

Golden Rice, VAD, Covid and Public Health: Saving Lives and Money

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Abstract

On July 21, 2021, Golden Rice was registered in the Philippines allowing cultivation and consumption. Research, as an intervention to combat vitamin A deficiency (VAD), started in 1991, and proof of concept for what was to become Golden Rice, was achieved in 1999. In the 1990s, 23–34% deaths globally of children less than 5 years old were caused by VAD, and in developing countries, the percentage was even higher. By 2013, progress against the Millennium Development Goals had reduced <5-y child deaths globally from VAD to about 2% of all such deaths. The progress included significant vaccination programs against measles, and better access to clean water, as well as vitamin A supplementation, all delivered through community health programs. Economic development and education about diet reduced food insecurity. In contrast to continuing VAD deaths, the Covid-19 pandemic has attracted huge political attention, including in low- and middle-income countries. Community health programs have been adversely affected by the pandemic. There is a danger that as a result VAD rates, child and maternal mortality climbs again toward 1990's levels. Adoption of Golden Rice provides a safe, culturally simple amelioration and is costless. Other countries should seize the opportunity. Bangladesh is first in line, possibly followed by Indonesia and India.

Keywords: vitamin A deficiency, micronutrient fortification, public health, costs of community health, Covid effects on VAD, vaccination, vitamin A supplementation, sustainability

1. Introduction

Vitamin A deficiency is almost non-existent in high-income country populations. Vitamin A deficiency (VAD) occurs in human populations of low- and middle-income countries and is associated with lack of dietary diversity, often associated with poverty. Staple food grains, such as rice, are readily available, easy to prepare and tasty, and an excellent source of energy, but polished white rice contains no micronutrients. Conversely, animal products (many of which contain vitamin A) and colored fruits and vegetables (which contain beta-carotene, which the human body converts to vitamin A) foods are expensive or unavailable.

From 1991 to 2013, the VAD rate among children in low- and middle-income countries declined from 39 to 29%, with notable improvements among children

in East and Southeast Asia [1]. Children in sub-Saharan Africa and South and Southeast Asia continue to suffer disproportionately from VAD and its associated risks: infectious and diarrheal diseases, irreversible blindness and other sensory losses, and premature death [2, 3].

Golden Rice is any variety of rice containing the GR2E¹ genetics [4]. In addition to the carbohydrate of white rice, Golden Rice also contains organically produced beta-carotene, imparting its color, which, following its consumption, the human body converts to vitamin A. The beta-carotene content is the only difference from white rice [5].

Beta-carotene is ubiquitous in nature—all colored plant parts contain it—and in a varied human diet. Vitamin A is not found in plants, but is present in animal products. Beta-carotene from food is non-toxic [6] and the human body excretes what it does not need. It is, therefore, impossible to induce vitamin A toxicity by consuming beta-carotene, so overdosing with Golden Rice is impossible [7].

On January 25, 2001 Professor Ingo Potrykus, one of the co-creators of Golden Rice, signed a license agreement with the Philippines Rice Research Institute (“Phil Rice”) to develop Golden Rice. Twenty years later, on July 21, 2021 Phil Rice received the Philippine Governments final regulatory clearance allowing cultivation and consumption of Golden Rice in the Philippines [8].

The causes of the long delay are described elsewhere [7, 9–17]. Undoubtedly, the delay has caused unnecessary human suffering and lost lives, mostly of young children and mothers.

2. Vitamin A deficiency and other nutritional deficiencies

The latest figures available estimate that of the world’s population about 2 billion people are macronutrient deficient, and about 800 million people suffer from “hidden hunger” another name for micronutrient deficiency [18]. Iron, vitamin A and zinc deficiencies are the most common micronutrient deficiencies. Folate deficiencies are also widespread. Where all these deficiencies occur is strongly correlated with the global burden of poverty and disease [19], and so the distribution of them is remarkably similar to the vitamin A deficiency map (**Figure 1**).

For many years, VAD was principally associated with childhood blindness. During the early 1970s, programs of vitamin A supplementation were started in India, Indonesia and Bangladesh. In Indonesia, a development specialist with Helen Keller International noted that the true public health weight of the problem is obscured because its victims often die before they can be reported as blind [21]. Indonesian data analysis demonstrated that children with “mild” vitamin A deficiency were at a high risk of dying [22]. Subsequently, a series of seminal studies demonstrated that a universal source of vitamin A would save 23–34% of global under 5 years, child mortality [23, 24] and also, later, [2, 25–27].

These findings [23, 24] gave huge impetus to expanding vitamin A supplementation programs from the 1990s [28], which involved significant costs [29] and at the time was highly controversial [21]. The Millennium and Sustainable Development Goals made significant progress from the base year of 1990, including in combating VAD, and with major advances in vitamin A supplementation, as well as

¹ Many transformation events were produced once in ~2004 from which event GR2E has been selected on the basis of molecular structure and insertion in the rice genome, together with agronomic performance when introduced to different rice varieties. It is the basis of the regulatory data generated and is the only form of Golden Rice, which is offered for approval and use.

vaccination programs against measles and other diseases, and improved sanitation and clean water access, in turn reducing diarrhea incidence.

