Undernutrition or malnutrition adversely affects host defenses against many invading microorganisms, thereby increasing the severity of infection. Studies of RNA viruses (e.g., coxsackievirus B and influenzavirus) have shown that selenium or vitamin E deficiency in mice increases disease severity and results in stable genomic changes in the virus that increase virulence. Changes in H3N2 influenzavirus were predominantly in the ordinarily stable M1 matrix protein. Whether this represents selection of already-existing variants or direct effects on viral RNA is unclear. Related questions include whether undernutrition in persons who acquire infection with influenzavirus H5N1 could promote genomic changes during infection that result in greater virulence and higher case-fatality rates, and whether undernutrition could help create the multiple mutations needed to instigate human-to-human transmission. These possibilities emphasize the importance of alleviating world poverty and malnutrition. In addition, these findings suggest that the neglected area of undernutrition affecting invading microorganisms merits intensive investigation in humans and experimental models.

This article will focus on 2 themes that are connected, for the purposes of this discussion, by influenza viruses: the effects of nutritional deprivation on the pathogenicity of influenza virus in the lung, and certain societal determinants that may influence the potential for human-to-human spread of the H5N1 avian influenzavirus. The concerns expressed herein relating to the first theme are based on stunning animal experiments that have not yet been shown necessarily to have relevance for humans; those related to theme two are largely speculative. However, the issues brought up by both themes are important.

In both humans and experimental models, there is clear evidence that malnutrition increases the susceptibility to and severity of infection with a variety of microbial agents [1, 2]. This has been attributed primarily to compromise in host immune defenses associated with single or multiple vitamin or mineral deficits and/or to protein-energy deficiencies. The monolithic focus on malnutrition-induced adverse effects on the host was shattered approximately a dozen years ago by the extraordinary (but largely underappreciated) studies by Melinda Beck and Orville Levander and their colleagues [3, 4] of coxsackievirus B3 infection in mice. They found that an ordinarily avirulent strain of the virus produced severe myocarditis in mice that were made to be deficient in either selenium or vitamin E. This finding was not surprising. However, when the virus was reisolated from heart muscle and then used to infect mice with normal nutrition, the cardiac pathology was similar to that found in the selenium-or vitamin E–deficient mice. Thus, the virus phenotype had been altered by growth in nutritionally deprived mice. Subsequent studies revealed multiple changes in the viral genotype that appeared to be related to the increased pathogenicity [5]. The same group then turned its attention to a relatively mild influenzavirus strain, H3N2. The pulmonary pathology was far more severe in selenium-deficient mice, although viral titers in the lungs of selenium-adequate and selenium-deficient mice were similar. The selenium deficiency in the host appeared to promote changes in the influenza virus genome, primarily in the ordinarily quite stable M1 matrix protein (but not in hemagglutinin or neuraminidase genes) [6, 7].

Beck and colleagues have recently studied epidemics of meningitis and optic neuropathy in Cuba that may have been due to coxsackievirus A9. They have suggested that nutritional deficiencies resulted in rapid evolution of coxsackievirus A9 that became the dominant strain, causing the unusual optic neuropathy epidemics and a subsequent epidemic of meningitis [8]. There are 2 alternative likely explanations for the findings. The first is that the nutritional deficit encouraged selection of virulent mutations in those high mutation RNA viruses. The other explanation is that the nutritional deficiency created oxidant or other stresses that directly affected the infecting virus's RNA [7, 9]. Some will
treat the findings dismissively as selection and, therefore, of no great moment. That would miss the point. At the very least, these studies show that nutritional deficits in the host can do much more than affect host defenses and can also select for more virulent genomes. It would indicate that a currently virtually neglected area needs intensive investigation. If the alternative explanation should turn out to be correct, that would be extraordinarily exciting.

Can the findings of influenza virus mutations in selenium-deficient mice be replicated with other forms of undernutrition or malnutrition? Saslaw et al. [10] found that influenza in monkeys that were made to be deficient in vitamin B complex was much more severe than in nondeficient monkeys, but these were primitive experiments in which the vitamin deficiency was so severe that it produced profound leukopenia. Furthermore, no analysis was made of possible effects on the virus. There is a clear dearth of applicable experimental studies in this area.

