Golden Rice: Evaluating “Nutritionism” and GM Food as Health Interventions in the Developing World

An honors thesis for the Department of Community Health

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PREFACE

I first developed the idea for this paper while reading Michael Pollan's book *In Defense of Food*. After examining his perspective on societal changes in our approach to nutrition and health, I realized how far we have deviated from our evolutionary need for food. I began to notice in food packaging how much we now focus on specific micro- and macronutrient components of food, rather than on the whole, natural foods themselves. Health advertisements that market processed foods rich in such nutrients as omega-3 fatty acids and antioxidants prevail over promotions for the natural foods from which these nutrients are derived.

In light of these current trends in nutrition and Pollan's perspective, I decided to analyze what we might gain from such a "micronutrient perspective" on health. Golden rice, a variety of rice that has been genetically modified to contain β-carotene in its endosperm, is an ideal embodiment of this philosophy that we can improve health outcomes by treating individual micronutrient deficiencies. The rice targets a single nutrient rather than complete nutritional needs.

Golden rice complicates the analysis of this micronutrient approach, as it also involves genetic engineering, a topic equally if not more controversial than the focus on micronutrients. Genetic engineering is a technology that involves directly modifying an organism's genome to achieve a desired phenotype, and it is a source of contention due to its potential environmental effects and the financial incentives behind it. My analysis of golden rice has led me to a deeper understanding of the pros and cons of using genetic engineering and a micronutrient approach as an intervention for food security in the developing world, and it is this perspective that I hope to share with my readers.

RESEARCH QUESTION

The goal of this project will be to illuminate the pros and cons of using genetic engineering and focusing on micronutrient deficiencies as a means of improving health and reducing health disparities. The paper will focus on the proposed use of golden rice to treat vitamin A deficiency (VAD) to explore the limitations of analyzing health problems through a "magic bullet" lens, a viewpoint that suggests that single solutions exist for complex health issues.

I will discuss four components of the golden rice debate to facilitate this analysis of "magic bullet" ideology. I will first look at whether it is technically feasible to create rice that contains sufficient β-carotene to meet the nutrient needs of individuals in the developing world. I will go on to evaluate whether the β-carotene in golden rice would be biologically available to its consumers. I will then investigate the political and social factors that predict whether golden rice would realistically change population levels of VAD. Finally, I will analyze the potential risks and benefits of golden rice that stem from its foundation in genetic engineering and its approach to VAD.

METHODS

Analysis of Golden Rice Research to Date

To evaluate golden rice as an intervention for VAD in the developing world, I conducted a review of the literature on golden rice. I searched such databases as Academic Onefile, BIOSIS Previews, and the Tufts library catalog using different combinations of the terms "golden rice," "micronutrient," "vitamin A," "deficiency," "hidden hunger," "genetic engineering," and "developing world." I classified my findings based on the four components of the golden rice debate: technical feasibility, bioavailability of β-carotene, ability of golden rice to alleviate VAD, and potential risks and benefits associated with golden rice.

Estimating the Ability of Golden Rice to Reach Its Target Population

To further analyze whether golden rice would reach affected individuals, I created maps to examine the overlay of staple crop consumption and vitamin A deficiency worldwide. I used the biochemical parameter of serum retinol levels as a measure of vitamin A deficiency. Data were available for populations considered to be "at risk" for vitamin A deficiency, from 1995 to 2005. Countries with a gross domestic product (GDP) greater than or equal to $15,000 were omitted from the analysis, because WHO has assumed that these populations were at low risk for VAD (WHO, 2009a). I obtained the data for rice consumption from the Food and Agriculture Organization (FAO) Statistics Division. I used consumption of "Rice (milled equivalent)," in grams per person per day, to estimate the importance of rice in the diet in each of 176 countries. While data was available from 1990-92, 1995-97, and 2003-05, I only used the data from 2003-05, because I assumed that it was the most accurate representation of current rice consumption in these nations (FAO Statistics Division, 2008).

I also looked at the overlay of wheat and maize consumption with VAD to estimate the potential for creating other "golden" staple crops. I used data for the consumption of wheat and maize in grams per person per day from 2003 to 2005 provided by the FAO Statistics Division. I assessed the importance of these foods in the diet in the same 176 countries (FAO Statistics Division, 2008).

Interviews with Key Informants in the Field

To gain additional insight into the risks and benefits surrounding golden rice use as a public health intervention, I conducted interviews with individuals involved in golden rice development and those critical of golden rice. The Social, Behavioral, & Educational Research Institutional Review Board at Tufts University approved the interview candidates and questions. Among the supporters of golden rice, I interviewed Adrian Dubock of the Golden Rice Humanitarian Board and Ingo Potrykus, a plant biotechnologist who was one of the original engineers of golden rice. Among the critics of golden rice, I spoke with Doreen Stabinsky, Professor of Agricultural Policy, International Studies, and Global Environmental Politics at College of the Atlantic, who is a member of Greenpeace.

INTRODUCTION

Between 2004 and 2006, nearly 873 million individuals worldwide, or 13% of the total population, were undernourished. More than 850 million of these people resided in developing nations, accounting for 16% of all individuals in the developing world (Food and Agriculture Organization of the United Nations, 2009c). Undernourishment, according to the Food and Agriculture Organization of the United Nations (FAO) (2009c), describes those individuals "whose dietary energy consumption is continuously below a minimum dietary energy requirement for maintaining a healthy life." The prevalence of undernourishment, particularly in the developing world, reflects widespread food insecurity in affected areas.

However, the FAO's current use of "undernourishment" as a measure of food insecurity is based solely on the caloric intake of individuals in the population. This measure does not account for other aspects of food insecurity, such as access to food and the quality or nutrient content of available foods. Barrett (2010) suggests that there are three components of food security that should be accounted for: availability, access, and physical and biological utilization. The current FAO definition fails to address these other dietary, economic, and health factors that could serve as predictors of future undernourishment. Also, the definition does not capture the number of individuals suffering from micronutrient deficiencies, as it is purely a calorie-based approach. Barrett (2010) estimates that nearly twice as many people suffer from micronutrient deficiencies as from undernourishment alone.

Before we can improve food security in the developing world, we must establish what food security is and how it is defined, because changes in the definition of food security have complicated efforts to intervene. Initial strategies to improve food security focused on the quantity of food available. At the World Food Summit in 1974, food security was defined simply as the “access to the availability of food” (Blakeney, 2009, p. 2). However, researchers and policy makers began to recognize that there is a quality component, in addition to a quantity component, of “food security for developing countries” (Potrykus, 2001, p. 3). By 1986, the World Bank had redefined food security to mean “access by all people at all times to enough food for an active, healthy life” (p. 1). The World Bank recognized that food insecurity resulted from poverty and “a lack of purchasing power,” rather than from problems with the quantity of food available (World Bank, 1986, p. 1). In November 2009, the World Food Summit on Food Security in Rome again redefined food security, suggesting that “food security exists when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food to meet their dietary needs and food preferences for an active and healthy life” (FAO, 2009a, p. 1). This current definition refers not only to access to more nutritious food, but also to the ability to achieve a healthy and productive life.

Shetty (2009) similarly suggests that interventions should focus on the broader concept of “nutrition security,” in addition to food security (p. 431). Nutrition security encompasses the biological utilization of foods, in addition to access to the foods. Nutrition security looks beyond availability of food, purchasing power, distribution, and use of food in the household to examine the “physiological needs for nutrients and the role of the environment in determining good health and nutrition” (Shetty, 2009, p. 431).

In light of these most recent redefinitions of food security, the question has been raised: how do we make people more food secure? Logic dictates that more food and a greater variety of foods should be made available to deficient populations. Improving food quality and diversity, in addition to quantity, would solve not only the problem of hunger, but also the problem of micronutrient malnutrition, or “hidden hunger.”

However, it may not be socially, economically, or politically feasible to address food insecurity by providing individuals with a varied diet. For example, cultural barriers and poor understanding of health needs could complicate efforts to introduce new, vitamin-A rich foods into the diet (Stein et al., 2008). Vitamin A-rich foods, such as fresh fruits and vegetables and animal products, are also expensive and therefore may not be affordable for poor individuals (Hirschi, 2008). Dietary diversification would also require political follow-through to support new agricultural initiatives and to promote the requisite educational and social marketing campaigns.

In areas where food insecurity and micronutrient malnutrition prevail, the diet commonly consists of a staple food, or one that is "eaten regularly and in such quantities as to constitute the dominant part of the diet and supply a major proportion of energy and nutrient needs" (Loftas & Ross, 1995, p. 21). These staple crops alone, which include foods such as rice, wheat, maize, and millet, do not contain adequate nutrients to sustain a healthy life (Loftas & Ross, 1995). Scientists have therefore begun to explore technologies that would allow them to modify the micronutrient content of the existing food supply.

Recent studies have looked at the potential for using genetic engineering as a means of introducing nutrients into staple foods. Through the use of genetic engineering, an existing food can be altered to enhance its nutrient content or to introduce a nutrient that is not found in wild-type varieties of the organism (Shetty, 2009). Golden rice is one such example of a genetically altered crop. The rice has been genetically engineered to contain β-carotene, a precursor to vitamin A. The theory behind golden rice was that it could replace traditional white rice in vitamin A deficient areas where rice is a staple crop (Al-Babili & Beyer, 2005; Potrykus, 2001).

Golden rice has attracted criticism from opponents of genetically modified foods, who reject health interventions that rely on genetic engineering. Opponents fear that the rice could have unforeseen environmental or biological repercussions (Enserink, 2008). Others suggest that golden rice is a technology designed to bring profits to big businesses and industry, rather than to the malnourished in developing nations (D. Stabinsky, personal communication, March 18, 2010; Shiva, 2002)

Golden rice and other interventions that target "hidden hunger" have also been hotly contested by critics who question whether this reductionist approach is worthwhile or effective. Treating micronutrient deficiencies focuses on the problem of malnutrition at the individual level. It fails to address such issues as poverty and lack of dietary diversity, which underlie the evident micronutrient deficiencies (Graham, 1999; Hirschi, 2008). Opponents fear that we are viewing golden rice as a "magic bullet," or "golden bullet" (Kimura, 2006, p. 50) that will eradicate the health problems and suffering associated with malnutrition in developing nations. However, is the solution to food insecurity really this simple? And if it is not, are golden rice and other genetically modified crops worth the investments in time and money that are required to bring them to fruition?

In this paper, I will explore the history behind golden rice and the ensuing debate about its efficacy and rationale. I will analyze golden rice through the lens of the "magic bullet" philosophy to evaluate the limitations of such an approach. I will argue that there is no ideal, all-encompassing remedy for food insecurity in the developing world. Rather, the food insecurity that plagues developing nations demands an integrated approach, one that can start but not end with genetically enhanced crops and a search for these proclaimed "magic bullets." Ultimately, the problems of food insecurity and poor health will persist unless the underlying issues of poverty and diet are addressed.

OVERVIEW

In the first chapter of my thesis, I will provide an overview of the evolution of "nutritionism" as a public health concept and the history behind the focus on micronutrient malnutrition in developing nations. I will also provide background information on the prevalence and manifestation of VAD, the health condition targeted by golden rice.

In the second chapter, I will detail the history of golden rice and its development. I will describe the biosynthetic pathway for β-carotene, and I will highlight the initial points of opposition to golden rice. Before we, as a society, engage in a debate over whether it is ethical or efficient to use golden rice as a public health intervention, we must first determine whether it would prove effective in reducing VAD. In the third chapter, I will thus describe the logistical issues surrounding golden rice, including the bioavailability of β-carotene in the rice. I will also provide an analysis of the geographic distribution of VAD and rice consumption to estimate whether golden rice would reach its target population.

In the final two chapters, I will analyze golden rice as a policy decision. Golden rice is controversial and has been so since its development. In the fourth chapter, I will summarize the current arguments for and against the use of golden rice as a public health intervention. These include concerns derived from opposition to genetic engineering and also to the limited scope of a micronutrient approach to health. Based on the literature I have read, the analyses I have performed, and the interviews I have conducted, I will provide my conclusions about golden rice and my predictions for its future. I will argue that, though golden rice cannot serve as a magic bullet to eliminate malnutrition in developing countries, it is the best available alternative at this time for addressing VAD in these nations. We should continue to pursue golden rice as a health intervention as part of a multi-faceted approach to improving food security, an approach that includes efforts to alleviate not only micronutrient deficiencies, but also the underlying burden of poverty.

CHAPTER 1: BACKGROUND

"Magic Bullet" Ideology

Public health problems, as viewed through the "magic bullet" lens, are concrete problems, with single, clearly-defined solutions. In his analysis of the history of venereal disease in the United States, Allan Brandt (1985) defines "magic bullets" as "specific treatments to root out and destroy infecting microorganisms" (p. 4). This ideology, which emerged with the discovery of antibiotics in the early 1900s, shaped medicine in the 20th century. Penicillin, one of the earliest examples of a supposed "magic bullet," was identified as a remedy for syphilis and gonorrhea in 1943 and seemed to be a panacea for venereal disease (Brandt, 1985). However, it soon became clear that there were some diseases that did not respond to treatment with penicillin and others that persisted in the population despite having a proven response to the drug (Brandt, 1985).

The failure of penicillin as a "magic bullet" for venereal diseases suggests that health issues are more than just biological problems that can be addressed with single remedies (Brandt, 1985). "Magic bullet" thinking allows us to overlook the social, cultural, and environmental components that are at the root of health problems. In order to design successful interventions, however, we must define health problems not only based on biologic deficiencies and malfunctions, but also based on the social constructions of disease and economic barriers to good health (Brandt, 1985).

Nutritionism Defined

In the latter part of the 20th century, this "magic bullet" thinking began to permeate nutrition science. Nutritionists sought simple, one-stop solutions to health problems that they had defined by equally simple biological parameters. They saw nutrients and micronutrients as "magic bullets" for hunger and malnutrition. As a result, recommendations for healthy food intake put forth by nutrition scientists shifted in focus from foods to nutrients. Healthcare professionals and lay individuals began to focus increasingly on incorporating specific nutrients into their diets, by consuming processed or genetically modified (GM) foods, overlooking the importance of fresh, whole, natural foods (Pollan, 2008). In his book *In Defense of Food*, Pollan (2008) discusses this current trend of "nutritionism." The concept of nutritionism, first identified by Georgy Scrinis in an essay criticizing margarine, is the philosophy that "foods are essentially the sum of their nutrient parts" (Scrinis, 2002, p. 28). This ideology suggests that by focusing on the consumption of single nutrients, nutritionists are ignoring the potential beneficial interactions between different nutrients or factors in whole food that could contribute to health (Scrinis, 2002, p. 31). Pollan (2003) agrees that "treating [foods] as collections of nutrients to be mixed and matched, rather than as the complex biological systems they are, simply may not work."

History of Nutritionism and the Micronutrient Approach

The concept of the nutrient first emerged in the 19th century when William Prout identified protein, fat, and carbohydrates as the three essential components of the diet, now referred to as macronutrients. The first micronutrients were discovered in the early 20th century, after the identification of nutrient deficiency diseases. In the 1920s, scientists recognized the relationship between vitamin A and improved immunity, consequently naming it the "anti-infective" vitamin (Semba, 2001). Scientists also discovered that sailors, who did not have access to fresh foods, were deficient in vitamin C and consequently suffered from scurvy (Pollan, 2008).

After the discovery of nutrients and micronutrients, scientists began to define health problems based on a deficiency of these dietary components. These simple definitions that suggested that health problems could be remedied with increased intake of specific nutrients was a consequence of the "magic bullet" ideology. Scientists found comfort in the belief that health problems could be pinned to a concrete source with a concrete solution. As a result, they engaged in a search for the "problem nutrient," or the nutrient that, when missing from the diet, was responsible for poor health and disease (Kimura, 2006, p. 50).

