Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CellPress

Trends in
Pharmacological Sciences

Science & Society

Malnutrition vaccines for an imminent global food catastrophe

Peter J. Hotez[1,2,3,4,*]

Together with climate change, both the geopolitical events in Ukraine and social disruptions in supply chains from the COVID-19 pandemic could produce global food shortages or even mass starvation events. Promising new interventions include vaccines to prevent infectious causes of malnutrition or infections disproportionately causing death among the malnourished.

Even before the Russian invasion of Ukraine in 2022, widespread hunger and malnutrition were important global health threats. According to the World Health Organization (WHO), in addition to overweight and obesity, the two major forms of malnutrition include undernutrition, related primarily to protein–energy malnutrition, and micronutrient-related malnutrition, especially from iron, vitamin A and iodine deficiencies[i]. However, in most of the world's low- and middle-income countries (LMICs), reduced nutritional intake does not occur in isolation. Chronic infections including diarrheal illness and parasitic infections accelerate both undernutrition and micronutrient-related malnutrition [1]. For children, the various forms of undernutrition include low weight-for-age referred to as underweight, which can progress to a more severe wasting form. Stunting or low height-for-age can result from chronic undernutrition or frequent recurrences of undernutrition and infection, with the consequence of impairing both cognitive and physical development. Micronutrient deficiency, especially iron but also zinc and others, can also exacerbate the cognitive and physical impairments of stunting.

Global burden of malnutrition

The WHO estimates that approximately 462 million adults are underweight, while in 2020 approximately 149 million children under 5 years were stunted, and 45 million children wasted. Moreover, almost one-half of the under-5-years' childhood deaths result from undernutrition, predominantly in LMICs[i]. The University of Washington's Institute for Health Metrics and Evaluation (UW-IHME) found that protein–energy malnutrition caused 212 000 deaths among children under 5 years in 2019[ii], such that protein–energy malnutrition is a leading cause of childhood suffering and deaths globally. In addition, iron deficiency and iron deficiency anemia was responsible for 42 300 deaths. The African Continent and South and Southeast Asia share some of the highest rates of both iron-deficiency and protein–energy malnutrition. Many of these regions also suffer the highest rates of infectious diarrheal disease and illness, as well as hookworm infection, and malaria (and other conditions), each of which exacerbates undernutrition. Table 1 shows a comparison between the geographic distribution of protein–energy malnutrition, and iron micronutrient deficiency, hookworm infection, and diarrheal disease and illness.

An ominous and looming crisis

In 2022, United Nations (UN) Secretary General Antonio Guterres warned of a looming global food shortage with potentially 1.6 billion people not having enough to eat and 250 million living at the brink of famine. The UN World Food Program finds that millions of people already face imminent famine, and project hundreds of millions are at risk for mass starvation. The major driver has been the war in Ukraine, where a significant percentage of the world's wheat and other grains and fertilizer is produced, in combination with drought, high temperatures from climate change, and supply-chain interruptions due to the pandemic. The interruptions from the war and the other factors listed in the preceding text caused the UN's food and agricultural price index to reach all-time highs. Many food-insecure areas of the world, including the African continent and South and Central Asia can no longer afford food imports, or face reduced access due to their dependence on Ukraine. The most vulnerable areas include East Africa and the Sahelian countries of West Africa, where climate change has produced soaring temperatures, profound drought, and diminished agricultural production.

Targeting the malnutrition–infection axis

Certain human infections, especially chronic infections, can cause micronutrient deficiency, undernutrition, or in some cases both forms of malnutrition. In turn, undernutrition can often worsen or exacerbate the clinical course of infectious diseases. Human hookworm infection is a classic example of a chronic infection producing a micronutrient deficiency. In Africa, hookworm often combines with malaria and schistosomiasis. Both children and women of reproductive age, including those who are pregnant, are especially vulnerable to the combined anemia that results from this polyparasitism [2]. Persistent or recurring diarrhea, especially from bacterial pathogens, may cause even greater levels of protein–energy malnutrition and stunting [1]. An exhaustive study to determine the etiology of childhood diarrheal illness concluded that enterotoxigenic *Escherichia coli* (ETEC) producing heat stable toxin (ST-ETEC) and *Shigella* rank among the most important bacterial causes of moderate or severe diarrhea in children under 5 years, in addition to cryptosporidiosis and rotavirus infection [3]. However, in some localities, *Campylobacter*, *Vibrio cholera* O1 (cholera), and *Aeromonas* are also important bacterial causes; with increasing rotavirus vaccination coverage the bacterial pathogens are becoming the dominant etiologies in LMICs (with many strains

