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Plant-based Oral Vaccine (POV)

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Bio-Engineered Plant-produced Antigens, Self-Administered for Oral Vaccination: A Cottage Industry for Vaccines for Less Affluent Nations?

Shoumen Bose Palit Austin Datta

MIT Auto-ID Labs, Department of Mechanical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, USA (shoumen@mit.edu)
MDPnP Lab, Cybersecurity Program and Center for Smart and Autonomous Medical Systems, Department of Anesthesiology, Massachusetts General Hospital, Mass General Brigham, Harvard Medical School, Research Building, 65 Landsdowne Street, Cambridge, Massachusetts 02139, USA (sdatta8@mgh.harvard.edu)

ABSTRACT

In this unconventional and non-systematic re-view, we re-present published results indicating that transgenic plants engineered to express (foreign) antigens show significant levels of mRNA (from viral coding region) and viral antigen (protein) in plant tissues (leaves). Oral administration of plant-produced antigens were immuno-stimulatory in humans, capable of conferring immunity from the viral infection (specific for the viral antigen bioengineered for expression in plant). Use of antigen-containing plant products for oral (or sublingual) administration does not require purification. The plant "paste" may be sufficient (?) for immunizing humans (and animals). Scientific evidence supports advocacy for oral administration of "raw" plant-based products (sublingual) without purification. Implementing this proposal may accelerate the pace of global vaccination and preventive healthcare for less affluent communities by [0] eliminating the need for purification,[1] eliminating the need for "cold" supply chain logistics, [2] eliminating the dependency on medical professionals for vaccination and [3] eliminating supply chain fulfillment dependencies by growing the antigen-producing "potted plants" in community gardens or at home, as a vaccine cottage industry. Communities may also brew the cottage industry for transgenic plants producing antigens as an entrepreneurial innovation endeavor and/or social business for vaccines. The latter, if built on pillars of ethical profitability, is expected to prioritize science as a service to society to improve access to global public goods with respect to health and healthcare.

The only thing necessary for the triumph of anti-science is for scientists to do nothing.

BACKGROUND

The quantum leap from nothing (12 January 2020) to a mRNA vaccine (11 December 2020) for SARS-CoV-2 during the CoVID-19 pandemic was a commercial "breakthrough" accomplished under one year. In reality it took ~50 years of academic engagement which finally exploded to substantiate the epitome of the age-old aphorism that *necessity is the mother of invention*.

From Edward Jenner (18th century) to Katalin Karikó (21st century) and others (e.g., John Enders, Jonas Salk and Albert Sabin in the 20th century) have made "vaccine" a part of the global vernacular even in households in remote corners of the world. Unfortunately, in recent years it has transmogrified into a socially divisive word, cherished by forward thinking people, the educated and wise, but derided by a few who may be uneducated, ignorant or irrational (*il n'y a pas plus sourd que celui qui ne veut pas entendre*).

INTRODUCTION

Unless prevented by immunization, global economic loss from future pandemics may exceed $250 trillion (~13x the GDP of EU or ~10x the GDP of USA or ~3x the global GDP[1]). The estimate is based on economic disaster data due to CoVID-19[2] and the list of microbes/viruses with pandemic potential[3]. Human mortality[4] due to CoVID-19 may be triple or quadruple the number of reported deaths (~15 million lives[5]). Governments invested ~$50 billion[6] for vaccines[7] against SARS-CoV-2 which produced ~13 billion doses, made available for the affluent[8] nations. For >80% of the global population, vaccines will be out of reach[9] due to corporate[10] need for profitability. To prevent healthcare mediated global economic meltdown due to microbes, vaccines or vaccine-alternates must be accessible to less affluent nations (**The Health of Nations**[11]), home to ~7 billion people (of ~8 billion global population).

PROPOSAL

We propose an alternative to classical vaccines (inactivated, live-attenuated, mRNA) for global healthcare, based on scientific results (see *The Health of Nations,* ref 11). The central thesis of this re-discovery begins with the confirmation[12] that Hepatitis B virus surface antigen (HBsAg) mRNA and protein were detected in (inedible) transgenic tobacco leaf. HBsAg from tobacco leaves elicited HBsAg-specific antibodies in mice[13] as proof of immunogenicity. **Human study**[14] with transgenic edible lettuce plant, expressing hepatitis B virus surface antigen, developed specific serum-IgG response to HBsAg. **Human study**[15] with potato-expressed E. coli labile toxin B subunit (LT-B) resulted in toxin neutralizing IgG antibodies (10/11) as late as day 59 (ingestion of ***raw*** potato expressing LT-B on day 0, 7, 21). **Human study**[16] with potato-expressed capsid protein of Norwalk virus (Norovirus; enteric pathogen) reported 95% of subjects (19/20) showing increases in antibody-secreting cells (IgA). Thus, plants engineered to express antigens, even when ingested (or sublingual administration of edible plants as a "leaf paste") are immunogenic in humans, which may be sufficient for immunization and protection from infection.