The first "problem nutrient" to be identified was protein, in the early 1900s. Scientists believed that pervasive health problems could be traced to insufficient protein intake (Kimura, 2006, p. 50). The identification of protein as the "problem nutrient" was driven in part by the Western belief in the value of a high-protein diet, as well as by milk surpluses in the U.S. and other wealthy nations (Cannon, 2002). In the post-World War II period, nutrition science focused on closing this "protein gap" (Solomons, 1999, p. 114). In the 1950s, the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) identified addressing protein deficiency as one of their goals (Kimura, 2006). In the late 1950s and early 1960s, engineers developed protein-rich foods, such as fish flour, that were designed to close this "protein gap." However, these engineered protein-rich foods failed to address the problems of hunger and poor health, and they did not reach their target populations (Carpenter, 1994). A strong association was also found between protein deficiency and overall caloric deficiency, suggesting that protein-specific interventions were not an efficient or effective means of addressing hunger (Carpenter, 1994).

The failure of the protein initiative led to a redefinition of the food problem as an issue of calorie and quantity shortage, shifting from a "protein gap" to a "food gap" (Kimura, 2006). The problem was traced to a need for population control and increased agricultural production to deal with a rapidly expanding population. This definition of the problem led to the Green Revolution of the 1960s and 70s, a period marked by increased farming of staple crops and the use of genetic engineering to create high-yield crop varieties (Kimura, 2006; Shiva, 2001). Chemical fertilizers and pesticides were also introduced during this period, as they were necessary for growing the high-yield crop varieties (“Borlaug,” 2009).

“Hidden Hunger”: Micronutrient malnutrition in the developing world

This trend in nutrition science has influenced food security policy in the developing world. In the 1970s and ‘80s, researchers believed that poor health in developing countries was driven by food shortages, and they sought remedies for the hunger and famine plaguing these populations (Kimura, 2006). The traditional approach to hunger measured the success of interventions by the number of calories that were delivered to populations in need and focused on sustaining life.

However, the 1990s brought a shift in the definition of malnutrition in developing nations, from one that focused on hunger to one that concentrated largely on “hidden hunger,” or micronutrient malnutrition (Kimura, 2006; Uvin, 1999). Agencies and organizations such as the World Bank considered micronutrient deficiencies to be the most important aspect of the food problems in the developing world. Kimura calls this trend “that sees the Third World food problem more in terms of quality or micronutrients, rather than quantity or calories,” nutritionalization (Kimura, 2006, p. 53). Kimura (2006) suggests, moreover, that the process of nutritionalization was driven by politics, rather than by science, as it emerged from partnerships between scientists, policymakers, and other organizations.

The World Health Organization (WHO) currently identifies the most severe cases of “hidden hunger” as the lack of three micronutrients in the diet: iodine, vitamin A, and iron

(World Health Organization, 2009b). This paper will look at vitamin A deficiency (VAD) as an example of hidden hunger and the rising trend towards a micronutrient approach to health.

VAD prevalence and at-risk populations

Approximately 500 million individuals worldwide are vitamin A deficient (Mann, 2002), and VAD is responsible for more than 6000 deaths each day (A. Dubock, personal communication, March 30, 2010). Individuals in the developing world, where there is limited food diversity, food shortages, and poverty, are most at risk for VAD (Mann, 2002). In developing nations, children under 5 years of age and pregnant women are disproportionately impacted by VAD. These individuals need more vitamin A in their diet than other groups, and the health consequences of VAD are more severe at these stages in life (World Health Organization, 2009a).

VAD can be assessed by clinical or biochemical methods. In terms of clinical symptoms, vitamin A deficient individuals may develop night blindness, while in terms of biochemical parameters, vitamin A deficient groups may have serum retinol levels below 0.70 µmol/l. An estimated 5.2 million preschoolers worldwide suffer from night blindness (Figure A1a) and nearly 190 million have biochemical VAD (Figure A2a). Approximately 9.8 million pregnant women suffer from night blindness (Figure A1b) and 19.1 million have low serum retinol levels (Figure A2b; World Health Organization, 2009a).

Vitamin A and Food Sources

Vitamin A is a fat-soluble alcohol that is an essential component of the human diet. Humans can obtain sufficient quantities of vitamin A from the foods they eat, either as preformed vitamin A known as retinol, or from precursors to vitamin A known as provitamin A carotenoids (“Vitamin A,” 2009). Preformed vitamin A is found predominantly in animal products, such as liver and fish oils. The provitamin A carotenoids, in contrast, are made by plants. While over 600 different carotenoids exist, only α-carotene, β-carotene, and β-cryptoxanthin are good sources of vitamin A (Shils & Shike, 2006). The bioavailability of vitamin A is lower for food sources with carotenoids than for those with preformed vitamin A, because the plants have a more complex food matrix.

Globally, individuals obtain vitamin A from different sources, based on the availability of food products. In developed nations, particularly Western countries, preformed vitamin A is the main source of vitamin A in the diet. Retinol is found in animal products, including milk, butter, cheese, egg yolks, liver, and fatty fish, and it is also added to margarine. In the developed world, some dietary vitamin A is also obtained in the form of provitamin A compounds, particularly β-carotene. Dark green leafy vegetables and some yellow- and orange-colored fruits and vegetables serve as sources of provitamin A. In the developing world, particularly in tropical nations, the consumption of animal products is less common. As a result, carotenes, especially β-carotene, serve as the main source of vitamin A in the diet. Red palm oil and carrots, for instance, both contain β- and α-carotenes, and papayas contain β-carotene and β-cryptoxanthin (Mann & Truswell, 2002).

Recommended dietary intake

The current recommended daily allowance (RDA) of vitamin A in the diet varies with age and gender (Table B1). Pregnant and lactating women, a high-risk group for vitamin-A deficiency, need more than the RDA for other women of the same age (“Vitamin A,” 2009). The RDAs are given in μg per day. One μg of retinol is referred to as one retinol activity equivalent (RAE). Since β-carotene must be converted to retinol in the body, it has lower bioavailability, and 12 μg of β-carotene are equivalent to 1 RAE (Coulston & Boushey, 2008).

Adequate vitamin A supplies can be obtained from foods that naturally contain vitamin A or its precursors (Table B2). A single sweet potato, with its skin, provides 16803 μg of β-carotene (1400 RAE), providing more than the recommended dietary intake for all age and gender groups, including lactating women. Similarly, one cup of raw carrots provides 9147 μg of β-carotene (762 RAE), more than the recommended daily intake for most individuals (Carotene, beta (ug) content, 2002).

Diet Composition and Staple Crops

Differences in diet composition in developing nations compared with developed nations offer further insight into the nutritional deficiencies that prevail in developing countries. Vitamin A deficiency is not a problem in the developed world, because individuals in developed nations have access to vitamin A-rich foods. In the United States, in 2000, the number one source of vitamin A in the diet was the meat, poultry, and fish food group, representing 27% of vitamin A intake. Vegetables, the second largest source of vitamin A in the diet, contributed 24% of vitamin A intake, followed by dairy products, which provided 22% of the vitamin A in the American diet. Vitamin A-fortified margarine, available beginning in the mid-1940s, and fortified breakfast cereals, available since 1974, also contributed to the vitamin A available in the American diet (Gerrior, Bente, & Hiza, 2004).

In most developing nations, staple crops make the greatest contribution to the food supply. In China, for instance, cereals make up 60-70% of the diet, compared with only 20-30% in the United States (Table B3). The USDA (2009) suggests that rice serves as a staple crop for more than 50% of the global population, with the highest consumption in Asia and Africa. Rice consumption accounts for approximately 23% of energy consumption worldwide and as much as 60% of daily caloric intake in nations where rice is the staple crop. In countries such as

Myanmar, Bangladesh, Cambodia, Laos, and Vietnam, for example, rice makes up over 60% of the energy consumed daily (Khush, 2003). Rice, however, does not contain any vitamin A (Table B2).

None of the vitamin A-rich food groups found in the United States' vitamin A profile are readily available in developing nations. This suggests that the lack of dietary diversity and access to fresh foods in the developing world is one cause of the widespread vitamin A deficiency.

Manifestation of the deficiency disease

Vitamin A deficiency is debilitating in that it results not only in a loss of productivity, but also in a loss of life. Night blindness is the first sign of VAD. It is an indicator of low serum levels of vitamin A. As the severity of VAD increases, an individual may develop xerophthalmia. This condition is characterized by the drying of the eye surface and results from changes in tear ducts and decreased tear production. Ultimately, VAD-induced changes in the eye can lead to blindness (Mann, 2002), which is debilitating and impairs an individual's ability to work. This perpetuates a cycle of poverty and malnutrition (Graham, Senadhira, Beebe, Iglesias, & Monasterio, 1999). It is ultimately poverty and poor access to foods that trigger VAD, and the blindness that results from VAD contributes further to poverty by impeding one's ability to work.

VAD is debilitating not only in its effects on vision, but also in its power to increase susceptibility to infection. Low vitamin A intake can result in decreased mucous and mucous cell production in the respiratory tract and in other mucous membranes. Mucous serves as an initial barrier to infection for the body, and its absence therefore weakens immune defenses.

VAD can also lead to changes in the ground substance of bone, cartilage, and teeth, resulting in defective formation of these tissues (Mann, 2002).

Is Vitamin A Necessary for Proper Immune Function?

Proponents of golden rice suggest that VAD demands attention in that it affects not only vision, but also immune function. However, will addressing VAD alone have any impact on immune resistance?

Studies suggest that vitamin A deficiency can affect recovery from some infections but that adequate vitamin A intake cannot prevent infection (Blakeney, 2009). Vitamin A adequacy or supplementation has been found to reduce the severity of measles, diarrhea, malaria, HIV infection, and some pregnancy-related infections. However, studies suggest that vitamin A does not act to reduce the morbidity or mortality of acute lower-respiratory infections (Semba, 2004; Stephensen, 2001).

There are several mechanisms by which vitamin A influences immune defense. Primarily, VAD affects innate immunity, the body's initial, nonspecific response to an antigen in the body, including physical barriers and the inflammatory response (Kindt, 2007). The skin is a major component of the innate immune system. Since VAD leads to the thickening of the skin, through the formation of a "keratinized" layer, VAD does not impede the skin's function as a barrier (Stephensen, 2001, p. 174).

Mucosal barriers represent another component of innate immunity, and VAD does affect mucosal epithelial layers in the respiratory, GI, and genitourinary tracts, as well as in the cornea and the conjunctiva in the eye (Wintergerst, Maggini, & Hornig, 2007). VAD causes a decrease in the mucous-producing goblet cells lining these areas (Semba, 2004). VAD also leads to squamous metaplasia, but only in people who have suffered from viral infections and other inflammatory conditions that result in a need for new mucosal linings. Squamous metaplasia is a condition in which normal mucosal epithelial cells are replaced by squamous, or scale-like, cells (Malpica & Robboy, 2009). Semba (2004) proposes several mechanisms by which VAD impairs mucosal immunity. Among them are the loss of cilia in the respiratory tract, loss of microvilli in the GI tract, and the loss of mucin and goblet cells in the respiratory, GI, and genitourinary tracts. The inability to regenerate the mucosal lining of the GI tract can slow recovery from some conditions, such as diarrheal diseases, that are prevalent in vitamin A deficient areas (Semba, 2004).

Vitamin A deficiency also impairs innate immunity through its effects on neutrophils and macrophages, two types of phagocytic cells involved in the immune response. The results of studies performed using rats suggest that VAD interferes with neutrophil development. As a result, the neutrophils have reduced phagocytic abilities and are less efficient at eliminating bacteria from the body (Stephensen, 2001). In addition, VAD causes an increase in the number of circulating macrophages, but the macrophages may have decreased phagocytic abilities (Stephensen, 2001).

Recent findings suggest that vitamin A also affects adaptive immunity, the more specific host response to infection that is mediated by B and T cells (Kindt, 2007). Vitamin A is necessary for the development and differentiation of T helper 1 (T_H1) and T helper 2 (T_H2) cell lineages. Vitamin A is essential for the antibody-mediated T_H2 response, because it suppresses the cytokines IL-12, TNF-α, and IFN-γ secreted by T_H1 cells that promote differentiation to T_H1 cells. Therefore, in vitamin A deficient individuals, the T_H1 response predominates over the T_H2 response. This leads to fewer T_H2 cells available to stimulate antibody-producing B cells, which in turn results in a poor antibody-mediated immune response to specific antigens (Stephensen, 2001).

Mucida et al.'s (2007) findings also suggest that vitamin A, or retinoic acid (RA), is important for controlling the differentiation of naïve T cells to T helper 17 (T_H17) and regulatory T (T_{reg}) cells. The cytokine TGF-β drives differentiation towards T_{reg} cells, which have anti-inflammatory activity. However, in the presence of IL-6, TGF-β drives differentiation towards pro-inflammatory T_H17 cells. RA is important for controlling TGF-β-driven differentiation. Studies suggest that RA can block the effects of IL-6, steering differentiation towards T_{reg} rather than T_H17 cells and thereby blocking the inflammatory response (Mucida et al., 2007). Nolting et al. (2009) propose that RA enhances T_{reg} cell conversion both by blocking the secretion of cytokines that stimulate T_H17 development and by reducing the ability of these cytokines to drive T_H17 differentiation. These findings support claims that vitamin A plays a role in moderating the intensity or magnitude of the immune response.

Not only does VAD increase the risk of morbidity and mortality from infectious diseases, but infectious diseases also exacerbate VAD. Stephensen (2001) proposes that infectious diseases can lower VA status by decreased food intake, as is observed in individuals with diarrhea or measles, or by poor nutrient absorption, which results from conditions such as diarrhea and gut helminth infections. Infectious diseases may also be responsible for "direct nutrient loss," increased metabolic needs or catabolic losses, and an impaired ability to use ingested vitamin A (Stephensen, 2001, p. 169).

Despite these findings that indicate that vitamin A may support immune function, research on the effects of VAD on immune resistance remains inconclusive. Many of the studies to date have been performed either on animal subjects or on individuals consuming a normal diet lacking only in vitamin A. The population of interest to golden rice advocates, in contrast, is deficient in other nutrients, such as iron and iodine, in addition to vitamin A. It is therefore unclear whether increasing consumption of vitamin A or its precursors will, in fact, alter immunity. Also, while it appears that adequate vitamin A intake has a positive effect on recovery from infection, it is unclear whether this is due to vitamin A intake or to other underlying factors, such as overall nutritional status, morbidity patterns, and access to primary or preventative health care (Wintergerst et al., 2007).

CHAPTER 2: GOLDEN RICE

The Story of Golden Rice 1

With the increased attention devoted to micronutrient malnutrition and food quality, researchers began to target their work towards interventions specific for nutrient deficiencies in developing nations. The prevalence of VAD and the severity of its physiological consequences suggested that it was an urgent public health issue. Researchers turned to genetic engineering as a solution.

The idea for golden rice was stimulated by the FAO/WHO World Declaration on Nutrition in 1992, which suggested that researchers should seek a more sustainable solution to nutrient deficiencies that could replace supplementation (Potrykus, 2001). Vitamin A supplementation involves the distribution of massive-dose vitamin A capsules to individuals, namely pregnant women and children, who are at a high risk for vitamin A deficiency (Shrimpton & Schultnik, 2002). While supplementation is often effective at reaching its target population (Shrimpton & Schultnik, 2002), it incurs yearly costs and is not sustainable (Stein et al., 2008).

