Malnutrition and infection: an update

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The original Scrimshaw, Taylor and Gordon conceptual framework for the interaction of nutrition and infection has well served the scientific community for almost half a century. At its core is the notion of synergistic (mutually reinforcing) and antagonistic (mutually nullifying) influences of the malnourished state on infectious conditions and vice versa. Research on a series of advancing fronts, however, has allowed the incorporation of both relevant public health issues (parasitosis, emerging infectious diseases, obesity and overweight, etc.) and advancing science (molecular immunology, oxidation biology, multiple micronutrient deficiencies, etc.). The present review is an interpretative update on close to 50 years of demographic and epidemiological evolution in the field of human nutrition and the implications for the interaction in the context of microbiological and immunological developments on the infectious side of the dialectic.

Infection: Malnutrition: Micronutrients: Immune modification

The interaction of malnutrition and infection

The literature review and critical analysis by Nevin Scrimshaw, Carl Taylor and John Gordon in the treatise Interaction of Nutrition and Infection, first published as a review article in 1959\(^1\) and then as a World Health Organization monograph in 1968\(^2\), set out a paradigm which has endured for almost a half century.

Demographics, food supply and epidemiological transitions determine the specific relevance of the malnutrition-infection interaction in individual circumstances. Until the advent of the AIDS pandemic, average life-expectancies were rising everywhere in the world; this was largely as a consequence of a reduction in early deaths from infectious childhood diseases. Today, it is in only one region of the world, Africa, where infectious disease is the leading cause of mortality. With receding infectious mortality and increasing age, chronic non-communicable diseases have become the leading causes of death everywhere else. With a rise in life-expectancy over the years since the publication by Scrimshaw et al\(^1\), the world’s population has grown to over 6 billion persons, such that the absolute number of potentially lethal infectious episodes remains the same, or continues to rise\(^3\).

Rates of severe protein-energy malnutrition have declined over the decades as food supplies have generally kept pace with population growth and distribution has improved. If agricultural technology cannot continue to keep up with the rising food demand, however, there could be a reversal of the current downward trend in macronutrient deficiency states\(^4\). The populations living in cities and experiencing rising affluence, moreover, are most likely to have access to a calorie-sufficient diet, and to change their selection of foods and beverages away from the national traditions. Such nutrition transition\(^5\) generally leads to an increase in consumption of animal fat and protein, with a reduction in the contribution of complex carbohydrates and a reciprocal increase in refined sugar intakes.

The purpose of this review is to provide an update for the first decade of the third millennium on the biological science and the public health relevance of the paradigm of the interaction of malnutrition and infection, in the face of dynamic and evolving changes in diet and infectious disease patterns and risks.

Micronutrients and disease resistance

International research has provided many insights in recent years on the therapeutic and prophylactic effects and efficacy of micronutrient fortification or supplementation on infectious disease resistance.

Micronutrients as an adjuvant to the mitigation of infections:
On the therapeutic side, extensive research and meta-analysis largely confirms a survival advantage and reduction in morbidity for complicated measles in hospitalised children with high-dose vitamin A supplementation\(^6–8\). Similarly, supplementation with oral zinc in diarrhoea, treated with oral rehydration therapy, reduces the duration and severity of episodes, and has been officially recommended by the WHO\(^9\).

Micronutrients in the prevention of infections:
Ensuring adequate micronutrient status is important for the prevention of certain infections. Although vitamin A has been termed the “anti-infective nutrient,” there is little evidence that it prevents the incidence of new infections\(^10,11\).

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It is more likely that the effect of vitamin A supplementation on preventing death from childhood disease\(^{12,13}\) is one of reducing the severity of infectious illnesses. The one area in which this vitamin has actually been strongly suggested to prevent infections is in small premature infants\(^{14,15}\).

Similarly, although iron supports components of the host defence system such as phagocytosis, there is no evidence of it preventing infections\(^ {15,16}\). In contrast, zinc is emerging as a nutrient whose supplementation can reduce the risk of infections\(^ {17}\) and re-infection\(^ {18}\). Vitamin D and infection is a recently emerging area of interest with promise for prophylactic application in epidemic viral diseases such as influenza and diverse microbial infections\(^ {19,20}\).