EVIDENCE

[A] EXPRESSION OF ANTIGENS IN TRANSGENIC PLANTS

Mason *et al* (1992) expressed hepatitis B surface antigen (HBsAg) by genetically transforming tobacco (*Nicotania tabacum; not an edible plant*) plants with the gene encoding hepatitis B surface antigen linked to a nominally constitutive promoter (Figure 1). The gene encoding HBsAg was integrated into the plant genomic DNA via *Agrobacterium tumefaciens*-mediated transformation.

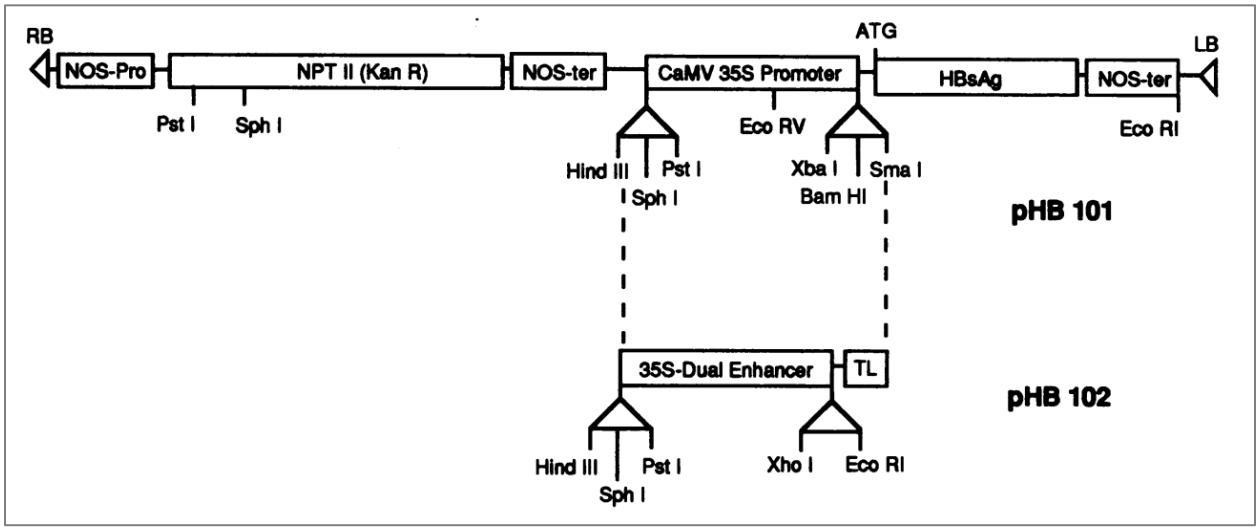


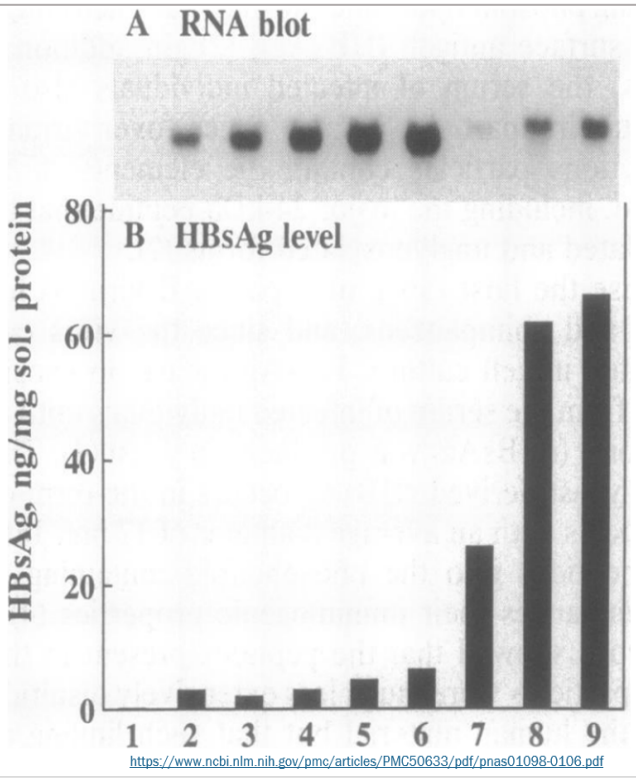
Figure 1: HBsAg coding region (gene) in plasmids pHB101 and pHB102. Left and right borders (LB, RB) demarcates the DNA sequences incorporated into *Nicotania tabacum* (tobacco plant) genomic DNA via *Agrobacterium tumefaciens*-mediated transformation. HBsAg coding region lies downstream of the CaMV 35S promoter in pHB101 (followed by the nopaline synthase (NOS) terminator). In pHB102, the 35S promoter is replaced by a modified CaMV 35S promoter with a duplicated transcriptional enhancer region, linked to the tobacco etch virus[17] (TEV) 5' non-translated leader (TL). From Mason *et al*, 1992.

Enzyme-linked immunoassays using a monoclonal antibody directed against human serum-derived HBsAg revealed presence of HBsAg in extracts of transformed tobacco leaves (correlated with presence of recombinant HBsAg mRNA in tobacco leaves). Therefore, expression of foreign antigens (e.g., Ebola virus surface antigen, EBOV; SARS-CoV-2 surface antigen, S [Spike] protein, bacterial toxins) in plants, may not suffer from any limitations of transcription or translation in plants.