Thus, from 1990 simultaneous progress was made in reducing VAD, thereby improving the immunity of populations of vulnerable children to common diseases, and at the same time reducing the incidence of those diseases.

Nevertheless, macronutrient deficiency is being reduced at a faster rate than micronutrient deficiency (**Figure 2**).

If greater attention is not paid to reducing micronutrient deficiencies, they will have a bigger impact on productive human life than macronutrient deficiencies [7].

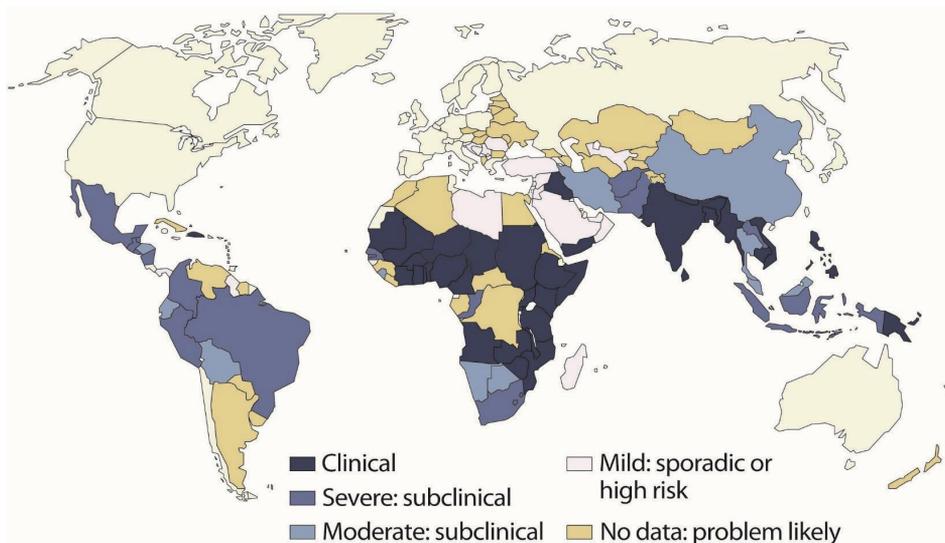


Figure 1. Public health importance for vitamin A deficiency, by country. Source [20]. Redrawn by & courtesy of Banson.

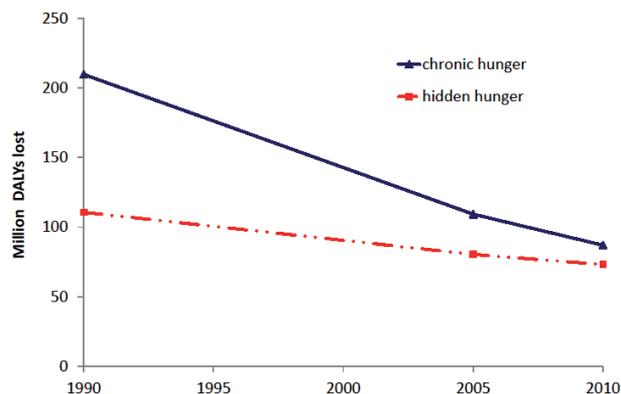


Figure 2. DALYs lost due to chronic hunger and hidden hunger between 1990 and 2010 (part of **Figure 2** from [30]).

3. Vitamin A deficiency in Bangladesh and the Philippines

Bangladesh and the Philippines are so far the only two countries where regulatory applications been made to cultivate and consume GR. It is clear that progress in combatting VAD has been significant, a reduction from 23 to 34% of under-five child deaths in the 1990s to *circa* 2% in these two countries in 2013, the latest data

available [31]. The 2013 data are useful as a proxy for comparison between countries, but has limitations [32] including that the “total VAD” deaths reported are actually solely deaths where measles or diarrhea are reported on a death certificate. But these are not the only causes of death due to immune system insufficiency due to VAD, and reporting may anyway be patchy in remote, poor districts.

In any event, a 2019 publication, reporting pre-Covid-19 pandemic data, determined that large-scale food fortification against VAD could protect nearly three million children annually [19].

In July 2021, Golden Rice was approved for cultivation and, previously for consumption, in the Philippines. Golden Rice is now awaiting final approval in Bangladesh. The Bangladesh Rice Research Institute submitted an application for consumption and cultivation in Bangladesh in 2017, which has stalled in the Department of Environment [33]; hence, no regulatory decision has been taken.

It was estimated that 3.08% of children of the 14.3 million children under age 5 in Bangladesh will die in 2019 [34, 35]. Two percent of these deaths may be attributable to VAD [31], resulting in an estimated 8826 deaths in 2019. The modified version of Golden Rice was available in 2004, and regulatory delay is the main reason why only one country as of now, The Philippines, has approved Golden Rice for cultivation. Every year of delay of approval of Golden Rice may cause at least 8500 child deaths in Bangladesh. Ten years of delay will result in over 85,000 deaths, at least some of which might have been avoided.

A recent study has estimated that substituting Golden Rice for white rice could provide 57–99% and 89–113% and of the recommended vitamin A requirement for preschool children in the Philippines and Bangladesh, respectively [5]. Such a boost to dietary beta-carotene could do much to combat VAD and is highly sustainable especially when the Golden Rice is grown by the communities which need it.