**Broadening the focus on human pathogens and malnutrition**

One of the important features of the past five decades has been the emergence of new infectious agents important to the overarching nutrition-infection paradigm which were not considered in detail by Scrimshaw \(\text{et al.}\)\(^ {2}\). This is true for parasites, because their importance to human health was not fully appreciated five decades ago. It is also true for the human immunodeficiency virus (HIV), which had not yet appeared, and for a series of other pathogens which have only since been emerging, or re-emerging, as causes of human infection.

**Malnutrition, protozoa and multicellular parasites:**

One classical scenario of pathogens depleting nutritional stores of the host is the blood loss caused by intestinal hookworms. The biology of protozoa and multicellular parasites is much more complex than that of viruses or bacteria, having a more intricate interaction with host nutritional status. The influence of human nutritional status on the success of parasitic infection has intrigued investigators\(^ {21}\). One particular such example is the interaction of host vitamin A status and certain filarial nematodes which have evolved elaborated retinoid receptor systems to access the vitamin A of their host\(^ {22}\).

**Human immunodeficiency virus:**

The HIV/AIDS pandemic began with the discovery of the syndrome in 1981. A large body of experience from experimental micronutrient interventions, aimed at potentially enhancing immune function, viral counts and disease outcomes in mothers and their offspring, is available for review\(^ {23}\). One paradoxical finding stands out: except for infants, in which vitamin A supplementation can be lifesaving, high-dose vitamin A often has adverse consequences for HIV. On the other hand, a multi-micronutrient supplement has produced benefits in mothers and infants\(^ {23}\). The effect of Vitamin D on HIV\(^ {24}\) is currently under inquiry, based on a series of theoretical considerations.

With the advent of AIDS, we observe that, in addition to the physiological, the social aspects of the infection can be detrimental to an individual’s nutritional well being. The social stigma surrounding AIDS, as well as the loss of working and earning capacity, compromises the food security of the household, contributing further to nutritional deficiencies\(^ {25,26}\). In retrospect, a similar social dynamic of marginalisation undoubtedly occurred with other infections of chronic evolution, such as leprosy and the white plague (tuberculosis) in the past, but they were not recognised in the infection-malnutrition context.

**Other emerging infectious diseases:**

AIDS is considered an emerging infectious disease, having only been recognised in 1981. It is, however, not alone in this category of diseases which have emerged, often by zoonotic transmission, to the human population. Table 1 provides a list of selected organisms or infectious syndromes in the emerging category for which virtually nothing is known of the nutritional influences – synergistic, antagonistic or nil – which offer opportunities for new discoveries of potential public health importance. Among the reasons for the emergence of new human pathogens are: migration and changing demographics, rapid international travel, microbial adaptations, altered land use and human behaviour\(^ {27}\).

**Overnutrition and infection**

The term “malnutrition” in the era of Scrimshaw \(\text{et al.}\)\(^ {2}\) was virtually synonymous with undernutrition. This was before the emergence of the nutrition transition\(^ {5}\). As argued by Uauy and Solomons\(^ {28}\), today we need to insist upon a broader and more comprehensive definition of malnutrition. In other words, one that spans the entire spectrum of deviant nutritional status, from short stature and below normal weight to

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<th>Table 1. A non-exhaustive listing of infectious agents and conditions in the domain of emerging and re-emerging infectious diseases</th>
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<td><strong>Organisms</strong></td>
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<td>Avian influenza H5N1 virus</td>
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<td>Bartonella</td>
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<td>Coxiella</td>
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<td>Ebola virus</td>
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<td>Ehrlichia</td>
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<td>Entericaggregative Escherichia coli</td>
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<td>Enterohaemorrhagic Escherichia coli</td>
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<td>Gymnophalloloides seoi (trematode)</td>
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<td>Hanta virus</td>
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<td>Human immunodeficiency virus (HIV)</td>
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<td>Nipah virus</td>
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<td>Nontuberculous Mycobacteria</td>
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<td>Norovirus (Norwalk agent)</td>
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<td>Metapneumovirus</td>
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<td>Monkey pox</td>
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<td>Penicillium mameffae</td>
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<td>Polymaviruses</td>
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<td>Saccharomyces cerevisiae</td>
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<td>Toscania virus</td>
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<td><strong>Infectious conditions</strong></td>
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<td>Babesiosis</td>
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<td>Coccidioidomycosis</td>
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<td>Meliodosis</td>
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<td>Mucormycosis</td>
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<td>Microsporidiosis</td>
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<td>Relapsing fever</td>
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<td>Rickettsiosis</td>
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<td>Severe acute respiratory syndrome (SARS)</td>
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<td>Tularemia</td>
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<td>Variant Creutzfeld-Jakob disease (mad cow)</td>
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<td>West Nile viral encephalitis</td>
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<td>Zygomycosis</td>
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the various grades of overweight and obesity. Indeed, sometime after the dawn of the new millennium, the number of persons worldwide classified as over-nourished, based on the criteria of the body mass index, became equal to those classified as undernourished, based on weight-for-age criteria.