Table 1. Comparison of protein–energy malnutrition with iron micronutrient deficiency and diarrheal disease[a]

Condition	Prevalence (no. of cases)	Deaths	Disability-adjusted life years	Worst affected areas
Protein–energy malnutrition	148 million	212 000	15.3 million	East Africa Sahelian West Africa Indonesia Mesoamerica Haiti
Iron-micronutrient deficiency and anemia	Not determined	42 300	31.3 million	East Africa Sahelian West Africa Yemen India and Pakistan Papua New Guinea
Hookworm disease	173 million	—	1.0 million	East and Central Africa Sahelian West Africa India Papua New Guinea, Laos
Malaria	181 million	643 000	46.4 million	Central and West Africa India
Diarrheal disease and illness	99 million	1.53 million	80.9 million	East Africa Sahelian West Africa India

[a]Data from the Global Burden of Disease Study 2019 (https://ghdx.healthdata.org/gbd-2019).

exhibiting multidrug resistance). In addition to the diarrhea-causing pathogens, *Mycobacterium tuberculosis* induces chronic inflammation leading to wasting or cachexia through the production of a cachectin inflammatory mediator [4].

The relationship between infection and malnutrition is bidirectional, meaning that the infections highlighted in the preceding text promote undernutrition, while undernutrition can simultaneously increase susceptibility to these infections [1]. The mechanisms proposed include destruction of the integrity and biogenesis of the gut and respiratory cellular mucosa, alterations in host microbiomes (microbiota), and dysfunctions in the hemopoietic and lymphoid organs and liver and biliary system [1,4]. Severe and chronic protein malnutrition also increases susceptibility to the orofacial destruction of noma and wasting or pancytopenia from kala-azar opportunistic infections. Malnutrition also exacerbates the progression and severity of HIV/AIDS, malaria, and tuberculosis. The link between tuberculosis and malnutrition is particularly noteworthy due to profound cachexia – the well-known consumptives in modern human history [5].

A new malnutrition vaccine portfolio

Based on the discussion in the preceding text, the major infectious and tropical diseases expected to amplify or exacerbate a pending food insecurity crisis, include three parasitic infections – human hookworm infection, schistosomiasis, and malaria; and two enteric bacterial infections – shigellosis and ST-ETEC, and tuberculosis (Table 2).

Parasitic disease vaccines

Through a European-based HookVac Consortium and the Texas Children's Hospital Center for Vaccine Development (CVD), a nonprofit product development partnership (PDP), a bivalent recombinant protein human hookworm vaccine has undergone Phase 1 clinical testing in Brazil and Africa and is entering Phase 2 trials [6]. Three different vaccines for schistosomiasis, also for Africa and Brazil, are also in development [7]. They each comprise a single recombinant protein found on the surface tegument (or elsewhere) of the schistosome parasite, with two antigens completing Phase 1 testing, and a third about to enter the clinic. The antimalaria vaccine Mosquirix is the first human parasitic disease vaccine to achieve licensure (by the European Medicines Agency, EMA) and approval by the WHO; it was developed by GlaxoSmithKline (GSK) Biologicals in collaboration with PATH (a nonprofit Seattle, Washington-based PDP formerly known as the Program for Appropriate Technology in Health) following years of research on the circumsporozoite protein [8]. A second recombinant protein vaccine known as R21 produced by the Serum Institute of India (SII) was formulated with a Matrix-M adjuvant from Novavax. The R21–Matrix-M vaccine has also shown early promise for efficacy in Phase 2–3 pediatric clinical trials in Africa [9], as has a live-attenuated sporozoite PfSPZ vaccine from Sanaria.

