Invited Commentary

Micronutrients and infections: Report of a multidisciplinary workshop held in Southampton, UK, 4–6 October 1998

Wellcome Trust and United States Agency for International Development*

Organization and objectives of the meeting

In October 1998, a small multidisciplinary meeting was held in Southampton, UK to address unresolved dilemmas in the area of micronutrients and infection. Representatives from developing and developed countries with expertise in clinical disciplines – nutrition, infectious diseases and immunology – were invited, as well as professionals from related fields, notably epidemiology and medical ethics. Within the nutrition field, experts in basic nutrition and the human biology of three selected nutrients, namely vitamin A, iron and zinc, were included among the participants.

A fundamental premise in convening this meeting was interdisciplinary isolation which is thwarting progress toward public health solutions. Much could be gained by cross-pollinating field observations with an understanding of the mechanisms provided by basic scientists. The final accountability for the resources invested in research and aid programmes is the satisfaction of the needs and expectations of the at-risk population. This will only come when the scientific communities of nutrition, immunology and infectious diseases mutually translate what is known – and what becomes known – to its appropriate application to policy and programmes for public health. Existing programmes that do not benefit the population, or do not benefit them in a cost-effective way, must be re-evaluated. Promising interventions to reduce the prevalence of micronutrient malnutrition, or to exploit the anti-infective properties of exposure to micronutrient supplements, must be guided to the target populations who can gain the greatest benefits.

The organizational strategy was to provoke a maximum amount of interaction and discussion among the multidisciplinary participants. The meeting therefore included a mixture of formats: plenary lectures, working-group sessions and workshops (Table 1).

Introduction

Along with redressing undernutrition, combating infectious diseases has been traditionally the major concern of public health officers responsible for the 80% of the world's population living in developing countries. Although the existence of a complex interaction between malnutrition and infection was first delineated 40 years ago by Scrimshaw *et al.*[1], events in the last decade suggest that this interaction must be reinvestigated[2,3]. This challenged researchers to apply the most modern concepts and techniques in human biology and programme designers to seek innovative, cost-effective and far-reaching interventions to improve the nutritional and health status of underprivileged populations.

The advances made by chemotherapeutic agents (antibiotic, antiviral, antimycotic, anthelminthic) and immunizations in the 20th century have transformed the demographic profile of developing countries. Increased child survival has resulted in the inexorable extension of life expectancy in developing countries. Despite these gains, in the last three decades, one child in three does not survive to adulthood.

Field studies of micronutrients and infection may be gaining momentum. Increased vitamin A intake can reduce mortality from childhood diseases[4–6]. Death from measles complications in hospitalized children is also reduced by high-dose vitamin A therapy[7]. Even maternal mortality related to childbirth may be reduced by weekly supplementation with vitamin A or β-carotene, although the mechanism is unclear[8] and further studies are needed. Zinc supplementation has been suggested to decrease the incidence of persisent diarrhoea in children[9,10]. In contrast, adding iron to complementary food in a developing country may increase the experience of diarrhoeal gastroenteritis[11] although this has not been confirmed[12]. For those interested in directing scientific research toward a new understanding of the interactions of micronutrients, infection and the underlying immunological mechanisms, the opportunity to identify the gaps in our knowledge would help refine priorities for research investment. For the bilateral and multilateral donor agencies, such as WHO, FAO, UNICEF and WFP, whose goals are to provide programme and social and economic development assistance, the challenge for combating infectious diseases has been to identify the

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Table 1 Propositions for discussion