Comparative reviews of body composition patterns in developing countries have shown the dual-burden of nutrition, with persisting sectors of the population in undernourished states while growing segments develop overnutrition. The underlying dynamics that have turned the traditional risk of being underweight to one of being overweight and obese in developing countries have recently been detailed. To the extent that problems of overweight continue to increase worldwide, these considerations will become even more important for infectious risk.

Overweight and infectious disease risk:
As far back as 25 years ago it occurred to Edelman to ask the question of whether obesity modulates infectious disease and immunity. It is surprising how few investigative responses this call received. In the realm of common consensus, it is suggested that obese individuals are more susceptible to infection than lean subjects. For reasons related to the anatomical suggestion that obese individuals are more susceptible to infections. Pregnant women taking iron-containing prenatal supplements in the context of iron excess and overload states while growing segments develop overnutrition. Indeed, some-what time after the dawn of the new millennium, the number of persons worldwide classified as over-nourished, based on the criteria of the body mass index, became equal to those classified as undernourished, based on weight-for-age criteria.

The immune system connection to nutrients and nutrition:
The most expansive evolution over the 4 decades of research has been the progressive accumulation of knowledge about the inner workings of the host immune system, from the biology of the cellular and humoral responses to the current peeling away of the molecular secrets. This progress in fundamental immunobiology has not been ignored by the nutritional community.

Antagonistic interactions of iron status and infection:
Weinberg has coined the term “nutritional immunity” to denote the situation in which the deficiency of a nutrient might provide protective advantage to the host by restricting the access to a nutrient required for the proliferation of a specific pathogen. The most common example of an antagonistic interaction arises in the context of iron excess and overload states. In 1949, Elsdon-Dew noted that fulminant amoebiasis was selective to certain ethnic groups in South Africa, namely Bantu males who have an excess of iron due to consumption of an iron-laden brew. Diamond et al. provided a mechanistic context for this phenomenon by showing in an animal model (the hamster) that the iron status of the animal conditions the systemic virulence of Entamoeba histolytica. In further experimental work, Beck et al. showed that a normally benign murine coxsackie virus damage heart muscle in vitamin E-deficient mice when overloaded with iron. In related clinical observations in pediatric patients, Brocks et al. documented an increased risk of gram negative sepsis with parenteral injection of iron dextran supplements.

Malaria has taken centre stage in the contemporary consideration of the antagonistic effects of iron and plasmodial infections. Pregnant women taking iron-containing prenatal supplements in Plasmodium vivax-endemic areas have increased susceptibility to malarial attacks. More dramatically, a major field intervention trial on the island of Pemba in Zanzibar, Tanzania, an area holo-endemic for the more lethal Plasmodium falciparum, was suspended. In-study monitoring revealed adverse effects such as increased hospitalisation and excess mortality in children under 36 months of age who had been randomised to receive 12.5 mg of iron daily, along with 50 μg of folic acid.

Molecular biology of the immune system:
The examples of discoveries concerning the role of the immune host defence at the molecular biology levels are too numerous and complex to summarise here. The insights began to emerge when immunologists with an interest in nutrition adopted and adapted the emerging tools of molecular biology. A case in point involving zinc is the work performed in Pamela Fraker’s laboratory in the late 1990s. She and her colleagues suggested the effects on lymphocyte glucocorticoid receptors from zinc restriction in laboratory rodents as a mechanism for immunosuppression. Emerging from the same era was the work of Melinda Beck and coworkers, which showed in a mouse model that the pulmonary damage due to an influenza virus is greater in a selenium deficient animal. At the molecular and cellular basis, the lack of oxidative protection led to an increased oxidative response, which directly spurred on the local inflammation.