Ingo Potrykus, a German plant biotechnologist, and his colleagues determined that a solution more sustainable than supplementation could only exist if the micronutrients were to be delivered through the staple crops in developing nations. Out of this philosophy grew the idea for golden rice, or rice fortified with β-carotene. Such a rice variety promised to alleviate the burden of VAD in nations where rice was a staple crop and access to foods naturally containing vitamin A or its precursors was limited (Potrykus, 2001).

Skeptics in the field questioned whether generating “vitamin A rice” was a feasible endeavor. The process of engineering rice to contain vitamin A precursors posed a challenge in that the endosperm, the edible portion of the rice, does not naturally contain vitamin A or its precursors. This precluded the use of traditional breeding methods, which rely on genes already in a plant's gene pool, for introducing β-carotene into the rice endosperm (Hirschi, 2008). Potrykus and his co-workers instead turned to recombinant DNA technology. In developing transgenic crops, scientists are not limited by the host plant's gene pool (Hirschi, 2008). This method would therefore allow the scientists to introduce genes coding for enzymes essential to the β-carotene biosynthetic pathway into the rice endosperm.

The Science

While β-carotene itself is not manufactured in the rice endosperm, a carotenoid precursor, geranylgeranyl diphosphate (GGPP), is produced in the endosperm. Four additional enzymes are needed to convert GGPP to β-carotene: phytoene synthase, phytoene desaturase, ζ -carotene desaturase, and lycopene cyclase (Figure A3; Potrykus, 2001). Phytoene desaturase and ζ-carotene desaturase each create two double bonds in the molecule; however, a bacterial carotene desaturase can be used in place of these two enzymes, to introduce all four double bonds (Fig. A4b; Ye et al., 2000).

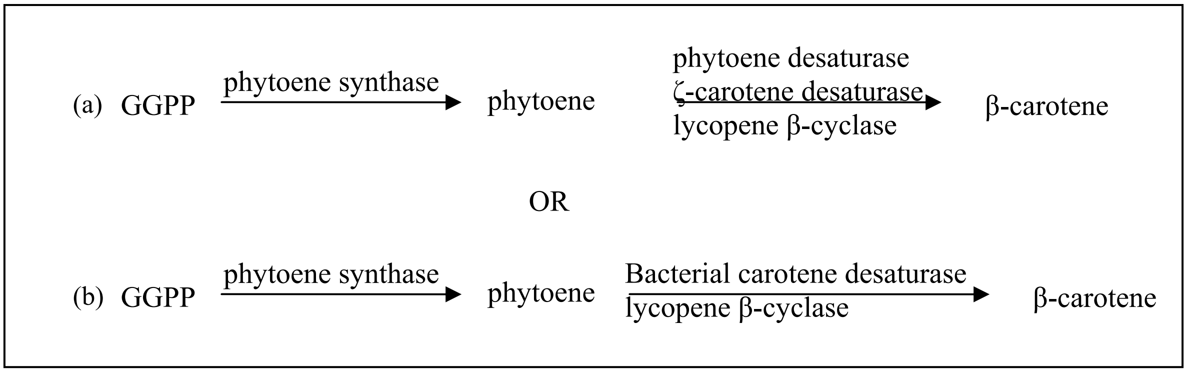

Figure A4. Pathways for β-carotene synthesis. (a) Traditional pathway (b) Modified pathway used in golden rice, where phytoene desaturase and ζ-carotene desaturase are replaced by bacterial carotene desaturase (Ye et al., 2000).

Potrykus recruited Peter Beyer, a scientist at the University of Freiburg whose work focused on the terpenoid pathway in the daffodil plant, to be his collaborator on the golden rice project. Beyer's work was integral to the isolation of the genes coding for enzymes in the biosynthetic pathway for β-carotene (Potrykus, 2001).

Once the genetic pathway is isolated, the next challenge is inserting it into the genome of the recipient organism. To insert the β-carotene pathway into the rice endosperm, an *Agrobacterium*-mediated transformation is used to introduce the *psy* gene for plant phytoene synthase from the daffodil plant, *Narcissus pseudonarcissus*, and the *crtI* gene for a bacterial phytoene desaturase from the bacteria *Erwinia uredovora* into the rice genome (Ye et al., 2000). Since lycopene β-cyclase is expressed naturally in rice plants, no genes are inserted for the enzyme (Schaub, Al-Babili, Drake, & Beyer, 2005).

Using this *Agrobacterium*-mediated transformation, a rice endosperm results that is "golden" in color, reflecting the presence of β-carotene. The initial product, later referred to as "golden rice 1," contained an estimated 1.6 µg of total carotenoids per gram of dry weight of grain, as measured by HPLC analysis (Ye et al., 2000). Beta-carotene represented, at most, 85% of the total carotenoid content of the rice, while other carotenoids that are not precursors to vitamin A, such as lutein and zeaxanthin, contributed to the remaining content (Potrykus, 2001).

Initial roadblocks

Potrykus and his colleagues had conquered what was once believed to be an insurmountable feat in science. However, they had yet to overcome the political and economic barriers that stood between the lab and the developing world. The golden rice researchers encountered an unexpected challenge in the distribution of golden rice to developing nations. Potrykus and his co-workers hoped to supply the rice to subsistence farmers free of charge and without restrictions, a task they deemed feasible given that their project was publicly funded. However, they were unaware that they had used approximately 70 intellectual property rights (IPRs) and technical property rights (TPRs), a detail that complicated their goal of free distribution. Potrykus and his co-inventor Peter Beyer joined up with Zeneca to address the property rights. This small company was given a license for the commercial use of golden rice, and the company agreed to the humanitarian use of the rice, as the inventors had hoped. Zeneca helped arrange for free licenses for other companies' IPRs and TPRs (Potrykus, 2001).

Soon after the agreement was made with Zeneca, Monsanto Corporation, the company who owned the rights to the 35S promoter used for the expression of the genes engineered into golden rice, offered royalty-free licenses for their IPR involved in the golden rice project (Normile, 2000; Potrykus, 2001). The company believed this action would help bring golden rice to farmers and those in need sooner. Potrykus hoped that Monsanto's move would encourage other companies to give up their intellectual property rights, as well, "for humanitarian purposes" (Normile, 2000, p. 843).

The Story of Golden Rice 2

Initial opponents of "golden rice 1" criticized the product for its low β-carotene content. With only 1.6 μg of total carotenoids per gram of dry rice, the grain did not contain sufficient levels of β-carotene to be a cost-effective and efficient option for VAD. Greenpeace (2002) claimed that an adult would need to consume nearly 12 times his normal intake of rice daily to get an adequate amount of provitamin A in his diet.

Critics suggested that the rice might have potential as a successful intervention in the developing world if it contained higher levels of the carotenoid. Researchers from Syngenta, a Swiss agribusiness, examined the engineered β-carotene pathway in search of the limiting step in β-carotene formation. Paine et al. (2005) hypothesized that the daffodil *psy* gene for phytoene synthase was the limiting factor in the β-carotene pathway. They tested the carotenoid content of variants of the rice engineered with the *psy* gene from maize, rice, pepper, tomato, and daffodil plants. Their results suggested that the highest levels of β-carotene in the endosperm could be generated using the *psy* gene from maize (Paine et al., 2005).

The results of Paine et al.'s (2005) experimentation with the *psy* gene enabled them to produce a new variant of Potrykus and Beyer's vitamin A rice, named "golden rice 2." In this variant, the *psy* gene of the maize plant replaced that of the daffodil plant. The rice grown with this modification generated a maximum of 37 μg of total carotenoids per gram of dry weight of rice, in contrast with only 1.6 μg per gram in golden rice 1. Most of the increase in total carotenoids observed was due to an increase in β-carotene, rather than an increase in all carotenoids (Paine et al., 2005). The richer orange color of golden rice 2, as compared with golden rice 1, reflected the increase in β-carotene content.

CHAPTER 3: THE POTENTIAL FOR SUCCESS WITH GOLDEN RICE

Efficacy

The efficacy of golden rice, or its ability to alleviate VAD and improve health, will be a major determinant of its utility as a public health intervention in the developing world. If the product fails to bring significant biologic benefits to its consumers, it will not be a worthwhile endeavor. The efficacy of golden rice depends on three factors: (1) the actual β-carotene content of the rice at the time of consumption (2) the bioavailability of β-carotene in the rice and (3) the bioconversion rate of β-carotene to retinol. The β-carotene content of the rice is a function both of the amount of β-carotene that accumulates in the endosperm as a result of genetic engineering and also of the post-harvest losses of β-carotene during storage, processing, and cooking (Zimmermann & Qaim, 2004). Bioavailability refers to the proportion of β-carotene that is extracted from a food source and reaches the circulation in the body ("Bioavailability," 2008; Yeum & Russell, 2002). The bioconversion rate is "the process of beta-carotene absorption by the human body and its transformation to retinol," its usable form (Zimmerman & Qaim, 2004, p. 156). Both the bioavailability and the bioconversion rate depend on the food structure containing β-carotene, the intake of other foods in the diet, nutritional status, age, and disease status. (Yeum & Russell, 2002; Zimmerman & Qaim, 2004).

β-Carotene Content

The value of golden rice as an intervention for VAD depends, in part, on the β-carotene content of the rice. Current estimates suggest that golden rice 2 accumulates as much as 31 μg of β-carotene per gram of dry rice in its endosperm (Paine et al., 2005). The post-harvest losses of β-carotene from the rice could also impact its β-carotene content. Studies to date suggest that exposure to extreme heat, either during storage or cooking, is the primary mechanism by which β-carotene content could be reduced. Though the research on this topic is scarce, current predictions suggest that post-harvest losses would be low or non-significant (Zimmermann & Qaim, 2004). Zimmermann & Qaim (2004) estimate that that post-harvest losses of β-carotene would range from 0% to 25%. These low estimates suggest that loss of β-carotene from the rice is not a primary concern in determining its efficacy.

Bioavailability and Bioconversion Rate

Few studies have been performed to determine the bioavailability and bioconversion rate of golden rice β-carotene to retinol in the body. Strict regulations on genetically modified (GM) foods require that they be tested for safety and stability before they can be fed to human subjects. Skepticism among consumers and opposition from anti-GM organizations, such as Greenpeace, have also discouraged charities from funding golden rice research, as they are uncertain about the future outlook of the crop (Enserink, 2008).

Though there is limited data available on bioavailability and bioconversion rate, Zimmermann & Qaim (2004) conducted an analysis of the potential benefits of golden rice in the Philippines, where VAD is prevalent. β-carotene dissolved in oil, its most available form, is converted to retinol in a ratio of 2:1. β-carotene from natural plant sources, such as fruits and vegetables, however, is converted to retinol in a ratio of only 12:1. Since rice has a simpler food matrix than fruits and vegetables, given that it consists of "totally digestible carbohydrates," Zimmermann & Qaim (2004) estimate a 6:1 conversion rate of golden rice β-carotene to vitamin A (p. 157). Similarly, Stein, Sachdev, & Qaim (2008) estimate that there will be a conversion rate between 6:1 and 3:1.

Tang, Qin, Dolnikowski, Russell, & Grusak conducted the only documented golden rice human feeding trial to date in 2009. The researchers concluded that β-carotene from golden rice is successfully converted to retinol in the body. The 36-day study involved five human volunteers, two males and three females, all of whom were healthy, had a BMI in the range of 22.2 to 28.5, and had normal vitamin A and carotenoid levels at the start of the study. The researchers gave test subjects golden rice with intrinsically-labeled provitamin A carotene. The provitamin A carotene was labeled by growing the rice in a nutrient solution with 23 atom% ^2H_2O, which resulted in rice with $[^2H]$β-carotene. By labeling the provitamin A carotene in the rice, the researchers were able to distinguish between vitamin A formed as a result of golden rice consumption and vitamin A produced by the body, or from other food sources. HPLC was used to isolate serum retinol and serum carotenoids and retinoids in the subjects' blood samples. Golden rice β-carotene was converted to vitamin A in the body at a rate of 3.8 ±1.7 (mean ± SD) to 1 by weight (Tang et al., 2009).

The results of the study suggest that there is a high bioconversion rate of β-carotene to vitamin A in the body. The data support previous assumptions that rice represents a simple food matrix from which β-carotene is easily obtained. Based on these findings, Tang et al. (2009) suggest that golden rice 2 would be a cost-effective intervention for alleviating VAD. They recommend biofortification of staple crops other than rice that are grown in areas with vitamin A deficient populations (Tang et al., 2009).

Despite the promising conclusions drawn from this small study, it is unlikely that the results are generalizable to the target population, which suffers from moderate-to-severe VAD, as well as other nutrient deficiencies. An individual's ability to absorb provitamin A depends on his or her nutritional status and food intake, and absorption of β-carotene is better with higher fat intake (Hirschi, 2009; Zimmerman & Qaim, 2004). In populations where rice is the staple food, and in nutritionally deficient populations, dietary diversity is low and fat intake is low (Hirschi, 2009; Zimmerman & Qaim, 2004). Therefore, it is unclear whether β-carotene will be metabolized in the same way in these nutrient-deficient groups. It will be essential to test golden foods as part of diets that do not favor absorption of β-carotene (Hirschi, 2009). A long-term study of the bioconversion rate in a vitamin A deficient population is needed to confirm or refute the findings from Tang et al.'s initial human feeding trial (Tang et al., 2009).

Coverage Rate

The "coverage rate" of golden rice, or the proportion of the population consuming the rice, is an additional factor that must be addressed in predicting the success rate of golden rice. Even if golden rice proves to be efficacious, in that it has a high β-carotene content and low post-harvest losses, it will fail as an intervention if it does not reach its target population. The coverage rate of golden rice will likely be between 40% and 60% of the target population. These estimates are based on the two key components of coverage rate: accessibility and acceptance (Zimmermann & Qaim, 2004).

Accessibility refers to the ease with which farmers in deficient areas can acquire the rice. Federal regulations surrounding bio- and food-safety influence farmers' access to agricultural products. The original plan for the distribution of golden rice was to supply it to farmers free of charge. The anticipated "farmer-to-farmer exchange of seeds" would then facilitate the spread of the crop, especially to hard-to-reach subsistence farmers and poor rural areas (Zimmermann & Qaim, 2004, p. 159).

Acceptance refers to consumers' willingness to purchase and eat the rice. While the enhanced β-carotene content of the rice is not expected to affect the taste of the rice, β-carotene does change the appearance of the rice, giving it a "golden," or orange, hue. In populations where rice is a staple crop, consumers are accustomed to white rice. For these consumers, the color is a signal of the product’s purity and quality (Graham, 1999). In a case study conducted in the Philippines, local farmers and consumers suggested that color would not be an issue; taste and cost were their primary concerns. VAD is prevalent in predominantly poor areas, and individuals are more concerned about having to pay more for a new crop variety than about how it looks. Farmers also expressed concerns about the yield of the new seeds, again suggesting that the economic burdens associated with golden rice would affect their usage of the product (Zimmermann & Qaim, 2004).

To ensure consumer acceptance of golden rice, it will be essential to implement educational and social marketing campaigns when the rice reaches the market (Zimmermann & Qaim, 2004; Stein et al., 2008). Such programs directed at consumers will raise awareness about the benefits and efficacy of the product. Though preliminary studies suggest that color will not be a major concern, it will still be important to explain the reason for the color change (Zimmermann & Qaim, 2004).

Will Golden Rice Reach Its Target Population?

To determine whether golden rice was an appropriate intervention for vitamin A-deficient populations, I conducted a geographic analysis to look at the overlap between VAD and rice consumption around the world. Golden rice was intended for areas where rice is a staple crop and where VAD is prevalent. Therefore, in order for golden rice to work as an intervention for VAD, there must be areas that meet both of these criteria.