Could these intriguing animal experiments apply to human H5N1 influenza and not only to virulence, but also to transmissibility? It seems likely that many persons who are exposed to infected poultry and who acquire the infection could have some type of undernutrition. The overwhelming lung involvement usually occurs at least several days after the onset of symptoms [11]; it is entirely possible that, in persons with undernutrition, the disease surge follows the supervision of a genome modified either by selection or as a direct effect of the consequences of undernutrition. To investigate this possibility, it would be necessary to sequence the virus early in the course of infection and then later, when the pneumonia becomes severe, in both persons with normal nutrition and those with abnormal nutrition. The genomic correlates of influenza transmission are not well defined; presumably, hemagglutinin plays a major role [12], but if transmission requirements are similar to those found in a recent analysis of human and avian influenza virus H5N1 strains relating to virulence [13], transmission may well require simultaneous mutations in multiple genes. Until we understand these genomic correlates better, it will be difficult to fully understand the lack of human-to-human transmission, despite the fact that the virus has been infecting humans for at least a decade. This lack of understanding will make it equally difficult to assess the potential role of undernutrition in promoting transmission in the coming years. Certainly, if multiple mutations are needed before human-to-human transmission occurs readily, as many experts believe, undernutrition or malnutrition could play a role in instigating the required mutations.

Do we have persuasive evidence that influenza virus infection is worse in impoverished areas or in persons who experience undernutrition or malnutrition? At present, we do not; it appears that careful assessment of that possibility has not been made, and it could depend on the characteristics of the invading virus strains. The last time we experienced a virus with the capacity to inflict such a severe, often lethal pulmonary process resulting from infection with the virus alone was in 1918. In the interim, serious or life-threatening pulmonary disease was usually caused by either a secondary bacterial infection or, less frequently, a mixed bacterial-viral pneumonia [14]. Severe influenza-associated pneumonia, in the absence of secondary bacterial infection, has been unusual in the epidemics that have occurred between 1918 and the current outbreak of influenza virus H5N1 infection.

In sum, the experimental studies of undernutrition may or may not apply to humans, may or may not relate to the severity of and high case-fatality rate for the current outbreak of influenza virus H5N1 infection, and undernutrition could be influential in the mutagenic changes required in the genome to enable human-to-human spread of the virus.

The other theme concerns the settings in which emerging and re-emerging infections (such as pandemic influenza) develop and the necessity for approaching them in a broad, holistic systems fashion. Infectious diseases experts, including those focused on epidemiology, tend to take a perfectly appropriate but narrow approach. In essence, that approach is as follows: detect the outbreak early, obtain proper specimens, identify the offending organism, and devise intervention strategies. That is perfectly acceptable, but it has one huge disadvantage—namely that it starts with the outbreak already underway. If we are going to minimize the frequency and severity of emerging and re-emerging outbreaks and epidemics of infection, it is essential to look at the determinants that provide the milieu in which such infections arise and thrive and at their interrelationships [15]. The best way to do that is to use a circular systems diagram, with unidirectional or bi-directional arrows showing the interrelationship of determinants to each other [16]. In addition, leverage points can indicate where changes in given determinants can beneficially affect the system, the output of which, in this case, is more (or less) severe epidemics.

In my judgement, the 2 overarching determinants for future emerging infection epidemics are population size and global warming, which directly affect urban crowding, resource depletion, the number of refugees and internally displaced persons, poverty, and hunger (figure 1). Some of the current figures in regard to these determinants are daunting.

- One billion people earn <$1 per day, which defines marked poverty.
- An estimated 850 million persons experience hunger on a daily basis.
- Some 400 million persons experience dire malnutrition.
- An estimated 1–2 billion persons experience more subtle undernutrition, as demonstrated, for example, by iron deficiency.
- As the population size has increased profoundly (from 2 billion to 6 billion persons from 1930 to 2000), urban
zation has also increased markedly. At the turn of the 20th century, 15% of people lived in cities; by the year 2005, 50% of people were urban dwellers, and that will increase to 65% by the year 2030, with an ever-increasing number of megacities. These urban centers are often characterized by areas of slums in which people are crowded together in unhygienic circumstances that are ideal for the initiation and spread of emerging and reemerging infections.

These current figures could well get substantially worse. The world will almost certainly be 0.5°C–1.0°C warmer by the year 2050, and at that time, the world population will grow from 6.5 billion to ~9 billion people [17, 18]. As a consequence of the worldwide disruptions that will follow global warming, combined with the population growth, hundreds of millions of people could become refugees or be internally displaced. According to one estimate, 120 million people would be displaced in Shanghai, Calcutta, Beijing, and Bangladesh alone [19]. These internally displaced persons and refugees—often malnourished, often living in crowded, unhygienic circumstances—are obviously susceptible to a variety of infections that can then spread rapidly from person to person.