Currently, Bangladesh spends annually between USD24 million and USD47 million (a 5–6 percent increase in the cost of rice at US\$480–US\$783 per metric ton), on chemically fortifying 1 million metric tonnes (4% of the country’s annual rice production) with at least vitamin A and zinc [36, 37]. This is sufficient rice to feed about 7% of Bangladesh’s population of 163 million people. The aim of the Bangladesh Department of Woman’s Affairs is to “make fortified rice available to all” [36]. The 2020 Bangladesh rice harvest was 25 million metric tonnes. The fortification program is presumably limited by the budget available.

Large-scale food fortification with chemicals represents an unusual confluence of commercial and public health interests, with useful focus on inputs and outcomes arising [19, 36, 38]. Similar focus needs to be applied to integrate public sector developed, and free, biofortified crops—conventionally bred and genetically engineered—for the same purpose, and integrates all approaches—chemical, biological, educational and cultural—to alleviate micronutrient deficiencies in populations, for least cost and maximum coverage.

In 2013, when the Bangladesh program started, there were no alternatives to industrial fortification with chemicals. Since then, high-zinc rices have been introduced by Bangladeshi rice breeders as part of the Harvest Plus program [39]. In November 2017, Golden Rice registration was applied for by the Bangladesh Rice Research Institute (BRRI) and they have been multiplying different varieties of Golden Rice seed since then. Adoption of both high-zinc rice and Golden Rice would reward Bangladesh science investment, save foreign exchange currently being spent on importing chemical fortificants, and allow the reach of biofortified rice to a greater proportion of Bangladesh society than the currently industrial fortification alone, which depends on distributive infrastructure.

The above can be achieved in steps; initially, the high-zinc rice varieties could be chemically fortified with vitamin A. Subsequently, now or after registration of Golden Rice, this and the high-zinc varieties could be introgressed (bred together) in two to three rice-growing seasons by Bangladesh's public sector rice breeders. It is very curious to understand, in light of the Bangladesh regulatory data submitted for official consideration in November 2017, 47 months ago at the time of writing, why very few regulatory meetings have been called and no regulatory decision about Golden Rice has been taken. Particularly curious, in light of the recent Philippine cultivation decision (taken 10 months after data submission) when the agro-environmental conditions for rice cultivation are so similar between the two countries. (Governments have approved Golden Rice as safe for consumption in Australia, Canada, New Zealand, the Philippines and USA [40]. Cultivation permission has not been sought in these countries, except for the Philippines, where it has been granted.)

Registration of Golden Rice for cultivation in Bangladesh would allow a refocus of the huge cost of chemical fortification of rice (currently USD24–48 m annually to chemically fortify only 4% of Bangladesh's rice production) by the Department of Women's Affairs to allow a much greater proportion of Bangladesh's population to be reached than will ever be possible if dependent on industrial fortification only. The Golden Rice option has zero cost increment, compared with white rice, to governments, growers or consumers.

What could be standing in the way of the Bangladesh's National Committee on Biosafety under the Ministry of Environment, Forest, and Climate Change, meeting and taking a positive decision, to benefit hugely VAD intervention in Bangladesh?

Delay is expensive: Delay of the use of Golden Rice in India cost USD199 per annum for the decade preceding 2014 [41, 42]. Even if all 25 million metric tonnes of Bangladesh's 2020 rice production were Golden Rice, the extra beta-carotene nutrition is free, saving a large proportion of USD600 million to USD1.17 billion if the same was achieved by chemical fortification with zinc and vitamin A. In practical terms, it appears that the Bangladesh Governments objective "to make fortified rice available to all" is unobtainable without fully embracing the results of the work of the Bangladesh governments own rice breeders, in producing high zinc as well as Golden Rice varieties.

4. Integration of fortification and biofortification

Chemical food fortification has been used to combat micronutrient deficiencies for 100 years in high-income countries and there are good data on positive impact. Conversely, there are few data, except for iodine fortification, concerning large-scale food fortification (LSFF) with vitamin A, iodine, iron and folic acid in low- and middle-income countries (LMIC), but what data there are is positive [19].

LSFF, with chemicals, is especially useful in LMIC where micronutrient deficiency is evidenced at a population level, and where rapid urbanization is accompanied by increased household purchasing power, leading to reliance on centrally processed foods [19]. One of the complex of issues in such settings, however, is to ensure that chemical fortification of different processed foods does not result in excessive intake, resulting in delivery of a tolerable upper intake level for the population (which is acceptable) and not toxicity (which is unacceptable) [19].

The Golden Rice project has been designed from its initiation principally to assist resource-poor growers and communities who do not rely on processed foods, but largely grow their own. And that remains the objective. Regarding toxicity, Golden Rice provides beta-carotene a non-toxic source of vitamin A, and not vitamin A itself (which is toxic when consumed in excess.)