The maps reflect the variation in rice consumption (FAO Statistics Division, 2008) and VAD, as measured by the biochemical parameter of serum retinol levels (WHO, 2009a). Consumption, according to the FAO, is defined as “the amount of food available for human consumption” (FAO Statistics Division, 2008).

Rice consumption and VAD in pregnant women (Figure A5)

In Southeast Asia, there is both high vitamin A deficiency and high rice consumption suggesting that, in theory, golden rice would be an appropriate intervention in this area. Nations with the highest rice consumption in the world, or more than 360 g/person/day, such as Cambodia, Bangladesh, Myanmar, Laos, and Vietnam, also have moderate to severe vitamin A deficiency among pregnant women. Therefore, if the safety of golden rice and the bioavailability of beta carotene were confirmed, golden rice could potentially alleviate some of the burden of VAD in these regions.

In nations in the Middle East, Africa, and parts of Central Asia, VAD is a public health problem among pregnant women. However, rice consumption is low in these regions and is not a staple crop. It is therefore unlikely that an intervention such as golden rice would have a significant impact on levels of VAD. However, these nations do rely on other cereals as staple crops. If golden rice is proven to be a successful intervention, there is the potential that other staple crops, such as wheat and millet, could be genetically engineered to contain vitamin A or its precursors.

There are no regions in which rice consumption is high and VAD is low. This offers further support for the conclusion that vitamin deficiency prevails in nations that rely on staple crops as their food source.

Rice consumption and VAD in preschool children map (Figure A6)

The patterns of VAD for preschool-aged children are similar to those for pregnant women, though the rates of VAD in preschool-aged children are even higher. VAD is a severe public health problem in several nations in Southeast Asia, where rice consumption is high (at least 180 g/person/day). Golden rice could therefore be an effective intervention in these areas.

However, VAD is estimated to be a severe public health problem among preschool-aged children in almost all nations in Africa, as well as in central Asia, Mexico, and parts of South America. In these regions, rice consumption is relatively low. It seems, therefore, that golden rice would only target a small proportion of the world's total vitamin A-deficient children.

Wheat and maize consumption and VAD in preschool children (Figures A7 & A8)

I conducted further analyses to look at the consumption of other staple crops in vitamin A-deficient regions where rice consumption is low. Together rice, wheat, and maize make up 50% of the world's caloric intake, with rice accounting for 23%, wheat for 17%, and maize for 10%. I therefore examined the overlay of wheat and maize consumption with VAD. I used data for VAD in preschool children, because VAD is more prevalent among young children than among pregnant women.

Wheat consumption is high in the Mediterranean region and Central Asia, where rice consumption is low. While VAD is not particularly high in northern Africa, it is prevalent in Central Asia. In Mexico, VAD is classified as a severe public health problem among preschool-aged children, though no public health problem is assumed for pregnant women. While rice and wheat are not consumed in high quantities in this region, it is estimated that more than 270 g/person/day of maize are consumed. Maize, like other cereals serving as staple crops, has low micronutrient content.

Conclusions

The maps confirm the assumption that rice consumption is high in some nations where VAD is prevalent. Therefore, an intervention for VAD implemented by means of rice consumption would effectively reach at least a segment of the target population. These findings also suggest that, if genetic engineering for enhanced micronutrient content is accepted as a means of addressing micronutrient deficiencies, further research should be pursued in altering the micronutrient content of other staple crops, such as wheat and maize.

However, biofortification of any staple crop still leaves a large segment of the target population untouched. VAD is a public health problem throughout Africa, yet consumption of rice, wheat, and maize is relatively low, as compared with the consumption of these foods in other affected nations. Therefore, alternative methods are needed to address VAD in Africa. This could include further analysis of the diet in search of another candidate for fortification. It could also involve efforts to increase the overall food supply to Africa, as VAD may simply serve as an indicator of insufficient caloric intake in these areas (Loftas & Ross, 1995).

This analysis also does not address the issue that individuals who consume rice as the predominant food in their diet are still deficient in other nutrients. Therefore, while there is insufficient evidence available to exclude golden rice as a potential intervention for VAD, it does not confirm its efficacy in improving food or nutrition security in developing nations.

The results of this analysis suggest that Southeast Asia is the only region that meets both of the criteria listed above: high rice consumption and high prevalence of VAD. Therefore, golden rice holds potential as an intervention for VAD only in this region. However, the simultaneous high staple crop consumption and high prevalence of VAD in Central Asia, Mexico, southern Africa, and the Mediterranean suggest that there is potential for β-carotene fortification of other staple crops to achieve the same effect. Nevertheless, we must refrain from viewing golden rice as a magic bullet for solving the problems of VAD and malnutrition, recognizing its limitations, even in Southeast Asia, in addressing all aspects of the problem.

It is also important to note the limitations of the conclusions drawn from these maps. These maps may be limited in scope in that they are based only on serum retinol levels as an indicator of VAD, rather than on clinical symptoms, such as night blindness. Given that the data do not account for waste that may occur in the household, the data may also overestimate the actual quantity of rice eaten by individuals in the population.

Cost Effectiveness

For some critics, concerns about the costs associated with golden rice override any doubts about the accessibility or acceptance of the rice. Graham (1999) suggests that researchers rarely consider the costs associated with large-scale distribution of new technologies during the development stages. As a result, a technology that seems feasible during development may prove to be unrealistic in practice. Therefore it may be more expensive to implement a new technology than its inventors may have thought. There are also additional costs associated with the education and social marketing campaigns that are essential for effective implementation of golden rice (Stein et al., 2008; Zimmermann & Qaim, 2004). These educational costs also contribute to the unanticipated financial burden of implementing a new public health intervention.

In spite of these concerns, in their analysis of the potential effects of golden rice in India, Stein et al. (2008) estimated that golden rice would prove to be a cost-effective intervention. While there are initial costs associated with research and development of golden rice, these costs will be absorbed by the government and by donors, in India at least. Moreover, despite initial costs, the rice would be a sustainable intervention, as it would not incur yearly costs, such as those associated with supplementation (Stein et al., 2008).

Golden rice would prove to be cost effective not only as a result of the low costs of implementation, but also due to its potential to increase the productivity of poor people in developing nations. These individuals would have better immune systems and decreased morbidity and mortality, leading to enhanced efficiency. Anderson et al. estimate that, as a result of this increased productivity, the distribution of golden rice could result in a $4-18 billion increase in Asia's GDP (as cited in Dubock, 2009a).

Safety and Toxicity

Given the lack of human studies of golden rice, it is uncertain whether the product is safe for human consumption. While the target populations are largely vitamin A-deficient, it is still important to determine whether vitamin A or β-carotene intake could reach toxic levels if golden rice were to become a staple food. The retinol and β-carotene content of natural foods does not pose a risk for toxicity (Mann & Truswell, 2002). However, vitamin A intake from supplements or from excessive consumption of vitamin A-rich foods, such as liver, can have adverse effects (Shils & Shike, 2006).

Hypervitaminosis A is the condition characterized by temporary or long-term consumption of an excess of vitamin A. There are three primary effects of hypervitaminosis A. The first is teratogenic effects, or birth defects, which occur during the first trimester of pregnancy. Studies suggest that vitamin A intake on the order of 10,000 to 30,000 IU per day by a pregnant women can result in spontaneous abortion or fetal abnormalities, such as microcephaly, hairlip, or heart, kidney, thymus, or CNS problems (Mann & Truswell, 2002; Shils & Shike, 2006). Hypervitaminosis A can also result in liver malfunctions; however, research suggests that a person must consume 1500 to over 14,000 μg of vitamin A per day for 1 to 30 years in order to present with liver symptoms. Finally, low bone mineral density can result from vitamin A intakes greater than 3000 μg/day, nearly four times the RDA (Shils & Shike, 2006). However, golden rice does not contain vitamin A; rather, it contains β-carotene, a carotenoid precursor to vitamin A.

β-carotene, unlike vitamin A, does not pose a risk of vitamin A toxicity ("Beta carotene," 2007). However, high intake of β-carotene can generate a unique set of side effects. Hypercarotenaemia is a condition marked by high plasma carotene. High levels of carotenes in the blood may be accompanied by yellowing of the skin, usually of the palms, the soles of the feet, and the nasolabial folds (Mann & Truswell, 2002). The excess beta-carotene is maintained in fat stores under the skin. There is also evidence that β-carotene consumption in extremely high doses in the form of supplements can be dangerous, because β-carotene can act as a prooxidant, stimulating cell division and causing the breakdown of vitamin A (Rolfes, Pinna, & Whitney, 2009).

Additional concerns about the potential for golden rice to generate adverse side effects stemmed from its basis in genetic engineering. The rice was originally engineered with genes from the maize plant, and critics proposed that maize was a potential allergen. Similar concerns arose about the adverse effects of using a bacterium-mediated transformation to engineer the biosynthetic pathway for β-carotene into the rice. In response to these criticisms, Hirschi (2008) suggested that the rice be tested as though it were a new drug or pharmaceutical, with a thorough investigation of its interactions with other nutrients and potential allergic responses.

Roadblocks

In 2000, when golden rice was first successfully engineered, Potrykus estimated that it would take approximately two to three years for the rice to reach Asian farms. He believed it would be a powerful remedy for the deficiency syndrome that had left over 5 million preschoolers with night blindness and another 190 million children at risk for clinical VAD (Enserink, 2008). However, it has been nearly 10 years since the first successful grains of golden rice were obtained, and the rice still has not reached the farms (World Health Organization, 2009a).

The failure of golden rice to reach its target population reflects the disconnect between laboratory science and field application. A public-private sector partnership may be necessary to bridge this gap between the laboratory and the field (Al-Babili & Beyer, 2005). Public sector scientists equate success with a new research finding and the corresponding article publication, rather than with product development. In the private sector, in contrast, scientists are rewarded for product development. In a partnership between the two sectors, the public sector should be responsible for ensuring that the product is put on the market, yet they should benefit from the findings from private sector companies (Al-Babili & Beyer, 2005). This could alleviate the problem posed by products, such as golden rice. that are of “high general interest” but not “commercially interesting” (Al-Babili & Beyer, 2005, p. 572).

Regulations on transgenic crops are also responsible for golden rice’s failed journey to the farms (Enserink, 2008). In many developing nations, genetically engineered products have not yet been commercialized. High regulatory costs for the government, businesses, and academic institutions prevent commercialization (Hirschi, 2008). Al-Babili & Beyer (2005) define deregulation as the “process that eventually leads to the registration of a product and the granting of its unlimited commercial or non-commercial use” (p. 568). They propose that there are several steps required for the deregulation of golden rice to occur. First, researchers will have to prove that rice genotypes found in targeted nations, such as Indica rice, can be enhanced with β-carotene. They will need to show that provitamin A in the grains is effective in treating VAD, both in the amount of provitamin A it contains and in its bioavailability. Moreover, Al-Babili & Beyer (2005) propose that researchers need to find a way to make the rice that does not involve an antibiotic selectable marker, due to its potential to cause allergic reactions and to create antibiotic resistance.

Summary

Current findings suggest that there is potential for success with golden rice as an intervention for VAD. Golden rice likely has sufficient β-carotene to meet the nutrient needs of vitamin-A deficient individuals. The accessibility of the rice for the target population should be high, as well, given that it is to be grown and distributed in place of current rice crops. There do not appear to be any safety or toxicity concerns associated with the rice and, based on current estimates, it would be cost effective in comparison with other competing interventions.

However, the rice has its limitations. While initial surveys suggest that golden rice will be accepted by the target population, in spite of its color, the success of the rice in this domain will depend largely on social marketing and educational campaigns. Golden rice is also limited in that it would be beneficial primarily for individuals in Southeast Asia but not in other areas of the world. Perhaps the greatest limitation of golden rice, however, is its inability to make the transition from the laboratory to the fields. The political roadblocks that have delayed this transition currently serve as the most powerful force acting against golden rice.

CHAPTER 4: AN ANALYSIS OF THE ISSUES/DEBATES SURROUNDING GOLDEN RICE

Nutrition Reductionism

While golden rice 2 may contain enough β-carotene to effect a significant reduction in VAD in the developing world, its roots in nutritionism has brought it to the center of the ideological debate surrounding nutrition reductionism. Golden rice contributes to the trend of nutritionism, because it focuses on a single micronutrient. The creators and proponents of the rice believe that engineering a single micronutrient into the food supply of a deficient population can alleviate health problems. However, advocates of golden rice as an intervention for VAD overlook the importance of consuming vitamin A and its precursors as part of a varied diet.

Beta-carotene and other carotenoids are fat-soluble compounds; therefore, consumption of β-carotene and other vitamin A precursors with lipids or fat products leads to better absorption of the nutrients from the diet and better conversion to vitamin A (Al-Babili & Beyer, 2005; Ribaya-Mercado, 2002). Studies on animals and humans support the idea that fat consumption is necessary for absorption of β-carotene and conversion of β-carotene to vitamin A. The uptake and bioconversion of β-carotene could also be affected by the carotenoid source, the vitamin A status of the individual, and helminthic infections (Ribaya-Mercado, 2002). A diet consisting primarily of golden rice would be low in protein and iron, in addition to fat. Protein, however, is essential for the production of carrier molecules needed for vitamin A transport in the body, and iron is used to convert β-carotene to vitamin A in the body (Chapter 5: Golden rice 2, 2008).

The use of golden rice as a staple crop in vitamin A-deficient populations therefore would not mitigate the prevailing problem of malnutrition in the developing world. Though there is the potential that these individuals would consume the recommended daily value of vitamin A, they would still fail to eat a balanced, varied, and nutritionally sound diet (Graham, 1999, p. 74). Even if the problem of VAD were resolved, other nutritionally based problems would likely persist in these populations.

Adrian Dubock suggests that this opposition to a single micronutrient approach is a "reasonable argument taken in an abstract context" (A. Dubock, personal communication, March 30, 2010). The ideal interventions for food insecurity and poor health in the developing world would eliminate poverty and provide all individuals with a balanced diet. While it is important to seek solutions for these underlying issues, there is no practical intervention available to address these issues at this time. Golden rice, however, is an intervention that is "practical and deliverable" (A. Dubock, personal communication, March 30, 2010). How can we deny these vitamin A deficient people access to an available intervention simply because it will not solve the whole problem of malnutrition if it will at least prolong their lives (A. Dubock, personal communication, March 30, 2010)?

Environmental Concerns

Opposition to Golden Rice

Opponents of golden rice criticize the crop for the potential environmental costs it may incur. Mass production of a crop, such as rice, can waste water, and the mining of ground water and irrigation needed for mass crop production can also cause water-logging and salinization of the water supply (Shiva, 2001). Vandana Shiva, a "physicist, ecofeminist, philosopher, activist, and author" (United Nations Environmental Programme, 2010), suggests that the growth of vegetable and fruit products that contain vitamin A, rather than the production of a single industrialized crop, would not have such an effect (Shiva, 2001). Moreover, Shiva questions whether growing golden rice in large quantities will have an impact on the food chain. What will happen to organisms, other than humans, who rely on rice or rice plants as a food source? It is unclear what effect golden rice will have on biodiversity and plant susceptibility to pests and disease (Shiva, 2001).

Environmentalists also suggest that golden rice will be part of a "second" Green Revolution (Shiva, 2001, p. 41). The Green Revolution of the 1960s and '70s was marked by increased farming of staple crops. The increased crop production was driven by the development of new high-yield crop varieties that required large quantities of chemical fertilizers and pesticides to achieve high yields ("Borlaug," 2009). These initial genetic engineering projects focused on increasing cereal crop production in developing nations to address hunger. Norman Borlaug, who was credited with the development of the first high-yield crops engineered during the Green Revolution, won the Nobel Peace Prize in 1970 for his efforts ("Borlaug," 2009). He, like Stein et al. (2008), might have argued that he was working on "genetic engineering for the poor."