Intramuscular injection with rHBsAg (recombinant HBsAg) produced in yeast[18] resulted in effective immunization[19] and protection from viral infection (agnostic of potential for any variation in post-translational modifications in yeast, *Saccharomyces cerevisiae*). Each subject received a 10-µg dose of HBsAg at 0, 1, and 6 months. By one month, 27% to 40% of the vaccinees had antibody to HBsAg, and by three months 80% to 100% were antibody positive (Skolnick *et al*, 1984).

Levels of rHBsAg (Figure 2) in transgenic tobacco leaves appear to be less than 0.01% (maximal levels are closer to 0.006%). Assuming rHBsAg concentration of 0.005% (50ng/mg protein), it will require ~200mg of soluble protein (extracted from tobacco leaves) to deliver a single 10-µg dose of rHBsAg. How many leaves of a plant are necessary to deliver an adequate dose is an open question with respect to sublingual administration in the form of raw leaf-paste (only from *edible* plants, ***not tobacco***).

FROM CHARLES ARNTZEN (MASON ET AL, 1992)



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC50633/pdf/pnas01098-0106.pdf

FIG. 2. HBsAg mRNA and protein levels in transgenic tobacco plants. (A) Total RNA from wild-type untransformed or independent transgenic tobacco lines carrying either the pHB101 or the pHB102 construct was hybridized with a probe specific for the HBsAg coding region. (B) Protein extracts from the same leaves were tested for HBsAg with the Auszyme monoclonal kit (Abbott), and HBsAg levels were quantified using a standard curve of human serum derived HBsAg. Numbers: 1, wild-type control plant; 2-6, independent transformants harboring the construct in pHB101; 7-9, independent transformants harboring pHB102 (dual enhancer).

[B] IMMUNOGENICITY IN HUMANS

The ability of the body to differentiate between the "edible" plant proteins (e.g., may not generate a detectable immune response to lettuce leaves, potatoes, watercress) and the foreign antigen in the transgenic plant product (e.g., *edible* lettuce leaves, potatoes or watercress expressing foreign antigen) lies at the heart of the anticipated specificity of antigen-induced immunogenicity in humans. Induction of immunity by foreign antigens (sufficient to protect from infection) in healthy individuals is the ultimate "litmus" test for recombinant antigens produced in edible plants. The choice of edible plant products (oral "edible" products or sublingual administration for rapid absorption in the blood stream) may influence the intensity and duration of the immune response. We re-present a few seminal but old experimental results demonstrating that ***unpurified*** edible plant-based oral vaccines can induce immunity in humans.

Kapusta *et al*, 1999, fed lettuce containing 0.1µg – 0.5µg of HBsAg (per 100g leaf) to volunteers (initial 200g of lettuce leaves; after 2 months, 150g). Blood samples were collected before (pre-immune) and 2 week and 4 week after first 200g lettuce and then 2 week, 4 week and 12 week after 150g of lettuce.