A 1992 UN Conference on Nutrition confirmed that for VAD alleviation, locally available food-based strategies are the first priority, with vitamin A capsules only an interim measure [43]. However, the bioavailability of beta-carotene from commonly available fruits and vegetables is very low. Even when they are available, a young child between ages 1 year and 3 would need to eat eight servings of dark green leafy vegetables per day in order to meet the Recommended Dietary Allowance for vitamin A. This results in “the virtual impossibility for most poor, young children to meet their vitamin A requirements through vegetable and fruit intake alone” [21]. The low bioavailability of vitamin A from plant foods explains, in part, the presence of vitamin A deficiency among children living amid ample supplies of dark green leafy vegetables and other plant sources of vitamin A [21]. Conversely, a recent study has estimated that substituting Golden Rice for white rice could provide 57–99% and 89–113% of the recommended vitamin A requirement for preschool children in the Philippines and Bangladesh, respectively [5]. Such a boost to dietary beta-carotene could do much to combat VAD and is highly sustainable.

A perfect food fortificant has been described [21] as one which exhibits the following characteristics:

1. It must be a dietary staple eaten daily, with little or no variation.
2. The fortified food must reach the whole population.
3. There must be minimal effect on the cost of the staple food.
4. The micronutrient must be chemically stable.
5. The micronutrient must be undetectable by the consumers.

Golden Rice, being consumed as a staple food, matches the requirements perfectly, except for the color imparted by the beta-carotene content.

However, the golden color imparts advantages. Golden Rice is easily recognizable, so consumers—even illiterate consumers—can exercise choice. And the color is also advantageous for government programs: Each grain is naturally labeled, so “passing off”² as biofortified rice is not possible. With the golden color as a marker, Golden Rice can also be used—after the traits are introgressed (e.g., bred together into one variety) as a carrier for invisible micronutrient traits of rice, such as high zinc, high iron and high folate (the natural form of the folic acid used for chemical food fortification.)

Multifunctional cooperation, including between different government departments not used to working together, will be beneficial for effective use of Golden Rice [44]. (This is also the case for LSFF with chemicals [19].)

Within this requirement for multifunctional cooperation, there is clearly a role for synergistic reinforcement of what may be termed urban and rural improvement of staple foods with additional micronutrients. Social marketing research has determined that consumers of rice growing communities are interested to try Golden Rice if they can afford it and if it is good for their family’s health [45], both being applicable to Golden Rice. However, although a small cultural change,

² Rice is fortified with chemicals by mixing rice powder with chemical fortificants, extruding and drying the result to resemble rice grains, and mixing the result in required proportion with polished white rice. If fortification is done badly, children may pick out and discard the fortified pellets, if done well unfortified white rice can be “passed off” as fortified rice by unscrupulous people.

changing from eating white rice to Golden Rice, even partially, is significant and will benefit from encouragement. There is an additional challenge to be overcome. The agronomic characteristics, such as yield, pest resistance and days to maturation, of any variety of Golden Rice are determined by the isogenic variety the beta-carotene-generating genetics have been bred into. So, there is little, except consumer demand, to encourage a grower to plant Golden Rice seed, rather than the isogenic variety. Demand may arise from the local community, if they know of the potential health benefits.

Another, more concrete demand generation, requiring cooperation between sectors, is for Government departments responsible for providing biofortified rice to urban populations to establish and communicate a buying price for Golden Rice sufficient to encourage growers to grow Golden Rice.

Another attractive program of demand generation is for school feeding programs to specify that Golden Rice must be used: simultaneously creating demand so that growers grow Golden Rice, children benefit from it nutritionally and learn about it, and inform their parents of it, generating demand also at home.

Such programs can assist Golden Rice's adoption in rural areas, as well as in urban areas, and save money compared with alternatives, at the same time as transferring wealth to growers for productive work. Such programs require cooperation between agriculture, education, women and children's affairs and public health functions of government with their own accountabilities, and should not be held back by narrow, unsubstantiated technology suspicions, which have been disproved [46–48] or for any other reason: the available health, welfare and economic benefits are too great.

Large-scale food fortification against VAD could protect nearly three million children annually by only a minimal 0.5% reduction in VAD prevalence, in a little over a year, “an effect that, importantly, would plausibly be compounded with increasing program maturity, and better intervention coverage and reach” [19].

Vitamin A capsules are only recommended for children of 6 months and older [49], and very young children do not consume solid food. These children are the most vulnerable to vitamin A deficiency: Neonate deaths in 2011 accounted for 43 percent (increased from 36 percent in 1990) of all deaths among under 5-year-olds [50]. Can a good source of vitamin A, such as Golden Rice, when part of the staple diet, improve the mother's vitamin A status, benefiting her health, and simultaneously *via* the placenta and breast milk increase the baby's resistance to disease, and reduce neonate and child mortality? [14].

For the first time since the UN's International Conference on Nutrition three decades ago [43], there is a beta-carotene-rich staple food—Golden Rice—with excellent bioavailability [51], and at no greater cost than white rice, capable of delivering a significant improvement, 57–99% and 89–113% of the recommended vitamin A requirement for preschool children in the Philippines and Bangladesh, respectively, when substituted for white rice [5]. Even partial substitution, for example, through school lunches, would contribute positively to health outcomes, especially for children from more disadvantaged households.