During this period, however, poor farmers were forced out of areas with high-quality land, which was needed for the mass production of commercial crops. Since the produce farmers grew, such as rice, wheat, and maize, was intended for mass export, farmers were forced to purchase their food. As a result, their diet shifted towards foods that were low in nutrients, refined, high in fat, and low in vitamins (Shiva, 2001). Moreover, the increased use of chemicals to foster the growth of high-yield crops spurred opposition, as there were concerns about the impact these chemicals would have on the environment and about the costs of the chemicals ("Borlaug," 2009).

Genetic engineering, according to Shiva (2001), would foster the "genetic reductionism" that characterized the Green Revolution (p. 41). Shiva (1997) defines genetic reductionism as the “reduction of all behavior of biological organisms, including humans, to genes” (p. 25). This applies to genetic engineering in that it allows for organisms to be “perceived in isolation of their environment” (Shiva, 1997, pp. 26-27). During the Green Revolution, farmers focused on single varieties of high-yield crops. Similarly, the genetic engineering that golden rice represents again sets the stage for focusing on single crop varieties as the primary food source. The growth of only a few staple crops would lead to decreased crop diversity. In effect, this would result in a decrease in farmers’ knowledge about agriculture, a reduction in biodiversity, increased pollution, and an increase in water waste (Crouch, 2001).

Stabinsky & Cotter (2004) of Greenpeace agree that a decrease in crop diversity would be detrimental to the environment. They suggest that genetically engineered crops could have an ecological advantage over other crop varieties, which would in turn lead to the extinction of wild strains of the original crops. Maintenance of crop diversity, however, is integral to the maintenance of food security. For instance, if a disease were to contaminate the existing supply of rice, it would be important to have a diversity of crops so that some might be resistant to the disease (Shiva, 2001). Moreover, once a genetic modification is introduced into the population, it will be difficult to remove it if it proves to have adverse effects. Seed exchange among farmers, as well as cross-contamination of wild crop varieties, will integrate the genetic modification into the food supply (Stabinsky & Cotter, 2004).

Support for Golden Rice

Adrian Dubock of the Humanitarian Board for Golden Rice, however, suggests that these environmental safety concerns are unfounded and exaggerated. According to Dubock, there is “not one substantiated claim of adverse effect” (A. Dubock, personal communication, March 30, 2010). Dubock (2009b) lists twelve “impartial institutions” who, between 1999 and 2004, concluded that genetically modified crops were not harmful (p. 19).

Dubock also suggests that golden rice is safe, because the only change that has been made to the rice is to add β-carotene, which is “ubiquitous in the environment” and in food (A. Dubock, personal communication, March 30, 2010). Beta-carotene is not toxic to humans, because the body converts only as much β-carotene as it needs to vitamin A. The nutrient has only been found to be toxic for smokers when it is consumed in supplements at extremely high levels (A. Dubock, personal communication, March 30, 2010). In addition, the genes involved in the biosynthetic pathway for β-carotene are found naturally in the rice, yet they are not switched on in the endosperm. The genetic modifications made to the rice also affect only two of the 30,000 genes in the rice genome (A. Dubock, personal communication, March 30, 2010).

In response to those who argue that golden rice is not “natural,” Dubock suggests that agriculture itself is “not ‘natural,’ nor is it static” (Dubock, 2009b, p. 19). Other technologies, such as the automobile, encountered similar initial opposition because they were unnatural, but they earned acceptance over time. According to Dubock, “it is the nature of progress that people are wedded to the past” (A. Dubock, personal communication, March 30, 2010). Moreover, while supplementation is widely accepted as an intervention for micronutrient deficiencies in the developing world, it is not natural either (A. Dubock, personal communication, March 30, 2010).

Misplaced Incentives – Big Business

Some critics of genetically modified organisms view golden rice as “a mere child of the biotech lobby” and see it as “a useless and rather harmful innovation for the poor” (Zimmermann & Qaim, 2004, p. 148). Critics propose that the motive behind golden rice is not to aid the poor but, rather, to bring profits to the large companies who own patents on the rice and the components of its genetically engineered biosynthetic pathway. For Vandana Shiva, vitamin A rice is at most “a very effective strategy for corporate takeover of rice production, using the public sector as a Trojan horse” (Shiva, 2002, p. 58). Golden rice, according to Shiva, is a tactic used by big business to introduce genetic engineering to the developing world and to earn the support of these populations.

Stabinsky similarly argues that golden rice, like its other genetically modified counterparts, is a “technology in search of a problem” (D. Stabinsky, personal communication, March 18, 2010). She sees golden rice as an “expensive distraction” from more appropriate methods of addressing food insecurity, including dietary diversification (D. Stabinsky, personal communication, March 18, 2010).

Potrykus, however, suggests that the opponents of genetically modified organisms (GMOs) who speak out against golden rice are engaged in “a radical fight against a technology merely for political success” (Potrykus, 2001, p. 10). He suggests that there are few, if any, valid claims against golden rice for its effects on the environment, its impact on health, or its ability to help the poor.

General Opposition to Genetically Modified (GM) Foods

For some, the opposition to golden rice stems from its basis in genetic engineering. Any form of genetic engineering is immediately associated with the financial interests of big businesses and detrimental effects on the environment. Some non-governmental organizations (NGOs), for instance, resist the use of genetic engineering “independently of its specific application or the facts” (Dubock, 2005, 8). Though genetically engineered crops such as golden rice might support the efforts of NGOs to improve poverty and promote human rights, the NGOs reject the crops solely because they are genetically modified (Dubock, 2005). This opposition to

GM foods has served as one of the primary limiting factors in the progress of golden rice (Dubock, 2005).

Golden Rice Differs from Other GMOs

In response to the opposition to golden rice, Potrykus emphasizes that the rice differs from other genetically modified foods in several distinct ways. Primarily, golden rice is part of a humanitarian project. Accordingly, it is “deliberately not aiming at a financial return,” as the goal is to provide the seed to poor farmers free of charge (I. Potrykus, personal communication, March 12, 2010). Moreover, golden rice was designed as an intervention for a severe public health problem, unlike its genetically modified predecessors (I. Potrykus, personal communication, March 12, 2010). The crop was developed to help the consumer, particularly the poor in the developing world. In developing golden rice, researchers were therefore addressing an important and pressing concern in population health (Potrykus, 2001). Finally, golden rice is a project designed and run by the public, rather than the private, sector (I. Potrykus, personal communication, March 12, 2010).

Stein et al. (2008) similarly suggest that golden rice, in contrast with other GMOs, will provide a greater benefit for the poor than for other socioeconomic groups. Improvements in health status are proportionally greater for deficient individuals than for those who are closer to meeting their daily requirement for vitamin A (Figure A9). Golden rice may therefore represent a form of “genetic engineering for the poor,” rather than for big business, because the poor suffer from more severe vitamin A deficiency than other populations (Stein, Sachdev, & Qaim, 2008, p. 150). The rice was designed first to help poor people in developing nations, not farmers or pesticide producers (Stein et al., 2008).

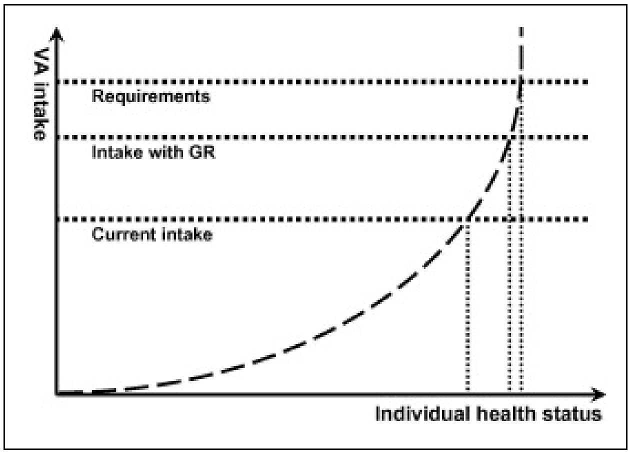

Figure A9. Relationship between vitamin A intake and individual health status. The graph reflects a proportionally greater increase in individual health status per unit of increase in VA intake for individuals who have poorer health initially. (Graph from Stein et al., 2008)

A Discussion of Alternatives

Scientists and policymakers agree that VAD is a public health problem that must be addressed. The issue at hand is how to define the problem and how to allocate resources to deal with VAD. Golden rice opponents propose several alternatives to golden rice for alleviating VAD in the developing world. They argue that these interventions are equal, if not superior, to golden rice in measures of efficacy and are better alternatives because they do not require genetic engineering.

Supplementation

Supplementation is a common public health strategy for addressing nutrient deficiencies. The strategy was first introduced in the early 1990s and while only 10 countries had adopted vitamin A supplementation programs by 1995, more than 70 countries had implemented programs by 2000 (Shrimpton & Schultnik, 2002). Supplementation is beneficial in that it offers a quick remedy for micronutrient deficiencies. It is effective at reaching high-risk groups, particularly pregnant women and children, and it focuses on the deficient part of the population, rather than on the entire population in an area (Shrimpton & Schultnik, 2002). Programs for vitamin A supplementation are already in place in some deficient areas. The results of a metaanalysis of supplementation with massive-dose vitamin A capsules conducted by Beaton et al. (1994) suggested that the program decreased mortality among 6-month- to 5-year-olds by 23%. Studies conducted by the World Bank have also suggested that supplementation is cost-effective, as the vitamin A pills cost between $0.25 and $0.45 per capsule. Vitamin A supplementation resulted, moreover, in an estimated cost per life saved of $325 and a cost per disability-adjusted life-year gained of $9 (Hirschi, 2008).

In spite of the potential effectiveness of supplementation, it is neither as cost effective nor as sustainable an intervention as golden rice. Supplement programs incur yearly costs, as countries must continuously replenish their supply of vitamin A pills (Shrimpton & Schultink, 2002). Countries must also maintain contact with their target population to deliver the supplements and to ensure that they take the supplements. The supplementation programs therefore require ongoing education and awareness campaigns (Lemaux, 2009). Golden rice, in contrast, requires only an initial investment in research and development, the cost of the seeds, and education programs. The crops of golden rice should then be self-renewing (Stein et al., 2008). Golden rice will also become part of the target population's food source, deeming continuing education programs unnecessary (Shrimpton & Schultink, 2002). It would cost between $3 and $20 to save one disability-adjusted life year with golden rice, compared with an estimated $134 to $599 per disability-adjusted life year with supplementation (Dubock, 2009a). Golden rice also has the potential to reach individuals in rural areas, who are difficult to reach with supplementation programs (Shrimpton & Schultink, 2002).

Adrian Dubock suggests, moreover, that the results of supplementation programs in the Philippines are evidence of the limitations of such an intervention. Vitamin A capsules have been distributed in the Philippines since 1993. VAD rates in the Philippines, however, are as high as 55% in children under five and 20% in pregnant women and young mothers (A. Dubock, personal communication, March 30, 2010).

Dietary Diversification

Another alternative to golden rice is to increase crop diversity and to improve the availability of food sources of vitamin A. Some golden rice critics have proposed the use of red palm oil and cod liver oil as food sources in India. However, these foods are not regularly consumed in India and foods such as red palm oil are expensive to refine (Stein et al., 2008). The cost of introducing foreign foods would therefore be comparable to the cost of supplementation, because there would be an initial cost to introduce the foods and subsequent yearly costs to process the foods (Stein et al., 2008). Moreover, food sources of vitamin A, such as meat and fresh vegetables, are expensive and would not be accessible for poor populations (Hirschi, 2008). Cultural barriers could also interfere with dietary diversification programs. In some vitamin-A deficient areas, such as India, there are many vegetarians. Though meats are richer sources of vitamin A than fruits and vegetables and are available year-round, they would not be acceptable in India (Stein et al., 2008). Emphasis on specific plant sources of vitamin A could also decrease biodiversity, if these foods were grown in excess or if they were to replace other indigenous crops (Stein et al., 2008).

Addressing the Underlying Issues behind Food Insecurity

According to Blakeney (2009), the causes of food insecurity cannot be traced solely to micronutrient deficiencies. The leading contributor to food insecurity is poverty (Hirschi, 2008; Shrimpton & Schultink, 2002; Stein et al., 2008). The persistent hunger and micronutrient malnutrition in the developing world, despite the existence of adequate food supplies, is attributable to a “vicious cycle of hunger and poverty” (FAO, 2009b, p. 13). Hunger not only results from poverty but also causes it, because malnutrition and its physiological consequences impair an individual's ability to work. Poor or malnourished children grow up to be the adults who are unable to provide for their families and their own children. This suggests the need for food security initiatives that focus not only on improvements in employment and productivity, but also on building social networks and safety nets for those individuals who are not self-sufficient (FAO, 2009b). Implementing an intervention such as golden rice would not provide the economic or social foundation that is necessary for widespread change in the developing world. While golden rice might remedy the present problem of vitamin A deficiency, it would fail to address the underlying issues of infrastructure and poverty that are predictors of future health in these populations.

Doreen Stabinsky of Greenpeace suggests that food security interventions should focus on working with small farmers since the farmers, rather than large corporations, are responsible for feeding 70-80% of individuals worldwide. According to Stabinsky, food security is "about people having the ability to produce their own food," rather than about genetic engineering (personal communication, March 18, 2010). Stabinsky argues that empowering small farmers would enhance food security by providing the poor farmers with a more secure livelihood (D. Stabinsky, personal communication, March 18, 2010). She suggests that, by using golden rice and other genetic engineering interventions, we are treating a symptom, rather than the root cause, of the problem. These high-tech alternatives are "high-cost," according to Stabinsky, and they distract us from "locally available solutions" (D. Stabinsky, personal communication, March 18, 2010).

CHAPTER 5: ANALYSIS AND CONCLUSIONS

Golden rice is not a magic bullet for food insecurity in developing nations, nor is it the "golden bullet" that we hoped would eradicate VAD. However, the rice has the potential to lessen the burden of VAD as a public health problem in high-risk areas. Introducing golden rice in combination with other interventions that target underlying economic and infrastructural problems offers a viable option for addressing malnutrition and food insecurity in the developing world.

Efficacy: Promising, but Unconfirmed

Golden rice has the potential to be effective in alleviating at least part of the burden of VAD in the developing world. Preliminary studies suggest that it is unlikely that post-harvest losses will result in a decrease in the β-carotene content of the rice and that it is likely that the rice will have a high bioconversion rate of β-carotene to vitamin A in the body. Golden rice seems to be safe for the target populations, in the short term, if the absence of immediate side effects demonstrated in Tang et al.'s (2009) limited human feeding trial is sustained in population-wide studies. However, it is important to keep in mind that Tang et al.'s (2009) study was small and executed with a homogenous group that was not representative of the target population.

Limits on Reaching the Target Population

While golden rice might be effective on a biochemical level, it would not be entirely successful in reaching its target population. The rice-consuming nations represent only a fraction of all nations suffering from VAD as a public health problem. Though it may be possible to engineer other staple crops, such as wheat and maize, to contain β-carotene, this would still leave gaps in regions, such as Africa, where none of these three foods serve as staple crops. Also, these crops could take a long time to reach the fields. Golden rice was engineered nearly ten years ago, and it has yet to make its way to the fields of Southeast Asia, or to other rice-consuming, vitamin A-deficient areas.