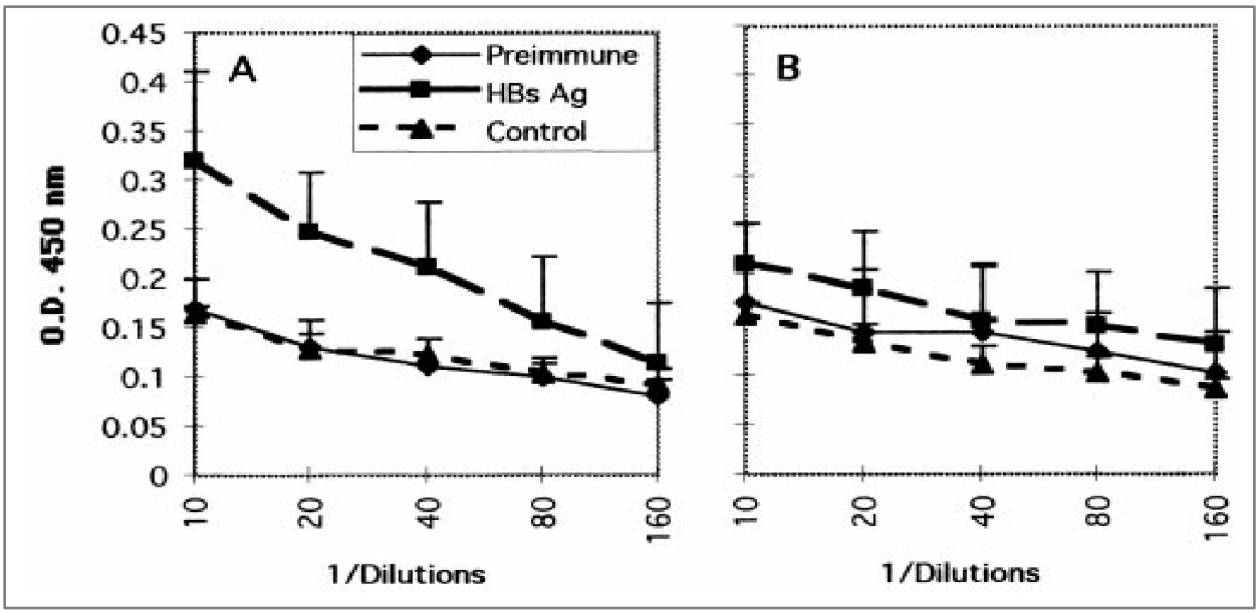
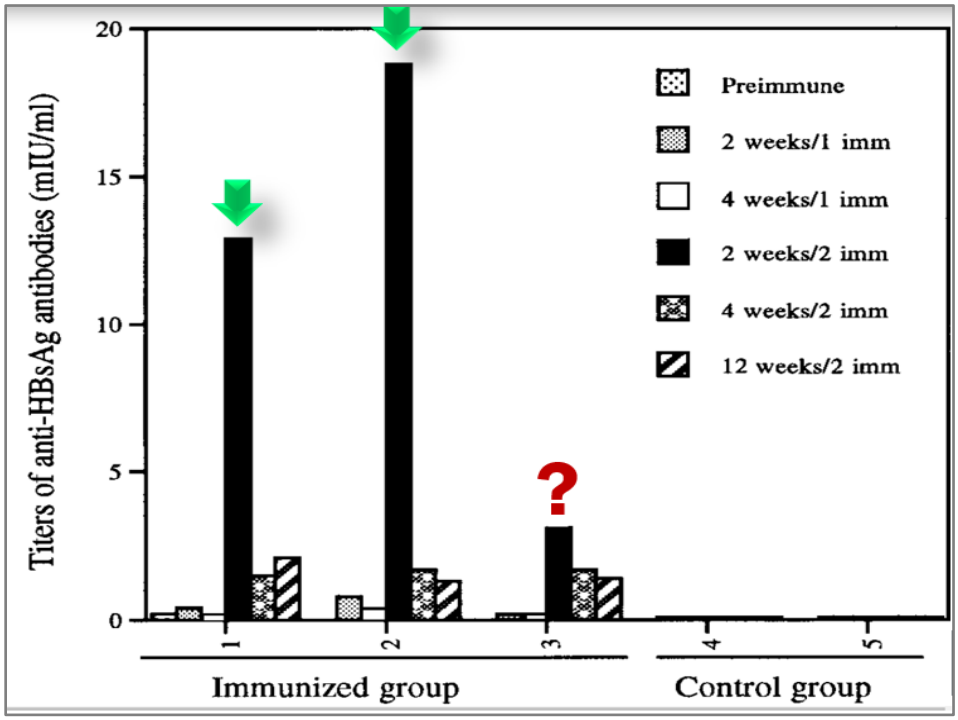


Figure 3: Titer of antibodies in three individuals [A] immunized orally with transgenic lettuce engineered to express HBsAg. [B] Control (two individuals fed with edible lettuce without HBsAg). Two of the three volunteers developed immunity potentially capable of preventing infection (bottom). Kapusta *et al*, 1999.



Tacket *et al*, 1998, fed volunteers with genetically modified raw (uncooked, ***unpurified***) potatoes expressing the enterotoxigenic *Escherichia coli* LT-B (B subunit of the *E. coli* enterotoxin is non-toxic and related to the B subunit of cholera toxin). Adult volunteers (n=14) ingested either 100 g of transgenic potato, 50 g of transgenic potato, or 50 g of wild-type potato. *E. coli* enterotoxin LT-B subunit protein in the potato was estimated to be 3.7-15.7 µg per gram. The amount of *E. coli* enterotoxin LT-B subunit protein ingested per 50g or 100 g dose ranged from 0.4mg to 1.1mg per dose (mean 0.75 mg/dose). Tacket et al, 2004, reaped similar success in delivering LT-B orally to humans via transgenic corn[20].

Table 1 Antibody secreting cell (ASC) responses among volunteers who ingested transgenic or wild-type potatoes on days 0, 7 and 21

	Geometric mean IgA anti-LT ASC per 10^6 PBMC*					Geometric mean IgG anti-LT ASC per 10^6 PBMC				
	Day 0	Day 7	Day 14	Day 21	Day 28	Day 0	Day 7	Day 14	Day 21	Day 28
Transgenic potato (*n*=11)	0.1	18.4	6.6	0.8	19.1	0	13.5	5.7	0.7	7.2
Wild-type potato (*n*=3)	0	0	0.7	0.3	2.4	0	0	1.8	0.4	0.6