5. How sustainable are the reductions in VAD incidence achieved since the 1990s?

The discovery of the huge hidden mortality due to VAD, from the 1990s, focused the attention of international communities, and national governments, on the excellent cost benefit of avoiding the preventable deaths and other morbidities associated with the deficiency. This included UN meetings in 1990, 1992 and 2004 [43, 52, 53],

as well as prominence in the Millennium Development Goals (MDGs) 1990–2015³. The huge benefit of addressing micronutrient deficiencies, compared with costs involved, was also endorsed by four rounds of the Copenhagen Consensus [54–57]. Good progress was made, although several MDG goals were missed [28]. The direction has been maintained by the sustainable development goals (SDGs) 2015–2030: 1 (no poverty), 2 (zero hunger), 3 (good health), 4 (quality education), 5 (gender equality), and 7 (decent work and economic growth) [7].

Given the progress achieved in combatting VAD reducing from in excess of 23–34% of child mortality (“in excess of” because these are global percentages but VAD does not occur in industrialized countries) to circa 2% in Bangladesh and the Philippines, it is perhaps unsurprising that relatively little attention is given to VAD caused mortality currently. Much of the reduction is due to annual cycles of costly vaccination programs, including against measles, and expensive vitamin A supplementation, and community health and education as well as general economic development together allowing more food security. However, the sustainability of the reduction in VAD has to be questionable when it requires repeat annual expenditures on materials and labor. Additionally, vitamin A supplementation is not only about preventing mortality [58].

The year before the Covid-19 pandemic struck in Bangladesh and the Philippines was probably the year when child mortality due to VAD was at its lowest, as a result of the community health programs in place. Nevertheless, in 2019 nearly 15,000 children died from VAD-related illness (**Table 1**).

	Bangladesh	Philippines	Source
Number of children age 5 years and under (millions)	14.3	10.6	UNICEF [34] & PSA [59]
Child mortality rate under age 5 years (per 1000)	30.8	27.3	UNICEF [60, 61]
Child mortality under age 5 years	441,302	301,256	Calculated from above
VAD-attributed deaths in 2013 (% of child deaths)	2.0	1.8	Stevens et al., supplementary information [31]
Estimated VAD-related child mortality cases in 2019	8826	5886	Calculated from above

Table 1.

Statistics on vitamin a deficiency (VAD) among children age 5 years and under, and child mortality in Bangladesh and the Philippines in 2019.

Table 1 provides estimates of VAD, and all-cause and VAD-related mortality rates, among children age 5 years and under in Bangladesh and the Philippines in 2019. Despite a decrease in VAD in some parts of the world [31], child VAD rates in both Bangladesh and the Philippines remain high, leading to preventable mortalities due to diarrheal and infectious diseases, among other sequelae. Hence, despite VAD interventions such as food fortification and vitamin A supplementation, additional

³ Goal 1: Eradicate extreme poverty and hunger

Target 2 Halve, between 1990 and 2015, the proportion of people who suffer from hunger.

Goal 4: Reduce child mortality

Target 5 Reduce by two thirds, between 1990 and 2015, the under-five mortality rate.

Goal 5: Improve maternal health

Target 6 Reduce by three quarters, between 1990 and 2015, the maternal mortality ratio

public health interventions to combat VAD are needed, even in normal, pre-pandemic, circumstances. We estimate that in 2019, VAD led to 8826 preventable deaths in Bangladesh and 5886 preventable deaths in the Philippines of children age five and under a total of 14,712.

For comparison, all ages COVID-19 deaths in calendar year 2020 in these two countries are recorded as nearly 19,000 (Bangladesh: 8127 and Philippines: 10,749) [62].

Thus, the scale of annual child deaths from VAD, pre-pandemic in 2019 and all-ages deaths from COVID-19 in 2020, the first calendar year of the pandemic, are of the same order of magnitude.

Even, at the time of writing⁴, in the two countries, the cumulative total of Covid-19 all-age deaths 41,585 (the Philippines), and 27,814 (Bangladesh), in total 69,299, is of the same order of magnitude as VAD child-deaths circa 19,000 pre-pandemic in 2019 [63].

Each death, from whatever cause is a family tragedy. And all these numbers are a vulnerable to reporting errors and therefore approximate. What is important it that whereas no political interest was expressed in the 2019 VAD deaths, all politicians in both countries, as in all other countries in the world, were totally focused on Covid-19, and all economies of the world were brought to a stop by the arrival of the pandemic.

The Covid-19 pandemic has, severely, impacted the social structure and economies of all countries, including, directly and indirectly, low- and middle-income nations. In stark contrast to the global media interest in Covid-19 in all countries, the VAD deaths, which only occur in developing countries, have been seldom reported for the previous 30 years and were probably the lowest ever in 2019, pre-pandemic.

Regretfully, the Covid-19 pandemic has increased poverty and increased food insecurity through job losses and food price increases [64, 65]. Covid-19 has also decreased the effectiveness of community health programs, including reducing dramatically the number of measles vaccinations [66, 67]. It is to be expected that vitamin A supplementation programs have also been negatively affected: they often share resources with measles vaccination programs. Indeed, in 2020, in the first year of the Covid-19 pandemic, despite the potential benefits of this key child survival intervention, vitamin A supplementation programs only reached 41% of the target child population globally, and below 50% in all regions [68], compared with much higher coverage previously: circa 70% [69] to higher than 90% [68].

Often food price shocks lead to social instability, including riots, in LMICs [70] where food costs can be as high as 70% of family income. Such effects would further exacerbate delivery of community health programs.