Single micronutrients
The observed effects of vitamin A supplementation on childhood mortality is related to the underlying nutritional deficiency: it is not a physiological effect of pharmacological doses of vitamin A
The mechanism of therapeutic and prophylactic effects of zinc on diarrhoeal disease is due to local, gastrointestinal effects and not via systemic effects associated with the alleviation of underlying zinc deficiency
Iron status determines susceptibility to – and severity of – infections
Multiple micronutrients
There are potentially significant toxic consequences of a population-based, universal supplementation of vitamin A, zinc and iron
Absorption and utilization of micronutrients (vitamin A, iron, zinc) are altered during infection
The effects of multiple micronutrient supplements on infection are not independent of each other, and are additive or synergistic
The acute-phase response
The acute-phase response to infection enhances survival
Cytokines mediate the acute-phase response's influence on vitamin A by transcriptional regulation
Cytokines mediate the acute-phase response's influence on zinc by transcriptional regulation

most cost-effective options for increasing child survival. These will invariably include a combination of interventions related to: environmental health; immunizations; chemotherapeutic agents that may adversely affect the intake of certain micronutrients; and nutrition and health counselling and education.

Discussion and conclusions

Consistent with the objective to provide research interactions between the different disciplines, plenary lectures by Gerry Keusch (NIH, USA) and George Griffin (St George's Hospital, University of London, UK) covered 'Micronutrients and acute infections'. This set the framework for the ensuing discussions on the specific propositions listed in Table 1. The major revelations and conclusions arising from the 2.5 days of deliberations related to: (i) diagnoses and assessment of populations; (ii) immunological mechanisms relating nutrition to infections; and (iii) the ethical conduct of research on public health interventions.

Diagnoses and assessment of populations

The limitations of reliability in the assessment of human nutritional status are widely recognized. Cross-sectional epidemiological surveys and longitudinal intervention studies associating micronutrients to infections frequently have no markers of nutrient status; when they do, the quality and validity of the diagnosis can often be called into question. The meeting addressed the persisting question of whether current knowledge is clouded by limitations in the diagnoses of nutritional, immunological and even infectious status.

Regarding nutritional status, it was widely emphasized that infection itself alters metabolism and redistributes circulating nutrients. Two contrasting views were put forward to explain why vitamin A, iron and zinc concentrations decline during active infections. One was that nutrients move preferentially from serum to tissue sites to participate in the humoral and cellular host defence response to the infection. The other was that nutrients are cleared from the circulation to deprive pathogens of the micronutrients they need for proliferation. Most importantly, however, it may be erroneous to interpret low micronutrient levels in the blood as defining a deficiency state. Correspondingly, it may also be impossible, or unwise, to try to restore normal circulating levels of micronutrients during episodes of infection.

In terms of infectious status, the reliance on simple symptom categories, unaccompanied by specific aetiological diagnoses, was lamented. All the diseases that present with watery diarrhoea or with bloody dysentery are unlikely to be equally susceptible to the same chemotherapeutic agents. They are also unlikely to have the same associations with nutrition. How does one interpret a strong cough in terms of the severity of an illness? Does it reflect a more severe infection or is it the result of a more robust immune response?

In terms of immunological status, the absence of suitable, non-invasive techniques to assess the immune status in relation to nutrition, and confounding from immune activation or suppression during infections, limits our understanding of the mechanistic relations between nutrition and infection. Also urgently needed are measures to monitor both the activation of the acute-phase response (APR) to infection and the systemic metabolic reaction to invasion by pathogens or exposure to their toxins.

Immunological mechanisms relating nutrition to infections

The APR is at the interface of the interaction between nutrition and immunity in acute and chronic infections. The metabolic response to infections includes the activation of fever, induction of anorexia, production of specific acute-phase reactant proteins, and proliferation of immune cells and antibodies that are all mediated by a cascade of hormonal peptides known as cytokines[13]. Consequently, nutrients are simultaneously lost from the body, redistributed from circulation to tissues, and blocked from utilization.

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The APR evolved, most likely, to mediate the survival of potentially viable victims of infections among members of the community. The ability to modify the human APR pharmacologically, either with agents that enhance or inhibit the production of the cytokine mediators both generally and selectively, is advancing. Moreover, various micronutrients have these modulatory effects. The clinical applications of the modifying drugs and the clinical consequences of supplementation with certain nutrients to infected individuals are issues of research concern. Pharmacological or nutritional manoeuvres to dampen or augment the APR in infected patients are currently fraught with uncertainties.