Bacterial vaccines

While there are no licensed shigellosis vaccines, there are several in various stages of development. Among the lead candidates is a detoxified *Shigella flexneri* 2a Artificial Invasin Complex ($Invaplex_{AR\text{-}DETOX}$) developed at Walter Reed Army Institute of Research (WRAIR), and two vaccines supported by the Gates Foundation and Wellcome Trust, including a monovalent *S. flexneri* 2a vaccine comprising a synthetic O-carbohydrate conjugated to tetanus toxoid, and generalized modules for membrane antigens (GMMA) AltSonflex1-2-3 O-antigen vaccine undergoing testing in Kenya[iii]. The WHO has issued a guidance document for future *Shigella* vaccines [10]. Several ETEC vaccines are in development, including an oral whole cell ETVAX vaccine and an injectable subunit CssBA vaccine combined with a double-mutant heat-labile toxin from the Naval Medical Research Institute (NMRC), WRAIR, and PATH[iii]. Two combined *Shigella*-ETEC vaccines are also in development, including ShigETEC from

Table 2. Selected malnutrition vaccines in development

Disease	Vaccine/antigens	Organization or company	Stage of development	Refs
Hookworm infection	Hookworm vaccine	Texas Children's CVD & HookVac Consortium	Phase 1–2 trials	[6]
Schistosomiasis	Sm-TSP-2 Sm-14 Sm-p80	Texas Children's CVD FIOCRUZ PAI Life Sciences	Phase 1 or 2 trials	[7]
Malaria	Mosquirix R21/Matrix-M PfSPZ Sporozoite	GSK-PATH SII–Oxford University–Sanaria	EMA Licensure and WHO approval infants 6–17 months Phase 2–3 Phase 2–3	[8,9]
Shigella	Invaplex$_{AR\text{-}DETOX}$ *Shigella flexneri* 2a conjugate AltSonflex1-2-3	WRAIR-PATH Institut Pasteur–WRAIR-PATH GSK Vaccines Institute for Global Health–PATH	Phase 1 or 2 trials	[10][iii]
ETEC and ETEC/*Shigella* combinations	ETVAX CssBA ShigETEC CVD 1208S-122	Scandanavian Biopharma NMRC-WRAIR-PATH Eveliqure University of Maryland CVD–Emergent BioSolutions	Phase 1 or 2 trials	[11,12]
Tuberculosis	VPM1002 M72-AS01 MIP GamTBVac	SII-Max Planck–VPM IAVI–GSK–Gates MRI Cadilla Russian Ministry of Health	Phase 3 trials	[13]

Eveliqure Biotechnologies GmbH in Austria, which is a live attenuated *Shigella* bacterium lacking in toxic lipopolysaccharide O antigens, yet expressing ETEC toxoids [11,12]. Another is CVD 1208S-122, a live attenuated *Shigella* hybrid from the University of Maryland CVD. Finally, there is an expanding pipeline of vaccine candidates for tuberculosis in development [13]. These vaccines use an array of biotechnologies ranging from recombinant proteins on familiar and next-generation adjuvants, virus vectors, and several that use live BCG genetically modified to express *Mycobacterium tuberculosis* antigens. Because BCG is already in use in many LMICs as a neonatal vaccine, it is potentially feasible to replace the existing vaccines with one of these next-generation BCG constructs [13].

Policy responses

Universal immunization programs have been shown in India and elsewhere to produce positive nutritional benefits for child growth [14]. In addition, there are at least 20 promising malnutrition vaccine candidates in mid- or late-stage development that could be accelerated to help avert an imminent food catastrophe or even potential mass starvation events. Such vaccines could be prioritized, just as the global policymakers accelerated COVID-19 vaccines starting in 2020. Such actions would be consistent with UN Decade of Action on Nutrition commitments launched in 2016 (and extending until 2025) to strengthen national health and food systems around nutritional needs and emergencies. Until now, vaccines and vaccine development activities have not featured prominently in food system security strengthening, but this approach offers promise. While averting an imminent food catastrophe may not be possible, there are options for accelerating malnutrition vaccines to reduce its impact. Given the unanticipated time lags and inequality gaps that we witnessed with COVID-19 vaccines during the pandemic, we must begin this process imminently. Otherwise, we risk similar vaccine access and inequity gaps, and all-too-familiar yet unnecessary losses in human life.