As a result of the Covid-19-induced disruption of health service provision in South Asia, child mortality could potentially increase by 18–40% and maternal mortality by 14–52% over the next year [71]. Globally, the effect will be an additional 1,157,000 child deaths, and 12,200–56,700 maternal deaths [71]. As an indirect result of the pandemic, a reversal of the progress against the Millennium and Sustainable Development Goals from 1990 to 2019 reported above is to be expected.

Pre-Covid from the 1990s, simultaneous progress was made in reducing VAD, thereby improving the immunity of populations of vulnerable children to common diseases, and at the same time reducing the incidence of those diseases.

Post-Covid from 2020, simultaneously the immunity of populations of vulnerable children to common diseases could well decrease, at the same time as the incidence of those diseases increases.

Thus, it is likely VAD child deaths will increase, in Bangladesh and the Philippines only, as a result of Covid-19-induced conditions, from 2% of all

⁴ October 24, 2021.

<5-y child deaths (~15,000 annually) in the direction of the previously normal 23–34% of all <5-y child deaths (170,000–250,000 annually).

We cannot know how long these second-order effects of the Covid-19 pandemic will continue, so cannot know how bad it will get. At the time of writing, 12.43% of the Bangladesh population are fully vaccinated against SARS-Cov-2 and 23.22% of the Philippine population [63], which are not indicative of a rapid return to pre-Covid normality. The VAD death figures could be even more startlingly bad if the post-Covid annual all causes child deaths in these two countries increases from the 2019 figure of 742,558 (**Table 1**).

The sustainability of VAD mitigation would be increased, and the dangers of the explosion of VAD child deaths could be significantly avoided if effective interventions appropriate to the current circumstances are quickly adopted in all relevant countries.

Practically speaking, Golden Rice is an excellent fit to the circumstances and is available.

6. Biofortification: Pioneers and the future

The creation of what became known as Golden Rice was announced by Ingo Potrykus at the XVI International Botanical Congress in St. Louis in early August 1999, a very large meeting involving 20,000 room nights and 4700 delegates from 85 countries [72], and published in “Science” in January 14, 2000 [73]. Golden Rice was widely reported, including on the front covers of the American and Asian (but not European) editions of Time Magazine on July 31, 2000.

The Second CGIAR-wide conference on Nutrition was held at the International Rice Research Institute in October 1999, organized by Howarth Bouis. On January 1, 2000 “Food and Nutrition Bulletin” (“intended for healthcare professionals”) published 41 papers of this conference: “Improving human nutrition through agriculture: the role of international agricultural research”, many of them anticipating feeding trials to be started soon [74].

The conference summary and recommendations were written by Dr. Bouis, subsequently Director, and then Emeritus Fellow, of Harvest Plus and a World Food Prize Laureate 2016. In his Abstract of the conference proceedings, Dr. Bouis recorded “The need for a shift in emphasis from protein-energy malnutrition to micronutrient malnutrition was recognized” [75].

The summary included comments by the then First Lady of the Philippines (a medical doctor), reporting her, and President Estrada’s commitment to medical and relief missions, particularly to poor communities that are not reached by regular public health and medical centers. The “Wheat flour Fortification with vitamin A Project” was one of the first major activities of the Estrada administration in its first 100 days. She encouraged the development of more nutrient-dense crops especially rice, corn and root crops. She also encouraged the production of micronutrient-rich food products, including livestock, poultry, fish and certain vegetables and fruits, especially those that can be easily raised in backyards and community gardens [75].

Also included in the summary were comments by Muhiuddin Khan Alamgir, the then State Minister for Planning, Bangladesh. He commented that Bangladesh’s Constitution recognizes “raising the level of nutrition and improvement of public health” as “among primary duties” of the state. He called for improvement in food grain quality and listed genetic engineering and technology as of special importance [75].

In 2002, the term “Biofortification” was first used [76] and in 2004, it was first defined as “a word coined to refer to increasing the bioavailable micronutrient

content of food crops through genetic selection via plant breeding” [77]. In the 2004 paper, it is made clear that the human nutrition definition of “micronutrients” will apply encompassing both minerals and vitamins.

Incidentally, in crop breeding for minerals such as “high iron” or “high-zinc” varieties, what is selected are plants that have the capacity to accumulate these minerals from suitable soils. The crop varieties cannot synthesize the minerals. In the case of Golden Rice, beta-carotene is organically synthesized within the plant, independent of the soil type. The same is true of folate rice [78].

It is clear that a lot of thinking was being applied to nutritional improvement of crops at the beginning of this century, and the high public profile of Golden Rice put staple crop biofortification with micronutrients on the donor map in 2000. Harvest Plus, starting in 2003, has now tested or released 400 biofortified staple crop varieties in 63 countries as a result. They are being grown by more than 10 million households globally [79]. All have been produced through conventional, selective breeding improving existing crop varieties.

For those crops where conventional breeding cannot biofortify sufficiently, genetic engineering is necessary, and progress has been slower. Not only Golden Rice, but GMO-biofortified rice with iron and zinc [80], and with folate [78] (eventually it is hoped they will be combined in one multi-biofortified Golden Rice). In 2005, the Bill and Melinda Gates Foundation created Grand Challenge #9 and, following competitive grant allocation, funded further research into genetically engineered biofortified rice (with Peter Beyer—Golden Rice’s co-creator—as Principal Investigator) as well as genetically engineered biofortified plantain/banana and cassava, and sorghum. All or some will be successfully and beneficially adopted with huge welfare and economic benefits to poor societies.