In a plenary session on the final day of the meeting, the importance of the interaction between the infective agent, the host and nutrition was illustrated by Melinda Beck (University of North Carolina at Chapel Hill, USA) using a new paradigm. In a murine model of Coxsackie virus cardiomyopathy, the virulence of the virus was shown to be genetically altered by the nutritional environment of the host. That is, a non-virulent strain that was used to infect mice with antioxidant nutrient deficiencies became virulent during replication in the host. This observation provides a new dimension to study micronutrient–infection interactions that may achieve greater prominence in the future.

Ethical conduct of research on public health interventions

The deliberations of the meeting were observed by a medical ethicist (Tom Wilkie, Wellcome Trust, UK). The history of research design and aspirations for improving investigations, especially in developing countries, was raised during the meeting. A set of precepts was emphasized in response to particular insights sought for the micronutrient–infection interactions. This was that we, as scientists, are responsible for the human volunteers participating in the research, the institutions that employ them or provide financial support, and our own self-respect and integrity. The ethical guidelines for human investigation of the World Health Organization's Council of International Organizations of Medical Sciences (CIOMS) should be consulted and adhered to when conducting research in developing countries[14].

Ethical issues permeate all aspects of the research and programme agendas related to micronutrients and infections. For many of the phenomena observed in large clinical trials, doubt remains as to whether the observed anti-infective effects of the administration of a micronutrient have a nutritional basis or are pharmacological in nature. This has important biological and programme implications, as well as practical consequences for both research donors and regulating agencies. By modern convention, a drug trial evolves in a series of sequential steps with Phase 1 being an examination of its safety, Phase 2 of its potential efficacy outside a comparative focus, and Phase 3 is a formal, controlled comparative trial. If nutrients are having their anti-infective effects via a pharmacological mechanism, subjecting huge populations to massive trials would need to become the last option, rather than the first. The safety aspect of the mass distribution of micronutrients is illustrated by the observations related to zinc intake and the progression of[15], and mortality from[16], HIV in a cohort of seropositive men. Higher intakes of zinc from the diet and the use of zinc supplements were associated with a faster progression to AIDS and to an earlier mortality.

Future challenges of micronutrient–infection interactions

The future challenges relate to developing improved research approaches to resolve the remaining issues on the interactions between vitamin A, iron and zinc with viral, bacterial and parasitic infections, and the translation of these findings to reducing mortality and morbidity from communicable diseases in developing countries. Achieving these goals will require better technology, advancing biological and epidemiological concepts, and improving interdisciplinary and intersectorial communication.

The design and implementation of basic and applied research needs to achieve an even higher quality. In epidemiology assessments of morbidity, specific aetiological diagnosis of the infectious agents – rather than simple recording of infectious symptoms or syndromes – are needed to make sense of the nutrient associations. With respect to nutritional status, we need to differentiate better when low circulating levels of a nutrient indicate metabolic alterations due to infections and when they signify true deficiency states[17]. Complementary to this, we need to develop diagnostic approaches to nutrition that are not confounded by the presence of active infections. It was suggested that perhaps too much emphasis has been placed on evaluating maximal response capacity and a more 'functional' approach, which recognizes immune responses are regulated and interactive, is needed for measuring populations in the field. In all three domains of infectious epidemiology, nutritional assessment and immune status evaluation, efforts to make specimen collection procedures minimally invasive, safe and culturally acceptable are paramount. There needs to be a heightened recognition of the risks involved in all studies, and the research community must take responsibility for the health of the participants in experimental interventions.

In the conceptual domain, the phenomenology of observing associations between nutritional status (or nutrient administration) and infectious diseases must give way to determining the underlying mechanisms of

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the host immune response. One of the foremost reasons for integrating the various disciplines is to design research that is both hypothesis-driven and based on current understanding, while targeted to filling in the gaps in our knowledge of the mechanisms through which they operate.

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