Nutrients, nutritional status and immunisations:
It has been considered whether simultaneous delivery of vitamin A and key immunisations (e.g. measles, polio) has any influence on the efficacy of the latter. The consensus was that no interference occurred. More recently, a similar question of nutrient-vaccination interactions has been raised with respect to zinc and a cholera vaccine. Studies in Bangladesh have shown that seroconversion and production of antibodies after an oral cholera vaccine were improved after zinc supplementation, whereas high-dose vitamin A had no enhancing effect.

Manipulation of the immune response:
The manipulation of the immune response takes on a number of creative formats. It has been speculated that early hunter-gatherers’ penchant for grazing on the roots of foraged plants introduced anaerobic microbes that protected evolutionary man from infections. The contemporary equivalent of this is the attempts to take advantage of probiotics (live anaerobic fermentation bacteria) to treat or prevent infectious human and animal diseases. This has been explored most with regard to gastrointestinal infections. Meta-analyses of published trials indicate the
effectiveness of prophylactic use of probiotics to prevent traveler’s diarrhoea and to avert antibiotic-associated infections with Clostridium difficile. When a more comprehensive view of all the explored applications is taken, diverse efficacy trials have provided more mixed results.

The earliest mammalian milk (colostrum) contains an abundance of immune factors. Since all of the passive immunity for ruminant newborns is passed on through the colostrum, the efficacy of bovine colostrum for treating and preventing human infections has been of clinical and public health interest. Reviews of the topic show that bovine colostrum immunoglobulins survive the passage through the human gastrointestinal tract intact and can have both therapeutic and prophylactic effects against selected pathogens.

A bold gambit for immunology has been therapeutic application of biological response modifiers, notably anti-cytokine therapy. Dampering down the systemic effects of the acute-phase response by antibodies to suppress inflammatory cytokines was pioneered in the treatment of inflammatory rheumatoid conditions. Its application to systemic inflammation caused by infectious pathogens is the next frontier.

Newer paradigms on the research horizon

As this narrative of concept development and basic and applied research in the area of infection and nutrition points out, there has been a continuous ebb and flow of shifting paradigms. One related to dietary pattern and another related to host nutritional status.

Dietary pattern for infections disease resistance:

To what extent the dietary pattern, per se, influences the risk of illness was first explored in the 1980s in the U.S. National Research Council report Diet and Health. Since then, dietary guidelines for long-term health and prevention of chronic disease have evolved. For the U.S. population, these are currently set out in MyPyramid.

The paradigm of an interaction between food, diet and acute disease has been explored to a much lesser extent. However, in the instance of infant feeding, a strong association between the exclusive or predominant consumption of maternal milk and protection from infections in the infant and toddler years has been documented.

Some interesting observations of diet-infection associations in somewhat older children (preschoolers) came from a field study in Tanzania. This was part of a vitamin A supplementation intervention, which failed to reveal any benefit in morbidity or mortality. However, the total intake of vitamin A from the diet was protective against childhood infections. Insofar as total dietary vitamin A in rural Tanzania may be a proxy measure for consumption of carotene-rich foods, e.g. herbs, vegetables and pigmented fruits, the disease resistance observed may be attributable to constituents of these pigmented foods.

Pathogen virulence and the nutritional status of the host:

Keshan disease was a progressive and fatal pulmonary disease in East Asia, which was found to be associated with low selenium status in the population. Beck et al. looked at murine models of pulmonary infections using a usually benign mouse coxsackie virus which produced a self-limited, mild respiratory infection in well-nourished mice. The same virus, however, turned virulent when selenium deficient mice were inoculated; the mutated virus isolated from the selenium-restricted host was also now lethal when passed into selenium-sufficient animals. This observation points towards a new departure in nutrition:infection interactions - where the micronutrient status of the host could determine the virulence of pathogens across a whole society.

Conclusion

Scrimshaw, Taylor and Gordon enunciated a paradigm for interactions of nutrition and infection that continues to serve both biological science and public health. The fact that half of all continuing infectious deaths are associated with a low weight-for-age is compelling testimony to the enduring relevance of the paradigm. Half a century of explosive population growth, scientific expansion in immunology and molecular biology, changing population demography, and evolving infectious and nutritional epidemiology places the interaction of nutrition and infection into a myriad of new and relevant contexts.

Conflict of interest statement

The author has no conflicts of interest to report.

References