The systems approach makes it clear that, absent interventions relating to global warming and population growth, the global conditions in future years and decades will virtually guarantee more epidemics of emerging and reemerging infections, some of which will be severe. Therefore, it is essential that the United Nations Millennium Project goals of cutting poverty and hunger in half by the year 2015 [20, 21] be vigorously supported both by organizational support (such as support from the Infectious Diseases Society of America) and by political advocacy. Underemphasized with regard to the goals of the Millennium Project goals are the interfering effects of population growth and global warming [20]. If unchecked, these could make it very difficult to achieve the goals for 2015 and beyond [21, 22], and even if the 2015 goals were achieved, success would be ephemeral, and the prevalence of poverty, hunger, and malnutrition would again increase as we move towards the middle of the century. Additionally, there is not enough focus on the effects of population growth on resource depletion, which, in turn, will likely exacerbate hunger, poverty, and malnutrition [23].

This underemphasis on certain critical determinants illustrates the importance of always using a systems approach when assessing major problems—an approach that is, fortunately, gaining adherents. In past decades, the particular interests of each advocacy group dominated; now, increasingly, population expert groups emphasize interrelationships with climate and resources [24], and ecology and resources expert groups also focus on population growth effects [25].

It is clear that, for the foreseeable future, there will be huge numbers of people around the world who experience malnutrition or the less severe undernutrition and act as a gigantic pool of increased susceptibility to many infectious agents, with the likelihood of more severe disease occurring and the potential that these persons could serve as incubators for host-induced genomic change in the infecting microorganisms that could increase virulence and/or transmission. Of course, it is uncertain whether alleviating poverty and malnutrition would have any influence on human transmission or the vir-

Figure 1. Interrelatedness of some major variables in emerging and reemerging infections

![Interrelatedness diagram](https://example.com/image.png)
ulence of avian influenza or whether it could be achieved in time to influence transmission potential. But, surely, it is an area deserving thorough investigation.

With regard to H5N1 influenzavirus, we now need to know the following:

- Whether human isolates recovered from persons with mild-to-moderate, non-lethal disease differ genetically from isolates recovered from persons with lethal disease.
- Whether, as I noted above, in severe or lethal cases of infection, isolates recovered early in the course of disease differ from isolates obtained late in the course of disease, after the surge in virus multiplication and host response, when lung disease becomes overwhelming.
- In addition, human and avian isolates that are known to be transmitted from bird to bird will have to be studied in animal models of aerosol transmission, to try not only to determine transmissibility genes, but also to determine whether transmission can be augmented by nutritional deficiency. A significant obstacle to determining the genomic determinants of transmission has been the lack of a good experimental model. Transmission among mice is poor, but it appears to occur more readily among ferrets and guinea pigs [26, 27]. The latter animal models could well be useful for elucidating transmission determinants.

It would also be interesting to know whether nutritional defects might enhance the activity of the PBI-F2 protein, which appears to be important in influenzavirus pathogenesis [28], thus augmenting virulence. However, the questions that can be asked and tested in this emerging field of investigation are, of course, far broader than those focused on influenza. Aside from the necessity for determining what types of undernutrition (aside from selenium and vitamin E deficiencies) promote infection-induced genomic change, each reader can develop a list of studies that could be informative. My own would include the following:

- Could the severity of combined influenza and staphylococcal pneumonia be related to whether the invading Staphylococcus species changes its genome during infection, to produce more severe pathology? And are such changes more likely or more extensive in the presence of host undernutrition? Combined influenza-staphylococcal pneumonia can be a terrible disease, characterized, in severe cases, by multiple-lobe pneumonia, profound leukopenia, and bone marrow showing striking maturation arrest [14].

- Could the severity of multidrug-resistant Mycobacterium tuberculosis be related in some degree to undernutrition or malnutrition? My colleagues have studied the epidemics in prisons in Russia and elsewhere in the former Soviet Union and have been impressed by the presence of obvious malnutrition, which would be expected to make the disease worse and to allow it to more readily spread to other prisoners. However, an additional possibility—that the tubercle bacillus genome could change in malnourished hosts, to increase transmissibility or severity—has not been adequately investigated. This might be considered to be somewhat unlikely, because the M. tuberculosis genome is quite highly conserved; however, who could have predicted that the influenza M1 matrix protein gene, which is ordinarily quite stable, would have been modified by selenium deficiency?

- Could the emergence of a highly toxic Clostridium difficile be related to host nutritional deficiency?

- What role does undernutrition play in the selection of strains that are resistant to a variety of antibiotics?

The work of Beck, Levander, and their colleagues has opened a whole new field for exciting and productive investigation, both in experimental models and in humans. In retrospect, one wonders why we did not focus on this possibility decades ago. After all, microbial invasion changes the host, often in dramatic ways. Why shouldn’t the host change the invading organism in sometimes dramatic ways?

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