In addition, scientists are underestimating the breadth of the public health campaigns that must accompany the distribution of golden rice. The success of golden rice will depend largely on the implementation of education and social marketing campaigns (Stein et al., 2008; Zimmermann & Qaim, 2004). Though studies suggest that the color would not be a significant deterrent, nor would the taste of the rice, it is likely that educating the public about the rationale behind and importance of golden rice would improve the likelihood of success. These educational campaigns would require significant funding. Though in the long term golden rice would prove to be more cost effective and more sustainable than its alternatives, researchers must acknowledge the initial costs of the project.

Impact on immune resistance

Current research suggests that vitamin A is in fact essential for proper immune function. However, there is no evidence that immune resistance will improve as a result of improved vitamin A status in deficient populations, because the target individuals are also deficient in nutrients other than vitamin A. It is unlikely that comprehensive studies will find vitamin A to be the sole determinant of poor immune resistance. Eliminating the problem of VAD may simply shed light upon yet another nutritional deficiency, for which yet another genetically modified magic bullet will be devised.

Reductionist approach

Though golden rice may be effective in improving the vitamin A status of deficient populations, it fails to address overall health in deficient populations. While golden rice is a sustainable intervention when compared with supplementation, it will not improve self-sufficiency and overall health in the population. It is a downstream public health approach that addresses one of the external indicators of a poor, uneducated, and nutritionally-deficient population that does not have access to the resources available in the developed world. While golden rice does seek to prevent VAD in the population, it does not address the underlying problems that lead to VAD, namely poverty and poor access to agricultural resources. The educational and vocational opportunities in the developing world are also limited, as is access to diverse fresh foods and medical treatment.

Golden Rice is Not a Magic Bullet

Though, upon its discovery, penicillin was believed to be a "magic bullet" for venereal disease in the United States, it simply exposed other diseases that were not responsive to penicillin. The same concept applies to golden rice and VAD, and other similar efforts to treat food insecurity one micronutrient at a time. Targeting individual micronutrients may simply expose other deficiencies, as well as other health problems and diseases, that are "unresponsive" to golden rice (Brandt, 1985, p. 161). Magic bullets fail to address the underlying "social and cultural determinants" of disease (Brandt, 1985, p. 161), and golden rice may similarly fall short in this domain.

The treatments we devise for health issues are largely based upon how we define the problem (Brandt, 1985). We must therefore look at how we are defining the problem of VAD. Whether we view it merely as a biologic deficiency or as a larger infrastructural and social problem will determine our success in improving health outcomes.

Genetic Engineering is Inevitable

Twenty-three countries around the world currently grow genetically modified (GM) crops. In reality, golden rice is not that different from what we eat already. We are all "eating genes" daily without realizing it (Raphael & Jones, 2009, p. 5). At this point, it is unlikely that the world will ever be "GM-free" (Raphael & Jones, 2009, p. 5). It is therefore in our best interests to determine how to use GM foods safely and effectively, rather than viewing all GM foods as a single detrimental entity. Genetic engineering is a powerful technology that has the potential to fill in gaps in population health where broader solutions are not politically, socially, or economically feasible.

Deregulation is a Necessity

Potrykus emphasizes the need for faster methods of deregulating genetically engineered products. He suggests that the safety of genetically modified organisms (GMOs) has been confirmed by "numerous academies" and that there is little evidence to suggest that GMOs differ from non-transgenic crops in measures of safety (I. Potrykus, personal communication, March 12, 2010). Therefore, the safety studies required for the deregulation of golden rice and its distribution to farmers are "unjustified and unnecessary" (I. Potrykus, personal communication, March 12, 2010). Potrykus further proposes that the ten-year delay between the development of golden rice and its distribution to farmers can be blamed entirely on GMO-regulation (I. Potrykus, personal communication, March 12, 2010).

While it is important to take the necessary precautions to ensure the safety of deficient populations and of the environment, the resources of time and money have been spent frivolously in the process of deregulation. This process is also a deterrent to future researchers, as even Potrykus suggests that if he and Beyer "would have known what it meant in reality to bring Golden Rice to the needy we, most probably, would not have started the project" (I. Potrykus, personal communication, March 12, 2010). Potrykus describes the years since 1999, during which time he and Beyer strove to bring golden rice to those in need, as "very unpleasant and difficult years – although it widened our horizon enormously" (I. Potrykus, personal communication, March 12, 2010).

Golden rice embodies the disconnect between theory and practice in public health. Regardless of the biological effectiveness of golden rice, the political barriers that lie between the laboratory and field application detract from its potential as a public health intervention in practice. If genetic engineering is to become more widespread and is to benefit those in need, scientists and policymakers will have to make faster deregulation a priority. This is not to say that safety should be overlooked or that genetically modified products should not be tested. However, policymakers will need to rethink the laws surrounding gene patents and intellectual property rights to ensure that they are aligned with scientific goals. At this point, new genetically modified crops are tied up in so much litigation and policy hurdles that it overshadows the interventions themselves.

Areas of Current and Future Research

In order for golden rice to gain acceptance as a public health intervention, several areas of research must be explored. Primarily, studies should be conducted to determine whether β-carotene uptake and conversion to vitamin A is as high in nutritionally-deficient individuals as it is in the healthy subjects used in Tang et al.'s (2009) study. Researchers are currently looking at the effect of animal or vegetable fat in the diet on the bioconversion rate of β-carotene to retinol (Raphael & Jones, 2009). This will be important for determining whether the bioavailability of β-carotene from golden rice is as high for nutritionally deficient individuals as it is for those consuming a balanced diet.

Safety trials will be necessary to confirm that golden rice does not pose risks to consumers or to the environment. Given that environmental risks are difficult to assess in the short term, it will be imperative that ongoing research be conducted to evaluate golden rice for years to come. Though Potrykus suggests that safety trials are unnecessary (I. Potrykus, personal communication, March 12, 2010), they will be essential for building public confidence and for gaining political support.

In addition, it will be important to develop more accurate estimates of the potential for cultural acceptance of golden rice. Preliminary studies, such as the analysis conducted by Zimmermann & Qaim (2004), suggest that the color of the rice will not be a deterrent to consumers if taste and cost remain unchanged. The Zimmermann & Qaim (2004) study, however, was limited in scope in that it was based only on focus group discussions with rice producers and consumers in two villages in the Philippines. The group was not representative of the Philippine population as a whole, nor could it have been an accurate representation of all vitamin A deficient populations (Zimmermann & Qaim, 2004).

Before attempts are made at widespread distribution, pilot studies of social marketing and educational campaigns should be run to test the effectiveness of the rice. These studies should control for potential incentives to eat the rice, such as distributing it to participants free of charge, as the target population is largely poor and malnourished. Dubock also identifies the need to avoid associating the rice with poverty (A. Dubock, personal communication, March 30, 2010). While genetic engineering may be the first example of what Stein et al. (2008) call "genetic engineering for the poor" (p. 150), if it is marketed this way, the rice may earn a stigma that deters those who need it most.

According to Potrykus, plans have been made for the distribution of golden rice in the coming years. Golden rice will be distributed to subsistence farmers in the Philippines in 2012, in Bangladesh in 2013, and in India, Vietnam, Indonesia, and China beginning in 2014. Potrykus projects that golden rice distribution in Cambodia, Myanmar, and other Southeast Asian countries, as well as in rice-consuming nations in Latin America and Africa, will follow (I. Potrykus, personal communication, March 12, 2010).

As was mentioned earlier, golden rice is limited in its ability to address VAD and other aspects of the global problem of food insecurity. Future research should explore the possibility of other "golden" foods. Enhancing other staple crops, such as wheat and maize, would allow for the reduction of VAD in a larger proportion of the deficient population. Similarly, genetic engineering could be used as a means of addressing other widespread micronutrient deficiencies in the developing world, such as iron and iodine deficiency. While efforts to enhance rice with other micronutrients would still represent a narrow approach to health, the resulting rice would be more likely to meet nutritional needs than golden rice alone. Currently studies are underway to fortify golden rice with additional nutrients, such as iron, zinc, protein, and vitamin E. This $500 million project is part of the Bill and Melinda Gates Foundation's Grand Challenges in Global Health Programme (Raphael & Jones, 2009). Dr. Peter Beyer of the University of Frieburg in Germany is the lead investigator on the study.

Given that VAD alone is not the sole perpetrator of poor immune resistance, future research should be conducted to identify other potential contributors to immune function. While the role of vitamin A in immunity is well-studied, it is unclear what other factors interact with vitamin A to generate immune resistance, and further research in immunology will therefore help to improve the health of deficient populations.

The Verdict

We must refrain from viewing golden rice as a panacea for the problems of hunger and malnutrition in the developing world. We will not find a magic bullet for food insecurity, because none exists. The rice will not offer a global solution to the problem of food insecurity, and it is not feasible to address food insecurity one micronutrient, or one individual health condition, at a time.

However, golden rice is at the frontier of genetic engineering in nutrition science. Instead of fighting the trend of genetic engineering, we must focus on how to use the technology safely and effectively to meet health needs. Given that golden rice is unlikely to bring harm to its consumers, it will be important to embrace it as an intervention, as it is the best available alternative for VAD at this time.

While golden rice shares some of the principles of nutritionism, in that it targets one micronutrient, it is appropriate to use this type of intervention in a situation where other alternatives are inadequate. Though ideally we would address micronutrient deficiencies by improving access to fresh and natural foods and by reducing poverty, these efforts will take time. In the interim, an intervention that targets VAD directly would be more efficient and effective. Golden rice is more sustainable and more cost effective than supplementation, a current standard for addressing VAD, and should therefore be considered.

Nevertheless, we must pursue golden rice as part of an integrative approach to food security that combines treatment of the symptoms with efforts to alleviate the underlying problems of poverty, infrastructure, and social inadequacies. While golden rice in no way serves as a comprehensive solution to the issue of food insecurity in the developing world, it offers a sustainable solution for a segment of the problem. If we can use golden rice to make the world even a little bit less food insecure, it will be a worthwhile endeavor.

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APPENDIX A: MAPS AND FIGURES

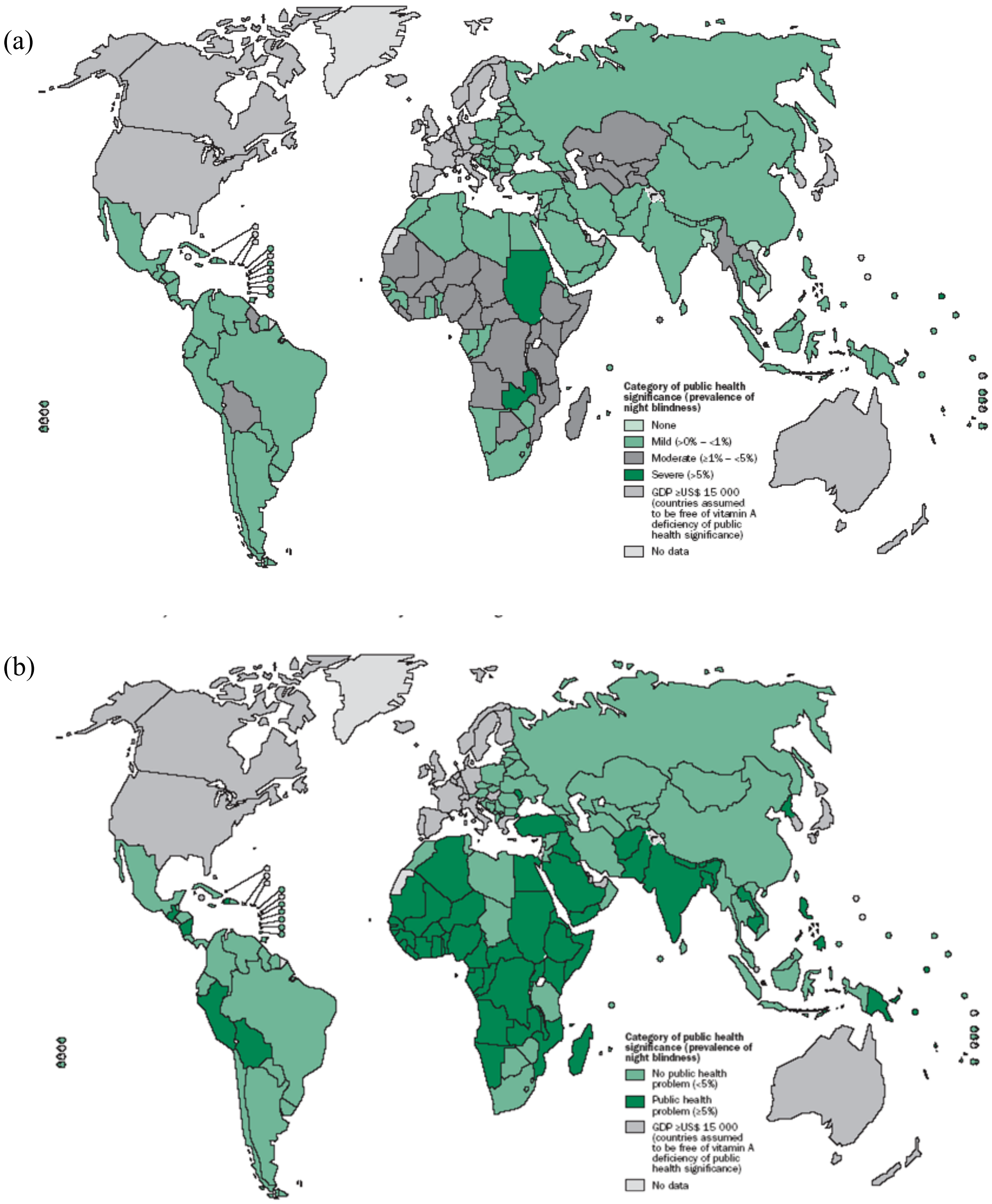

Figure 1. Global prevalence of night blindness among (a) children and (b) pregnant women, 1995-2005 (World Health Organization, 2009a).