Declaration of interests

The author is an inventor on nonrevenue generating patents for hookworm and schistosomiasis vaccines. These vaccines are in Phase 1–2 clinical trials through the activities of the Texas Children's Hospital CVD, a nonprofit product development partnership, through government and philanthropic grants.

Resources

[i]www.who.int/news-room/fact-sheets/detail/malnutrition

[ii]https://ghdx.healthdata.org/gbd-2019

[iii]www.defeatdd.org/blog/shigella-and-etec-vaccine-pipeline-advances-despite-pandemic-slowdown

[1]Texas Children's Hospital Center for Vaccine Development, Departments of Pediatrics and Molecular Virology and Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX, USA
[2]Department of Biology, Baylor University, Waco, TX, USA
[3]James A. Baker III Institute for Public Policy, Rice University, Houston, TX, USA
[4]Hagler Institute for Advanced Study, and the Scrowcroft Institute of International Affairs, at Texas A&M University, College Station, TX, USA

*Correspondence:
hotez@bcm.edu (P.J. Hotez).

https://doi.org/10.1016/j.tips.2022.08.007

References

1. Walson, J.L. and Berkley, J.A. (2018) The impact of malnutrition on childhood infections. *Curr. Opin. Infect. Dis.* 31, 231–236
2. Kinyoki, D. *et al.* (2021) Anemia prevalence in women of reproductive age in low- and middle-income countries between 2000 and 2018. *Nat. Med.* 27, 1761–1782
3. Kotloff, K.L. (2022) Bacterial diarrhoea. *Curr. Opin. Pediatr.* 34, 147–155
4. Baazim, H. *et al.* (2022) The interplay of immunology and cachexia in infection and cancer. *Nat. Rev. Immunol.* 22, 309–321
5. Sinha, P. *et al.* (2019) Undernutrition and tuberculosis: public health implications. *J. Infect. Dis.* 219, 1356–1363
6. Adegnika, A.A. *et al.* (2021) Safety and immunogenicity of co-administered hookworm vaccine candidates Na-GST-1 and Na-APR-1 in Gabonese adults: a randomised, controlled, double-blind, phase 1 dose-escalation trial. *Lancet Infect. Dis.* 21, 275–285
7. Hotez, P.J. *et al.* (2019) Advancing the development of a human schistosomiasis vaccine. *Trends Parasitol.* 35, 104–108
8. Nadeem, A.Y. *et al.* (2022) Mosquirix™ RTS, S/AS01 vaccine development, immunogenicity, and efficacy. *Vaccines (Basel)* 10, 713
9. Datoo, M.S. *et al.* (2021) Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. *Lancet* 397, 1809–1818
10. World Health Organization (2021) *WHO Preferred Product Characteristics for Vaccines against Shigella*, World Health Organization
11. Khalil, I. *et al.* (2021) Enterotoxigenic *Escherichia coli* (ETEC) vaccines: priority activities to enable product development, licensure, and global access. *Vaccine* 39, 4266–4277
12. Girardi, P. *et al.* (2022) Evaluation of the safety, tolerability and immunogenicity of ShigETEC, an oral live attenuated *Shigella*-ETEC vaccine in placebo-controlled randomized phase 1 trial. *Vaccines (Basel)* 10, 340
13. Dockrell, H.M. and McShane, H. (2022) Tuberculosis vaccines in the era of Covid-19 - what is taking us so long? *EBioMedicine* 79, 103993
14. Solis-Soto, M.T. *et al.* (2020) Relationship between vaccination and nutritional status in children: analysis of recent demographic and health surveys. *Demogr. Res.* 42, 1–14