* Peripheral blood mononuclear cells

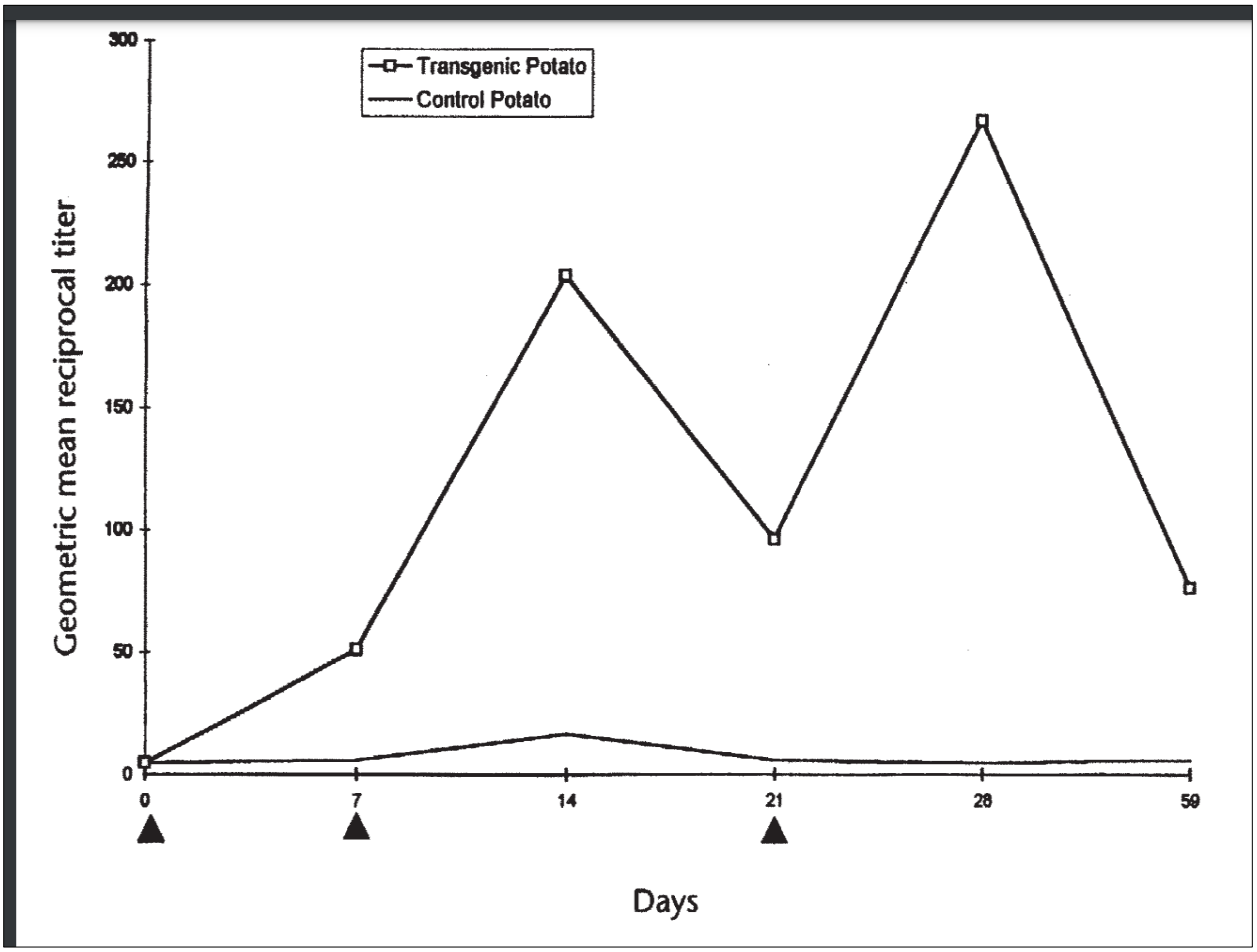


Figure 4: Geometric mean LT-B neutralizing antibody titers in volunteers who ingested transgenic potatoes (n = 11) or wild-type potatoes (n = 3). Potatoes were ingested on days 0, 7 and 21 (arrows). Tacket *et al*, 1998.

Tacket *et al*, 2000, explored immunization against Norovirus (causative agent for gastroenteritis, commonly referred to as stomach flu) using plant-based oral vaccine (POV). The first norovirus outbreak occurred in Norwalk, Ohio, USA, in a school in 1968. For this reason, the first strain of norovirus is also known as the Norwalk virus[21]. Tacket *et al*, 2000, used "Norwalk virus capsid protein (NVCP), assembled into virus-like particles (VLP), as a test antigen, to determine immune response in volunteers who had ingested transgenic potatoes (uncooked, ***unpurified***). Healthy adult volunteers (n = 24) received 2 or 3 doses of transgenic potato (n=20) or 3 doses of wild-type potato (n=4). Each dose consisted of 150g of uncooked, raw, peeled, diced potato (***unpurified***) that contained 215–751mg of NVCP. 19 (95%) of 20 volunteers who ingested transgenic potatoes developed significant increases in the numbers of specific IgA antibody–secreting cells (ASC). 4 (20%) of 20 volunteers developed specific serum IgG, and 6 (30%) of 20 volunteers developed specific stool IgA. Overall, 19 of 20 volunteers (95%) developed an immune response of some kind, although the level of serum antibody increases were modest."

The significance of edible potatoes for oral vaccination (POV) is simplicity of delivery, as a food lifestyle for immunization. Potatoes can be grown from potatoes, potatoes can grow anywhere, potatoes can be grown indoors, potatoes can be grown in tires, potatoes can be grown in cardboard boxes or any container and potatoes are suitable for hydroponic growth[22]. In addition to potatoes, ***edible*** leaves (thale cress, watercress, mustard greens) may be suitable for sublingual administration as "leaf paste" for rapid absorption in the bloodstream. Thus, these *edible* global vaccination solutions will benefit poor people.