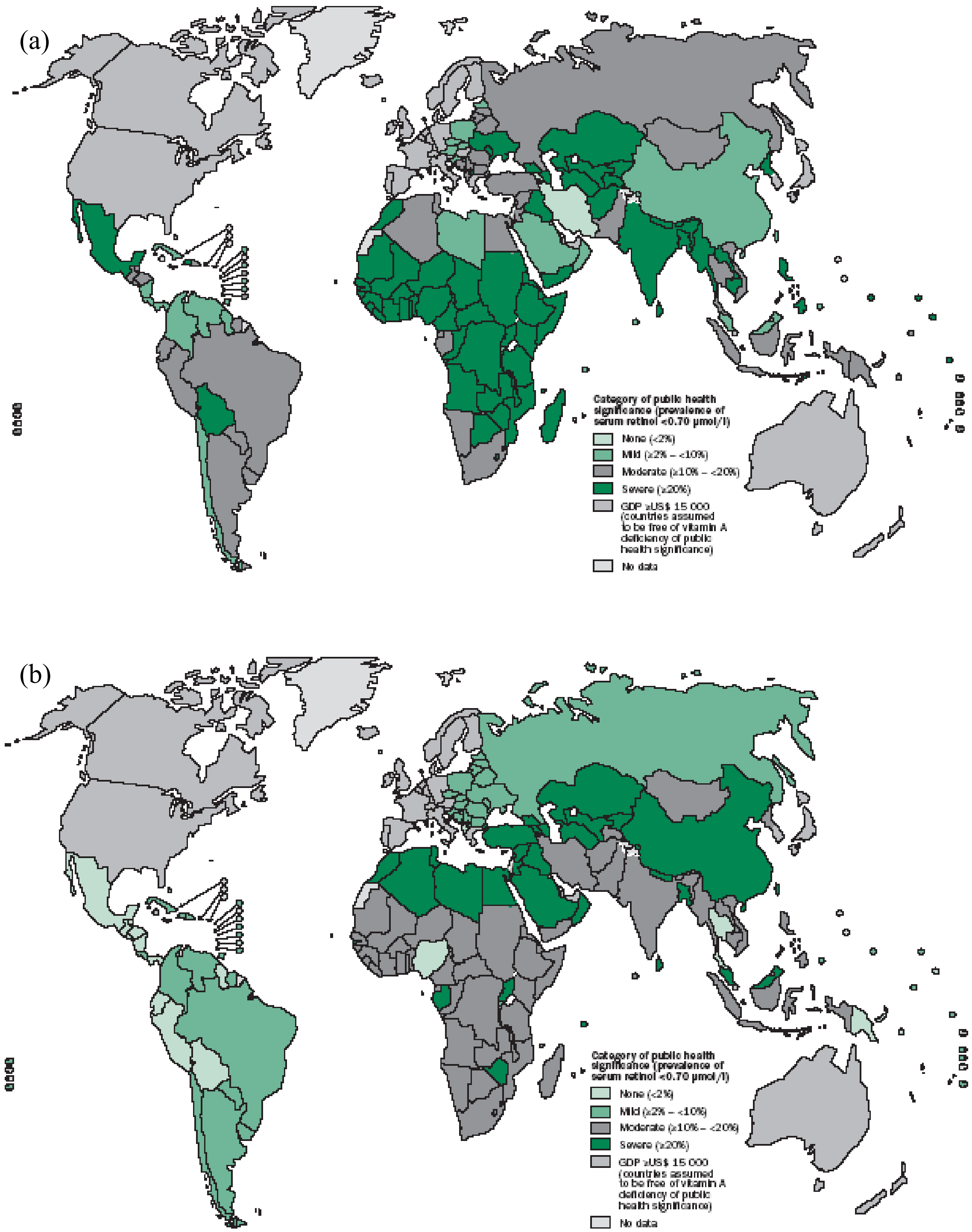

Figure 2. Global prevalence of biochemical VAD among (a) children and (b) pregnant women, 1995-2005 (World Health Organization, 2009a).

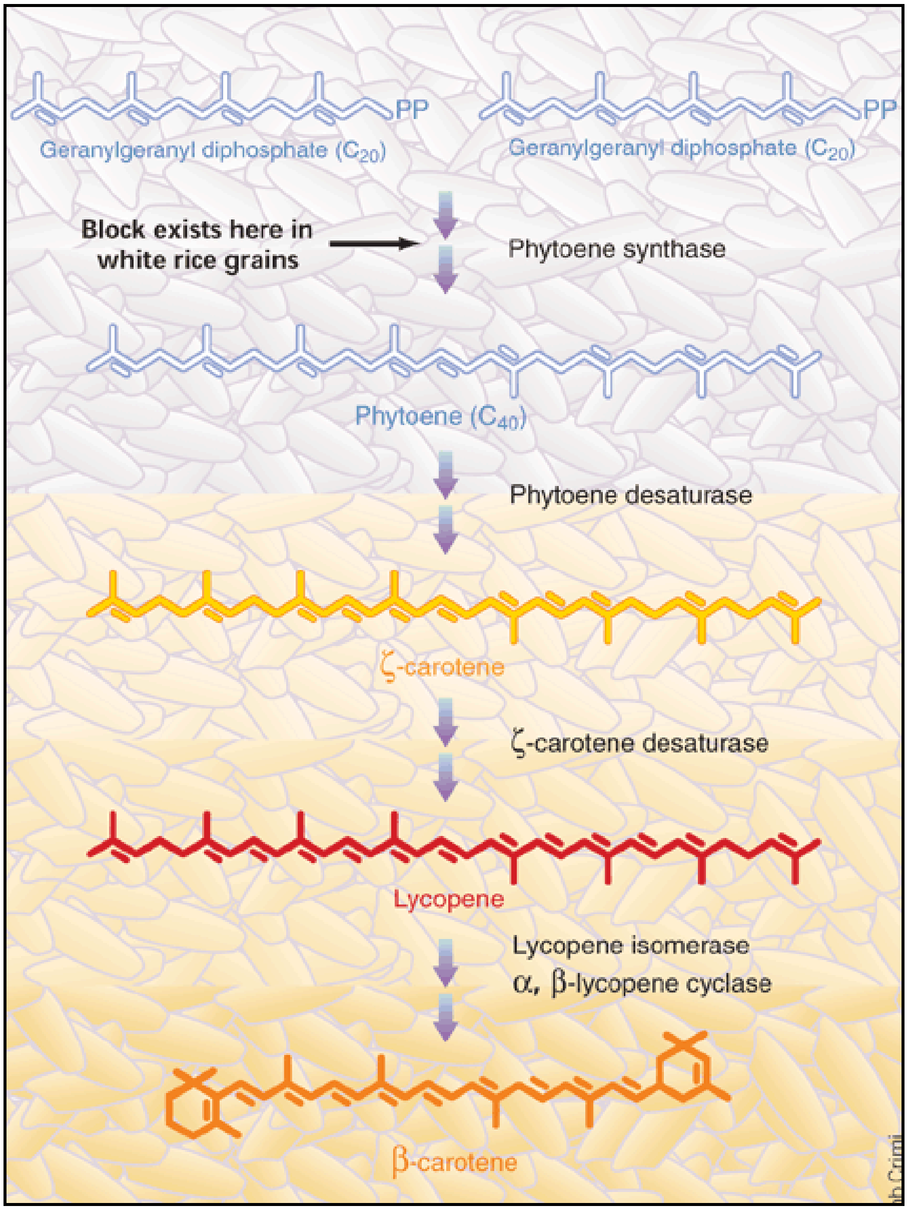

Figure A3. Pathway for β-carotene synthesis. Geranylgeranyl diphosphate (GGPP) is found naturally in the endosperm, or edible portion, of white rice. The enzymes phytoene synthase, phytoene desaturase, ζ-carotene desaturase, and lycopene β-cyclase must be switched on in the endosperm to convert GGPP to β-carotene (Grusak, 2005).

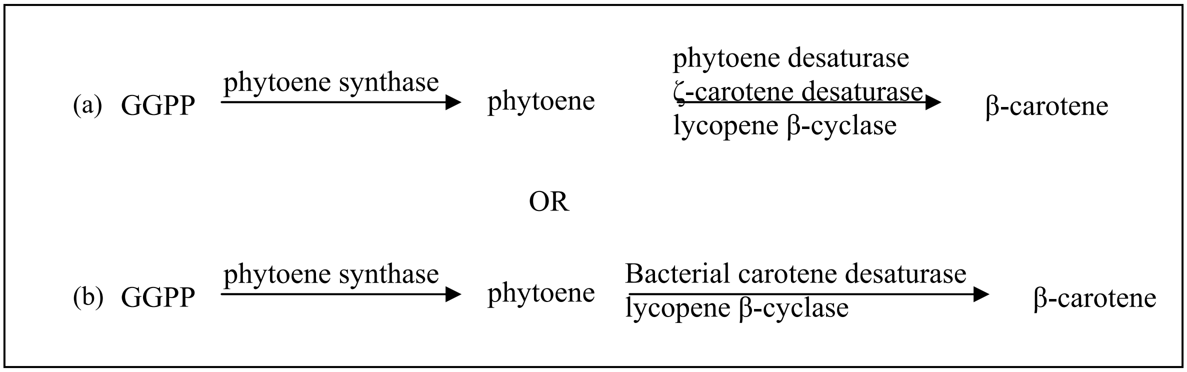

Figure 4. Pathways for β-carotene synthesis. (a) Traditional pathway (b) Modified pathway used in golden rice, where phytoene desaturase and ζ-carotene desaturase are replaced by bacterial carotene desaturase (Ye et al., 2000).

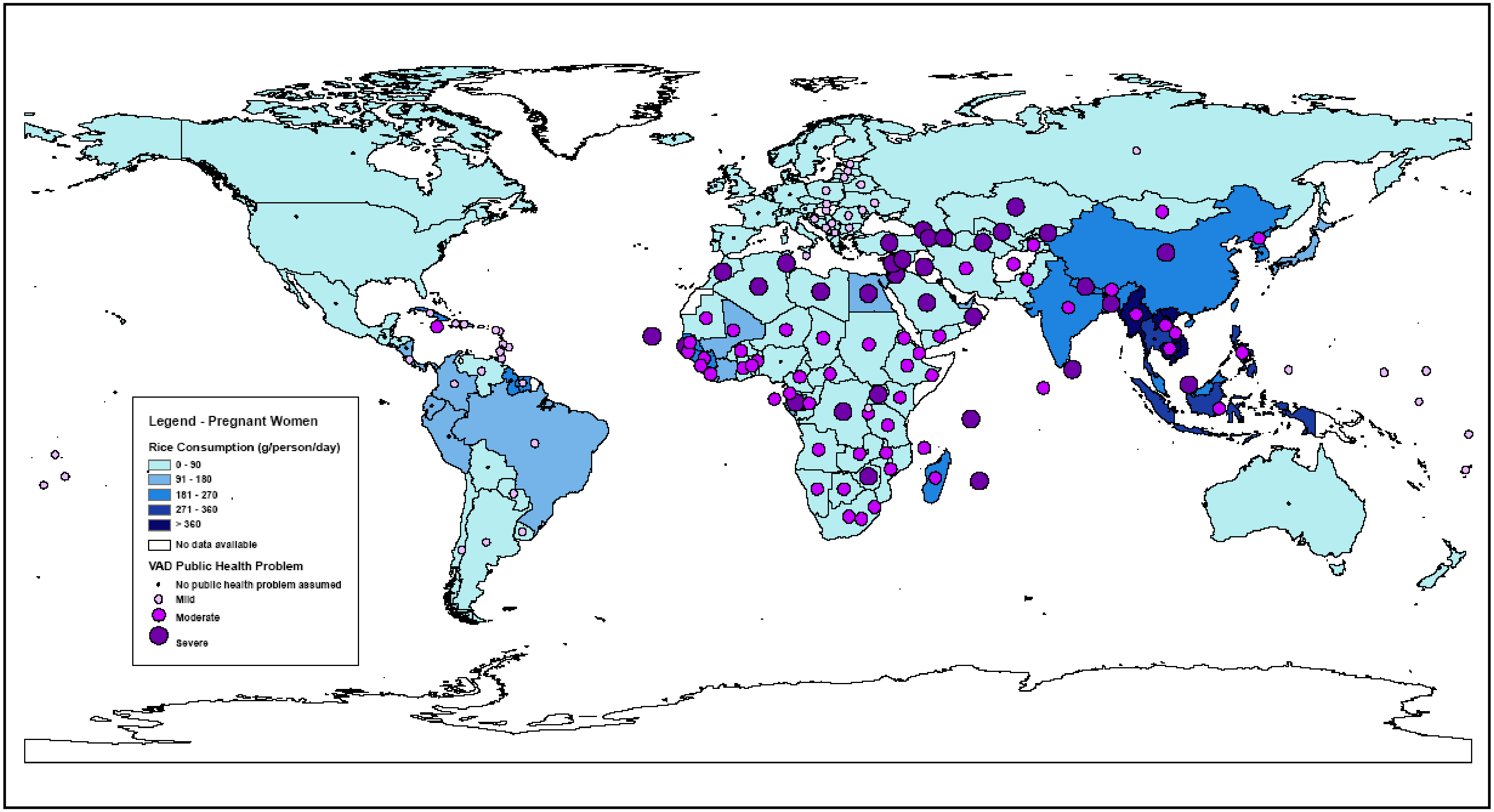

Figure 5. Rice consumption and VAD prevalence among pregnant women by country. The map shows the overlay of rice consumption and VAD among pregnant women in high-risk populations. Serum retinol levels (1995-2005) were used as a measure of the severity of VAD as a public health problem. Rice consumption data was based on data collected for the period 2003-05 (FAO Statistics Division, 2008). The map reflects a strong overlay between VAD and rice consumption in Southeast Asia, but poor overlay in central Asia and Africa.

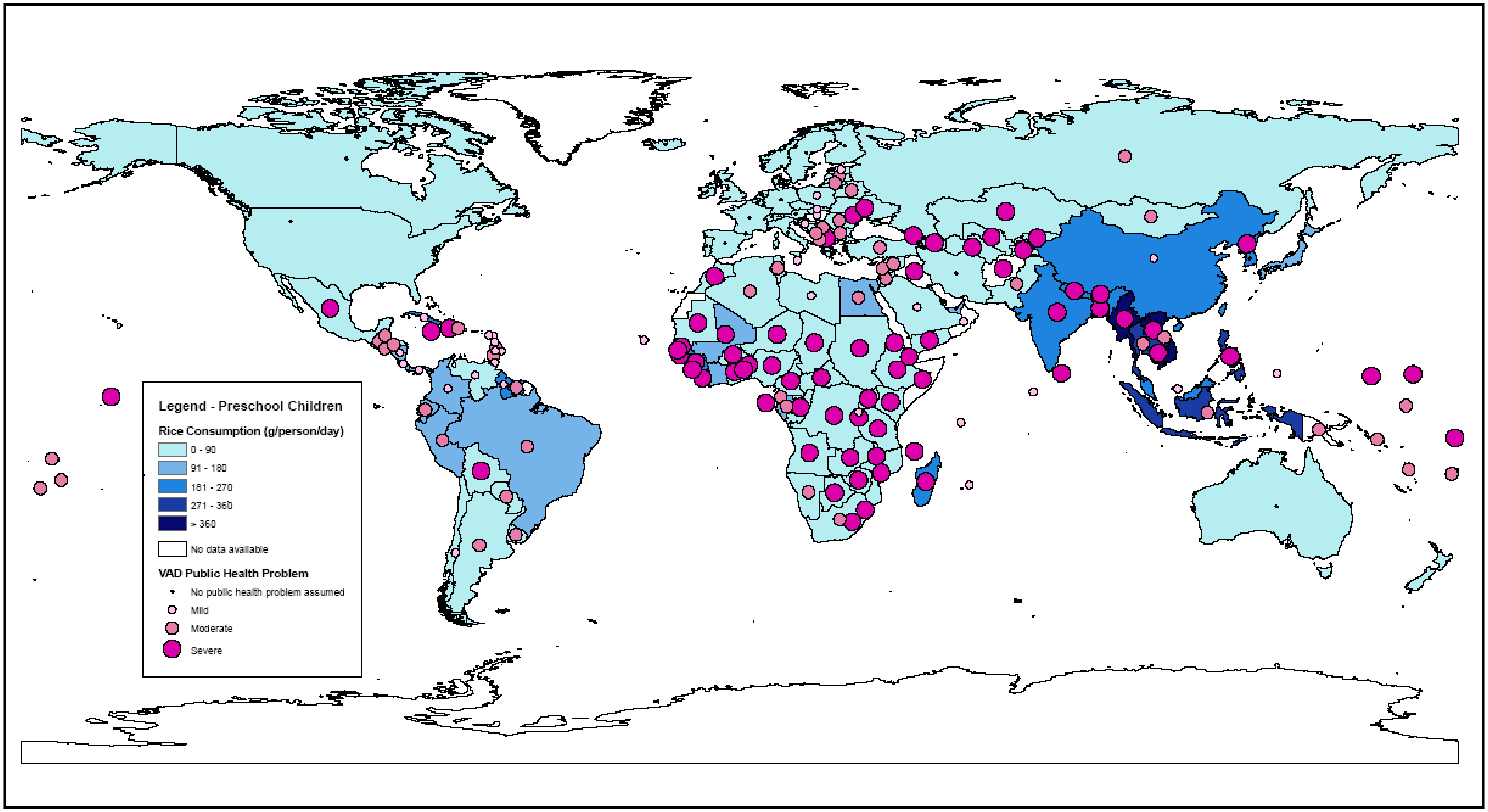

Figure 6. Rice consumption and VAD prevalence among preschool children by country. The map shows the overlay of rice consumption and VAD among preschool-aged children in high-risk populations. Serum retinol levels (1995-2005) were used as a measure of the severity of VAD as a public health problem. Rice consumption data was based on data collected for the period 2003-05 (FAO Statistics Division, 2008). The map reflects a strong overlay between VAD and rice consumption in Southeast Asia. However, VAD is severe throughout Africa, where rice consumption is predominantly low. A similar trend of high VAD and low rice consumption is observed in Mexico and Central America.