All of the successes of Harvest Plus are with single nutrients in each case—all so far conventionally bred. In the case of iron and zinc, biofortification of rice Harvest Plus has found that genetic engineering can achieve levels unattainable by conventional breeding [80]. As proposed above already for Bangladesh, the combination of delivery mechanisms—conventional and existing transgenic crops being conventionally bred together—can quite easily produce, for example, “High Zinc Golden Rice” identified by its color.

Genetic engineering can also produce combination traits: rice with beta-carotene, and simultaneously, the ability to accumulate high iron and high zinc has been developed experimentally [81]. However, with current regulatory constraints and costs it would be preferable to first register and then introgress, the different traits individually.

Gene editing has been used to construct beta-carotene rice [82], but as the construct introduced foreign genes, it was anyway a “GMO.” As Beyer and Potrykus have commented, gene editing may be useful to delete function in crop plants, but with current levels of genetic knowledge, to add function requires adding genes, which makes GMO crops [83], with associated regulatory challenges under current rules.

The safety for consumption of Golden Rice has been confirmed by the regulatory authorities of Australia, Canada, New Zealand, the Philippines and the USA [40]. That cultivation is also safe has received official endorsement by regulators in the Philippines. On a separate occasion, the Philippine Secretary of Agriculture, Dr. William D Dar said of Golden Rice: “It smells and tastes the same as ordinary rice, except it is colored yellow. But I will choose ‘Golden Rice’ over white rice, because it has more health benefits.” The Golden Rice-tasting event was part of the inauguration of the Philippines Department of Agriculture Crops and Biotechnology Center, and launch of Golden Rice, on September 30, 2021 ([84], Video 1). In an accompanying press release, Dr. Dar commented that “The recent [*September 2021*] UN Food Systems

Summit held in New York, USA, underscored the important role of biotechnology and other scientific innovations in attaining food security by all countries” [85].

GMO-produced insulin was commercialized from 1979 with no opposition, and genetic modification techniques are commonly employed in discovery and manufacture of pharmaceuticals, and beer, wine, cheese and bread are manufactured using genetically modified enzymes. Hundreds of millions of people in the United States and elsewhere and billions of farm animals have been consuming since 1997 products from genetically modified crops using the same techniques employed by Beyer and Potrykus to create Golden Rice. The European production of pork and chicken, the whole market in Europe, would collapse if it were not for imported GMO-maize and GMO-soy meal. Imported because, with very small exceptions, the Europeans will not allow cultivation. Yet, not a single case of any disease or other difficulty associated with genetically modified crops has been verifiably recorded in any human or other animal.

Every single academy of science in the world has attested to the fact that there is no scientifically valid reason for assuming that GMOs could cause harm [47]. Additionally, the European Food Safety Authority, stated, in 2010, that “The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than, for example, conventional plant breeding technologies” [86].

The technology—of conventionally bred as well as genetically engineered biofortified crops—is in the seed and breeds true season to season. The biofortified traits are only introduced into modern, high-yielding crop varieties and can be easily transferred by plant breeders to new varieties as they become popular.

It is time to embrace all available tools, both forms of biofortification as well as chemical fortification, to improve the nutritional quality of staple foods by the incorporation of micronutrients, together with the macronutrients that have been the focus of plant breeding for the previous millennia since humans stopped being hunter gatherers.

These tools are complementary to other public health interventions, education, vaccination, supplementation, home gardens, breast feeding and economic development all important to population welfare.

Not only are all these tools required. Also required are all functions of the private, public, NGO and especially government sectors, working across silos of expertise to support each other’s objective of improving societal public health.

Other countries should follow the Philippines example. Bangladesh is poised to do so. India has a huge VAD problem [2], equivalent to the total of the VAD of the 28 sub-Saharan African countries [21]. India has been held back from vitamin A supplementation, because “the issue of vitamin A has commercial overtones”: “[W]e must look to our farmers, not to pharmaceutical companies, to protect the health of our children. The main solution to vitamin A deficiency should not be drug-based, but food-based.” [21].

Golden Rice is “food based” and there are no “commercial overtones.” Golden Rice does depend on farmers, first and foremost to grow it before it can be consumed, especially by their communities, as an additional intervention for vitamin A deficiency.

All the biofortification tools, and related biofortified crops described here and developed by the public sector are available without cost for use of governments, growers and consumers, as by the time of introduction the development costs have been paid.

On World Food Day, October 16, 2020—during the Covid-19 pandemic—Indian Prime Minister Narendra Modi gave a strong endorsement to staple crop biofortification as a sustainable and cost-effective solution to alleviate malnutrition [87].

The World Bank has recommended that micronutrient biofortification of staple crops, including specifically Golden Rice, should be the norm and not the exception in crop breeding [88].

The movement to common sense and reality has now become unstoppable.