Immunoassay	Transgenic potatoes			Wild-type potatoes, 3 doses (n = 4)
	3 doses (n = 10)	2 doses (n = 10)	Total (n = 20)	
IgA ASC anti-NVCP response rate	9/10 (90%)	10/10 (100%)	19/20 (95%)	0/4
Geometric mean peak ASCs per 10^6 PBMC[a]	32	26	28	—
Range IgA ASCs per 10^6 PBMC[a]	6–245	6–280	6–280	—
IgG ASC anti-NVCP response rate	2/10 (20%)	4/10 (40%)	6/20 (30%)	0/4
Geometric mean peak ASCs per 10^6 PBMC[a]	103	34	49	0
Range IgG ASCs per 10^6 PBMC[a]	92–115	25–62	25–115	0
Serum IgG anti-NVCP response rate	3/10 (30%)	1/10 (10%)	4/20 (20%)	0/4
IgG peak geometric mean titer[a]	1:468	1:3200	1:757	—
Mean peak fold rise[a]	13.3	8	12	—
Serum IgM anti-NVCP response rate	4/10 (40%)	0/10 (0%)	4/20 (20%)	0/4
IgM peak geometric mean titer[a]	1:100	—	1:100	—
Mean peak fold rise[a]	7	—	7	—
Stool IgA response rate	4/10 (40%)	2/10 (20%)	6/20 (30%)	0/4
Stool IgA peak geometric mean titer[a]	1:48	1:38	1:45	—
Mean peak fold rise[a]	17.8	16.6	17.4	—

NOTE. ASC, antibody-secreting cell; PBMC, peripheral blood mononuclear cells.
[a] Among responders.

Table 2: Immune response to Norovirus – ***unpurified*** potatoes expressing Norwalk virus capsid protein (NVCP) vs control (wild-type potatoes). Tacket *et al*, 2000. Can we increase the level of serum antibody?

DISCUSSION

Bio-engineered ***edible*** transgenic (genetically modified) plants expressing recombinant vaccine immunogens for oral vaccination offer an attractive and potentially inexpensive alternative to classical vaccine approaches, an idea proposed, proven and even patented[23] ~40 years ago. Other alternative[24] potential[25] vaccination[26] strategies exist in various[27] stages[28] but none focused on the less affluent.

Bio-engineered transgenic plant-produced antigens, self-administered for oral and/or sublingual vaccination (POV) eliminates industrial production, purification, packaging, storage, distribution and the "last mile" physical (injection) bottleneck due to the need for trained personnel. Potted plants or produce can be grown locally, anywhere. Sublingual[29] consumption of leaf paste or raw produce may be less palatable but does not require special training. Eliminating upstream purification and downstream "cold" supply chain of vaccines as well as the "last mile" fulfillment problem will facilitate availability of POV for preventive healthcare (plant produced oral vaccines). Developing immunity in communities near and far is key to prevention of transmission/infection to reduce morbidity and mortality.

This is a clarion call for scientific leadership as well as others in finance, politics, policy and diplomacy to focus on the ***output*** from a rational scientific measure aimed specifically for the neglected less affluent ~7 billion people. Paralysis due to analysis and "purified to perfection" are hackneyed platitudes ready for retirement in the face of 22nd century challenges in global health and healthcare.

Translating the patent-free (or expired) published research to pragmatic working reality requires a few scientists who believe in science as a service to society, a few students skilled in molecular biology and plant genetics, a few human volunteers and a few host laboratories in a few corners of the world.

Operating funds may be sourced as a consortium with contributions from donors/foundations or ethical use of crowd funding. The entity can also be a business if investors agree to the convergence of for-profit and not-for-profit endeavors *under one roof*. Products and services for affluent nations may be a for-profit operation (signatories[30] at The Convention on the OECD, on 14 December 1960) while the not-for-profit operation will apply to the rest of the world where ~7 billion people are trying to survive/live.

The scientific credibility of this proposal assure ***outcomes*** which will be catalytic to rapidly build capacity (potted plants) for global vaccinations, focused on saving ~7 billion lives. However, sourcing the recombinant antigen vectors (plasmids) and creating the transgenic plants will need help from scientists (geneticists) and other global experts, from affluent as well as less affluent nations. There is a great need for education, scientific training and standardization of protocols in order to scale the production of transgenic plants and address public resistance to ***edible*** transgenic plants.

Logistics, however nominal, may become an inhibitor. An efficient distribution system with *distributed control* at local nodes is key to differentiating and adapting to the needs of the community. It is not enough to use supply chains as usual or depend on US/EU type of operations management practices.

STEPS: GLOBAL HEALTH SOLUTION IN 7 STEPS FOR ~7 BILLION PEOPLE?

The vision of POV is half century old. Several vaccine[31] efforts are in progress[32]. But, we are still waiting to build the ramp to transform POV into reality to lift ~7 billion lives. It may not happen by committee. We need commitment from a few committed individuals who will provide the leadership.