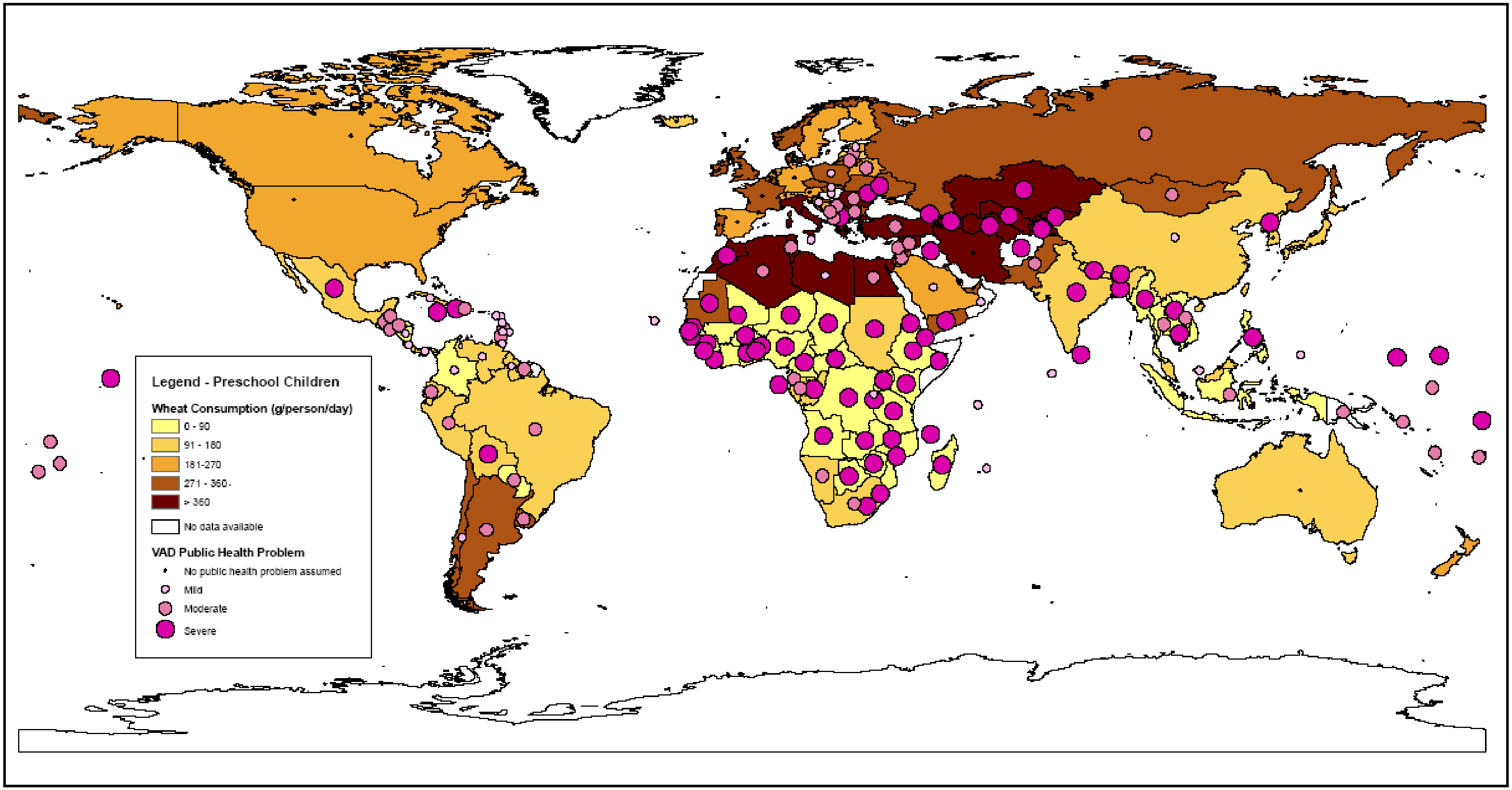

Figure 7. Wheat consumption and VAD prevalence among preschool children by country. The map shows the overlay of wheat consumption and VAD among preschool children in high-risk populations. Serum retinol levels (1995-2005) were used as a measure of the severity of VAD as a public health problem. Wheat consumption data was based on data collected for the period 2003-05 (FAO Statistics Division, 2008). There is an overlap between VAD and high wheat consumption in the Mediterranean region and in Central Asia.

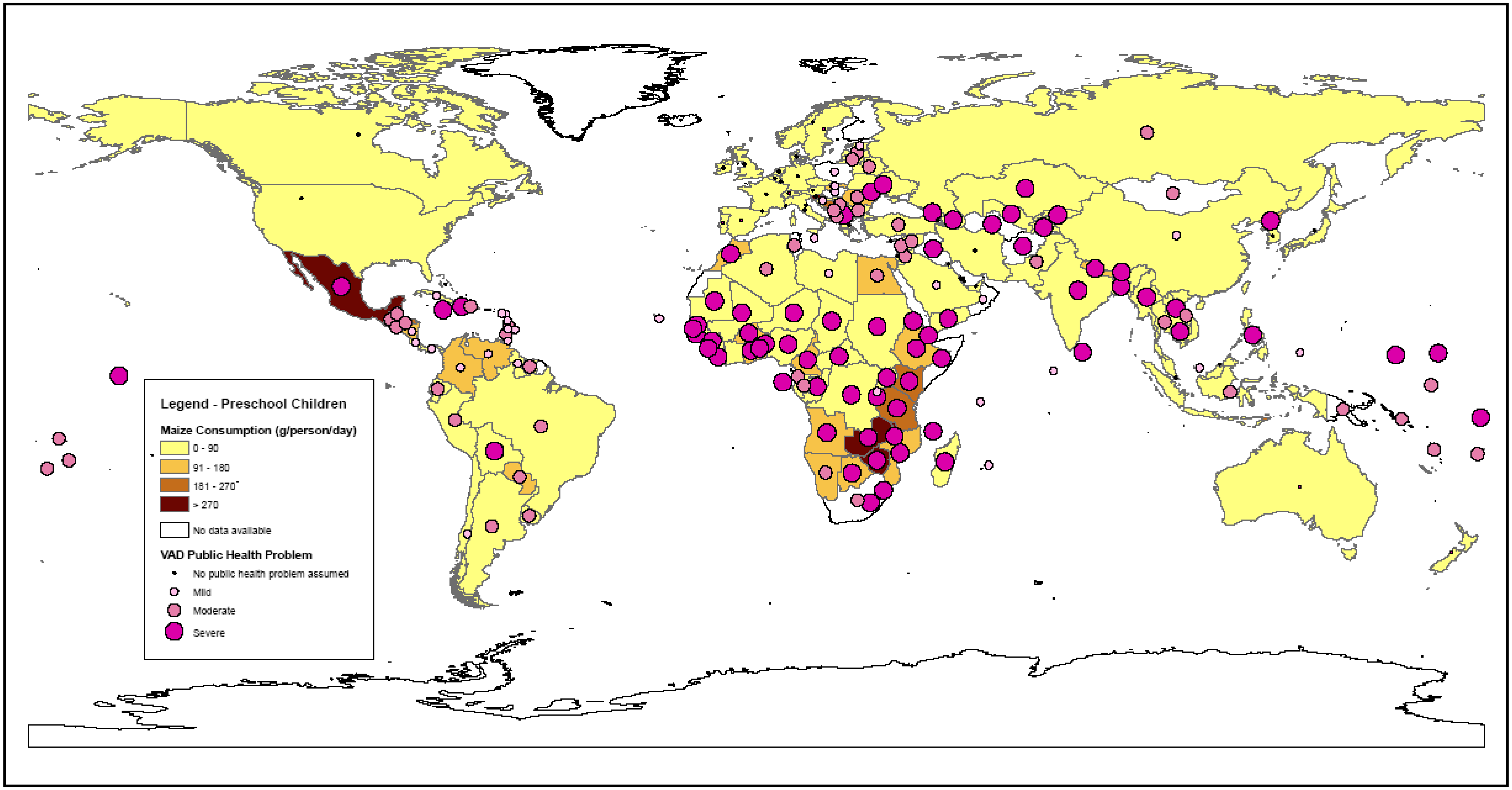

Figure 8. Maize consumption and VAD prevalence among preschool children by country. The map shows the overlay of maize consumption and VAD among preschool children in high-risk populations. Serum retinol levels (1995-2005) were used as a measure of the severity of VAD as a public health problem. Maize consumption data was based on data collected for the period 2003-05 (FAO Statistics Division, 2008). Both VAD and maize consumption are high in Mexico and in parts of southern Africa.

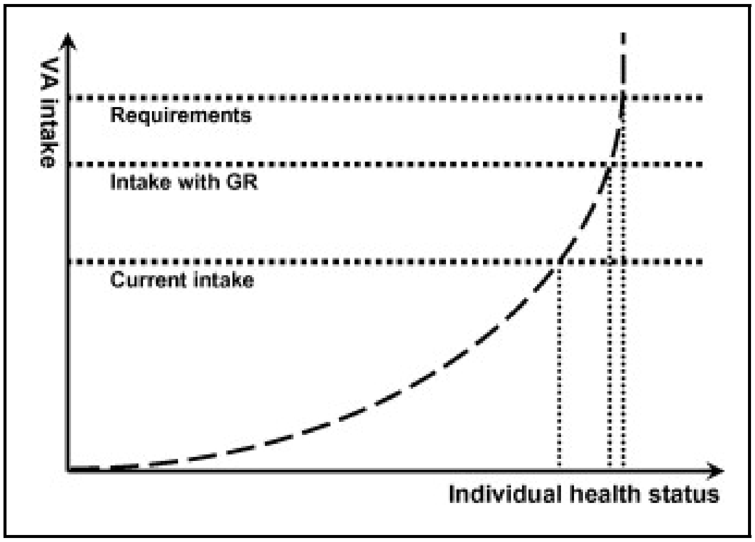

Figure 9. Relationship between vitamin A intake and individual health status. The graph reflects a proportionally greater increase in individual health status per unit of increase in VA intake for individuals who have poorer health initially. (Graph from Stein et al., 2008)

APPENDIX B: TABLES

Table 1. Dietary Reference Intake for Vitamin A

Population group	Age	Dietary Reference Intake for Vitamin A (µg/d)
Infants	0-6 mo	400
	7-12 mo	500
Children	1-3 y	300
	4-8 y	400
Males	9-13 y	600
	≥ 14 y	900
Females	9-13 y	600
	≥ 14 y	700
Pregnant women	14-18 y	750
	19-50 y	770
Lactating women	14-18 y	1200
	19-50	1300

*Data from (Coulston & Boushey, 2008)

Table 2: Vitamin A Content of Common Food Items (from high to low content)

Food item	**Single portion size**	**Retinol Activity Equivalents (1 RAE = 1 µg of retinol = 12 µg of β-carotene)**
Sweet potato with skin	1 potato	1403
Spinach, cooked, boiled, drained	1 cup	946
Carrots, raw	1 cup	919
Kale, cooked, boiled, drained	1 cup	885
Turnip greens, frozen, cooked, boiled, drained	1 cup	882
Carrots, raw	1 carrot	601
Milk, nonfat, fluid, with added vitamin A and vitamin D	1 cup	149
Spinach, raw	1 cup	140
Eggs, whole	1 large	70
Rice, white, long-grain, regular, cooked	1 cup	0

*Data from (Carotene, beta (ug) content, 2002)

Table 3: Diet Composition by Region (%)

	World (1988-90)	U.S.	China
Cereals	51.0	20-30	60-70
Oils, fats, sugars	19.1	30-40	--
Meat, fish, eggs, milk	13.5	20-30	10-20
Fruits and vegetables	8.2	--	--
Roots and tubers	5.3	--	--

*Data from (Loftas & Ross, 1995)

APPENDIX C: INTERVIEWS

Participants:

Supporters	***Critics***
Ingo Potrykus Adrian Dubock	Doreen Stabinsky (Greenpeace)

General Questions:

1. I have read some of your comments about Golden Rice in the past. How are you thinking about Golden Rice today?
2. How did you first hear about Golden Rice? What was your initial response to the idea? (*not for Potrykus or Beyer*)
3. Safety
    a. Do you think golden rice is safe for consumption, based on your knowledge?
    b. Would you taste the rice if it were offered to you?
4. How do your views about golden rice translate to your overall views on genetically modified foods?
    a. What are your feelings about genetic engineering, or genetically modified foods, in general? Do you see golden rice differently in any way?
5. Future
    a. Where do you see the golden rice project going in the future? Do you think the interest in the product will die out or do you think it will make it to the fields?
    b. How do you think golden rice functions as an indicator of acceptance for genetic engineering?
    c. What impact do you see Golden Rice having on food security in the future?

General Questions – Supporters:

1. How do you think golden rice addresses the problem of food security in the developing world?
2. Nutritionism
    a. How do you respond to those who suggest that we are narrow-minded in focusing on a single micronutrient as a means of improving health or eliminating health disparities?
3. Safety
    a. There are questions about the safety of golden rice, both for individual consumption and for the environment. Do you believe there are any reasons for concern with golden rice? If so, what are your concerns? What research should be done in terms of safety? Are these trials even feasible?
    b. What are your thoughts on the implications of golden rice on the environment and other organisms? Do you think the enhanced beta-

carotene content will have any effect on the environment? How do you think golden rice will affect other organisms?

4. Roadblocks
    a. What do you see as the main obstacles keeping golden rice from being distributed in the developing world, or making it to the fields? Do you feel that it is really worth the time and money required to bring the rice from the laboratory to the fields?

General Questions – Critics:

1. What is your primary concern with using golden rice as a public health intervention in the developing world?
2. How should we address the problems with food security in the developing world, in your opinion, if not with golden rice?
3. Would you say that your concern with golden rice is based more on ethics or logistics and efficacy?

Specific Questions:

Ingo Potrykus

1. Alternatives
    a. What led you to the idea of golden rice for treating vitamin A deficiency? Why not work towards a broader strategy to improve overall health and nutrition in the population?
2. Efficacy
    a. Do you think that the absence of other nutrients, such as protein and fat, in the diet will inhibit the uptake of beta-carotene from the rice or its conversion to vitamin A?
3. Roadblocks
    a. You have indicated that you expected golden rice to be available in the developing world two or three years after it was developed. What do you see as the main factors that have contributed to the delays in its distribution?
        i. What steps could be taken to bring golden rice to the fields?
        ii. Babili and Beyer (2005) suggest that the incentives for seeing a product put to use are weak for scientists (the reward comes with the publication of the article) and proposes that a public-private sector partnership is necessary to bridge the gap between the laboratory and the field – do you agree?
4. How did you envision the process of golden rice development and distribution when you first developed the idea for the rice? How has the journey differed in reality?
5. Do you feel that it is worth the time and money required to "deregulate" the rice and to distribute it in the developing world?