7. Conclusions

In the 1990's, when vitamin A deficiency's importance was recognized not only as the principal cause of irreversible blindness in children, but also the principal cause of child mortality, VAD killed in excess of 2.0 million young children and mothers annually. At that time, VAD was responsible for between 23 and 34% of all deaths of young children globally (and a greater proportion in developing countries), and a greater cause of mortality globally than HIV or TB or Malaria [7].

A combination of successful community health programs, including vaccinations and vitamin A supplementation, as well as economic development resulting *inter alia*, in better access to clean water and sanitation, had reduced the death toll from 23 to 34% in the 1990s to circa 2% in 2019, of young children in Bangladesh and the Philippines.

The Covid pandemic, which started in 2020, has reversed the progress of community health programs achieved during the past three decades. Covid has also increased food insecurity. We cannot know for how long these conditions will last. There is an acute danger that they will result also in a reversal of VAD induced mortality from circa 2% toward in excess of 23–34% of child deaths in all LMICs.

In Bangladesh and the Philippines, in 2020 the first year of the pandemic, Covid killed as many people as VAD killed children only, in the previous year, 2019. Yet far greater attention was paid to Covid's arrival than children's deaths from VAD, which had been continuing for decades. It is long past time to pay more attention to alleviating VAD.

In 2021, for the first time since the 1992 UN International Conference on Nutrition, which recommended locally available food-based strategies are the first priority to combat vitamin A deficiency, such a staple food source with sufficient quantity and bioavailability of beta-carotene (a human source of vitamin A) is available: Golden Rice.

Golden Rice has been proven as safe to consume by Government regulators of four high-income countries and as safe to consume and cultivate in the Philippines. In only one other country has registration for Golden Rice on the same basis as in the Philippines been applied for, in late 2017, and with, at the time of writing⁵, no regulatory decision: Bangladesh.

As the technology is in the seed, Golden Rice adoption requires no use of foreign exchange or industrial infrastructure. It is designed to be useful to resource poor rural communities that grow their own rice staple for consumption. And governments can pay growers to grow the Golden Rice supply necessary for urban use. The color of Golden Rice reduces the opportunities for "passing off" of normal white rice, as micronutrient-fortified rice. And Golden Rice introgressed with, for example, high-zinc and or high-iron rice and or folate rice, using conventional plant breeding will be a multi-micronutrient rice and a golden color.

All departments of government have a responsibility to work together, also with those supranational institutions supporting government public health programs, to use newly available Golden Rice.

⁵ October 2021

There is a huge potential for saving lives and money—multi-millions of US dollars annually—by adopting Golden Rice, not only in the Philippines, but also Bangladesh and other countries where VAD continues to be problematic.

Video Materials

<https://www.facebook.com/DAPhilRice/videos/6274026146003384/>

(You can skip to minute 3:08 to see the dignitaries and congresspersons eating Golden Rice and the Philippine Secretary of Agriculture, Dr. William Dar, saying Golden Rice should be favored over white rice. Or look at 2:02 for Philippines President Duterte's address in favor of agricultural biotechnology.)

Appendix

What support is available to countries which are interested in introducing Golden Rice as an additional intervention for vitamin A deficiency?

Especially as most rice is consumed close to where it is grown, and Golden Rice will cost no more than white rice, Golden Rice should be increasingly useful, including in post pandemic circumstances, as an additional intervention to combat VAD, in all countries where rice is the staple crop of the resource poor and VAD endemic.

For such countries, and where a public sector rice breeding institute is available (in the country or a neighbouring country) to introgress the GR2E transformation event into locally adapted and preferred rice varieties, the following is required and available without cost:

1. A Golden Rice license defining responsibilities and obligations, for humanitarian development of the technology in locally adapted and preferred rice varieties, including the obligation not to charge for the extra beta-carotene in Golden Rice.
2. Breeding parent physical rice seed containing the GR2E trait from another Golden Rice Licensee.
3. Advice on establishing analytical procedures for monitoring the progress of the introgression of GR2E trait.
4. Membership of the Golden Rice licensee network for ongoing support.
5. The regulatory data package for event GR2E. Locally generated environmental impact data may be required, or regulators may agree to use data from a similar agro-ecological habitat. (The 'food, feed and processing' data package alone developed for Golden Rice GR2E is extensive, 42 megabytes of data). In due course, these regulatory studies may be published, as for example in a series of papers with Golden Rice data [5, 89–91].

Most countries make their regulatory deliberations and decisions publicly available, for example Australia and New Zealand, Canada and USA. Included in this openness are inputs from the various Government department involved, including in the Philippines.

It is a pity that in the case of Golden Rice this is all necessary even though the only difference in comparison with white rice is that the normally white endosperm, contains beta-carotene [5], a source of vitamin A for the human body [51].

6. Finance is not available, and must be sought by the potential new, or new licensee from normal sources.

It is normally a requirement that a Golden Rice licensee country has relevant laws in place governing the development and deployment of transgenic crops. If this is not the case, nevertheless discussion is encouraged.

It is to be expected that national rice breeding institutions can introgress the GR2E beta-carotene inducing trait into any public sector owned rice variety, within 2 to 4 growing seasons taking perhaps two or three years.

Other crops than rice, are also potentially able to benefit from the same technology to introduce beta-carotene synthesis to the edible parts. (Peter Beyer has already advised on this for a number of crops.)

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