1. Money from grant or philanthropic contribution to lead without IP

2. Recombinant vector lab (molecular biology) and a plant bio lab

3. Few enthusiastic molecular biology students and plant bio students

4. Create EBOV vector, transfect, harvest leaves, make "leaf paste"

5. Administer RAW LEAF "paste" to sublingual volunteer (S. Datta)

6. Check volunteer's blood for EBOV antigen and EBOV antibodies

THE CHALLENGE

7. Challenge the volunteer (S. Datta) with live Ebola virus to verify that EBOV antigen from plant is capable of providing immunity from the Ebola virus (i.e., to remain uninfected).

TRANSLATIONAL SCIENCE

Translating these 7 steps into a production phase (when/where end users can obtain plants and know-how, i.e., how much to self-administer at what frequency) calls for establishing baselines, ranges and a skeleton of standard operating procedures. Errors due to estimating the immunogenicity of the plant-derived antigen (PDA) and improper tests to establish the level of circulating immunoglobulins (mainly IgG but IgA, too, for mucosal membranes[33]) in response to the recombinant antigen introduced orally (PDA) could be harmful. IgG antibody (to antigen) serves as an accessible quantitative biomarker of post-vaccination protection because T-cell responses (umbrella response of CDn+ cells) are important but difficult to quantify. IgG titer and its duration is salient to "sterilizing" immunity which is the desired post-vaccination outcome for complete clinical protection from contracting infection (dose dependent). Viruses/bacteria invading the mucosal surfaces complicates the "sterilizing" immunity scenario because the number of invading infectious particles (e.g., virions) will influence (may overwhelm) the outcome.

Establishing threshold values for IgG antibody response to antigen (PDA) is confounded by the immune status of (test) individuals, pattern of cytokine response to antigen, pre-existing conditions, sex, age, race, ethnicity (population genetics) and per capita income level (proxy for nutritional status). In addition, the quest for a protective titer[34] may/will be influenced by [i] type of expression vector used in creating the transgenic plant (source of PDA) [ii] expression level of protein (antigen in ng/mg of soluble protein) in plants (leaves) [iii] ingested vs absorbed amount of PDA [iv] individual (gut) microbiomes[35] in the interplay between immune health and nutrition[36] [v] testing/monitoring constraints [vi] others.

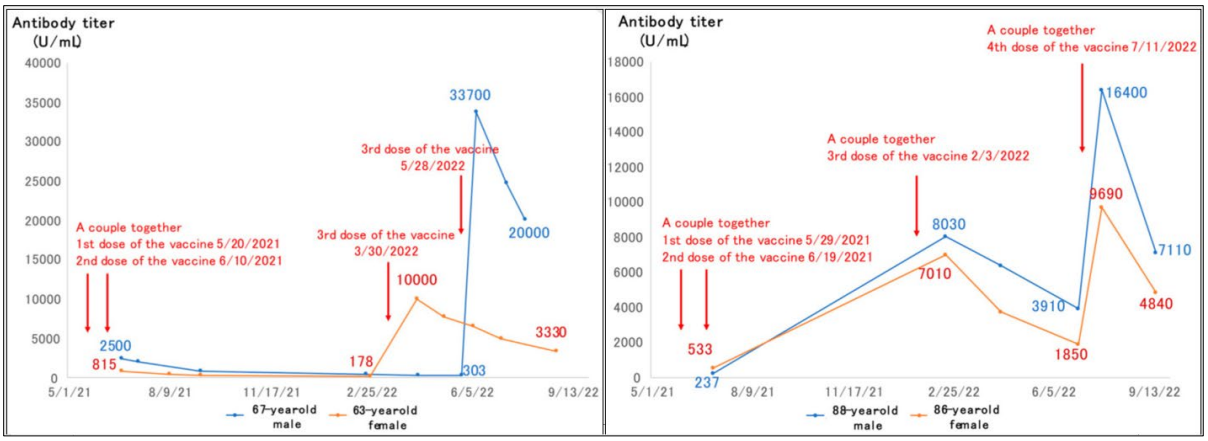


Figure 5: Couples selected from a homogeneous background (race, ethnicity, economic status) respond differently to SARS-CoV-2 mRNA vaccine[37]. What is the protective titer for "sterilizing" immunity?

Identification of thresholds for the IgG antibody levels for sterilizing immunity (collect titer data for different infections, globally) is the translational science data for POV to inform the transition from the lab to locals. Establishing a "green zone" threshold of circulating IgG levels in response to PDA is the "target" that individuals want to know to assess (from self-testing) acquisition of immune protection. To arrive at this "target" the users must ingest a minimum weight of plant product to absorb PDA in their body (blood) within a specific period. Declaring the "green zone" threshold target for IgG antibody levels must take into account risk mitigation strategies. The latter must make room for high fault tolerance due to mis-steps, mis-information, and mis-calculations, inevitable from the self-administration of PDA.

