice. On the one hand, incidents such as the one that occurred in the Assam vitamin A–distribution campaign allow a forum for the naysayers and the doomsayers to spread truly lethal disinformation, ie, that conducive to inaction. On the other hand, expediency and efficiency justifications for accepting some collateral damage cannot be a priori answers to the ethical dilemmas that arise in the battle against vitamin A deficiency. Although it may cost more efforts and resources, we must seek approaches that are both effective and safe. Such approaches will include providing the greatest good for the greatest number, ie, both those at risk and those not at risk of deficiency. They will also allow for true informed free choice among the recipients of the interventions. These are the challenges and the ethical lessons of the Assam incident.

REFERENCES