The bridge of translational science knowledge from the lab to locals (LTL) holds the potential to save ~7 billion lives. But, the path to global vaccination will be non-linear even if the science of POV may be summarized in 6 (*not 7*) relatively simple sequential steps. There is a non-zero probability "new" lies will be manufactured to transform saving lives into a dying art. Scientists must be cognizant of their own hubris and desist from their desire to pursue perfection in determining the titer for "sterilizing" immunity. The latter is our penchant to understand immunological dynamics. ***If*** we are challenging uninfected humans with a live dose of a potentially fatal virus (Ebola, Lyssa, Marburg) then we should know the IgG levels for "sterilizing" immunity and adhere to safety measures advocated by the US FDA.

Steps 1-6 must proceed without any delay due to translational science related efforts. We must implement POV. The risk from exposure to deadly viruses far outweigh the risks due to ingestion of potatoes or watercress or mustard greens as a source of PDA even without any standard protocol or dietary guide to induction of immunity (IgG titers in blood). While we work in labs, the locals must not be kept waiting for this proven solution (steps 1-6) in hand. ***Even low levels of IgG may reduce fatalities*** and dampen the severity/acuity of infection. Should the luxury of pursuing translational science prevent us from the urgent implementation of POV and deliver potential death sentences for billions of people?

CONCERNS

Legitimate concerns about possible negative effects of plant-based antigens (PDA) include people who may unknowingly eat such plants and will be exposed (without their consent) to material that will trigger an immune response. The latter may result in negative effects such as induction of autoimmunity or chronic inflammation. Reasonable caution by labelling plant products producing any foreign antigen, prevention of uncontrolled spread and assessment of potential side effects are prudent safety measures.

Few may not share the enthusiasm for administering Ebola virus to a volunteer (S. Datta, author) in step 7 and US safety regulations/criteria should apply. Should we test, first, in animals? To mitigate unknown health risks due to POV, edible plant-based antigen (ePDA) administration in humans may test a virus that is widespread, already, so that the relative effectiveness of the vaccine can be assessed with minimal harm (e.g., for CoVID vaccines). Testing in humans demand prior knowledge of "sterilizing" immunity. Establishing serum IgG levels for sterilizing immunity proportional to "dose" depends on determining the number of infectious particles (e.g. virions) but estimating the number of particles (10^n) at the *initial point of infection* could be quite error prone (where n = {0, …,10}, if n=0, then it is 1 particle; n=1 indicates 10 particles; n=10 indicates10 billion particles at the initial point of infection[38]). Thus, any claim for individual "sterilizing" immunity data may be overwhelmed if the number of infectious virions outweigh the individual's immune preparedness to accept a certain challenge dose of infectious particles.

COMMENTARY

For decades, the destructive demonization of transgenic plants and ill-informed fanatical resistance to genetically-modified[39] crops has robbed the poor of global public goods, food, nutrition[40] and healthcare. The cruel march of unreason[41] is a debilitating blow to our sense of the future by forcibly destroying[42] the fruits of science which could be of service to society, especially for communities under severe economic constraints. We view malicious, mis-information fueled social cataclysms as a point of inflection. We are optimistic that the tide is beginning to turn[43] from bad[44] to good[45] in the court of public opinion, both in Africa[46] and Asia[47], the geographies with the greatest need for bio-engineered edible plant-produced antigens, self-administered for oral immunization (POV). The ability to prevent infection through low-cost self-vaccination and **edible** plant-based oral vaccines for immunization can reduce the horrendous scale of mortality and morbidity due to future infectious diseases and/or chronic diseases. Ethical globalization demands that affluent nations enable the less affluent nations to develop and implement this cottage industry of edible potted-plant based vaccines, in the economic interest related to immigration, travel, commerce, and growing markets. Our collective inaction and neglect of scientific proof to alternate sourcing of **edible unpurified** antigens from transgenic plants for global immunization is inhuman, unethical and immoral. Turning a blind eye (*il n'est pire aveugle que celui qui ne veut pas voir*) to preventive healthcare measures for the global poor (~ 7 billion) is a form of anti-science and should not remain in the category of irremediable injustices[48]. US CoVID-19 misinformation campaign by anti-science anti-vaxxers resulted in 232,000 preventable deaths[49] (05/2021-09/2022).

TEMPORARY CONCLUSION

Based on published papers, it is a fact that foreign antigens can be produced in transgenic plants. Table 3 (below) indicates that that outcome is largely ignored by the nations[50] preparing for pandemic regulatory capacity. Oral (sublingual) administration of plant-produced ***unpurified*** antigens are capable of inducing immunogenicity in humans. Step 7 may prove that the immune response to plant-produced antigens are adequate to induce sterilizing immunity (i.e., protects from and prevents infection). The use of edible *Arabidopsis thaliana* (thale cress) and/or *Brassica rapa* ("fast" plants) may be palatable as transgenic plants of choice. Exploring the use of watercress (*Nasturtium officinale*) may offer an even more "tasty" option. Further explorations using potyviruses as vectors to deliver the recombinant antigen may lead to use of flowers (rose, tulips) to serve as vehicles for oral administration of foreign antigens (edible flowers are used in Eastern foods and tulips[51] represent the world's first financial bubble).

US and EU may balk at Step 7 but most nations in Asia and Africa will embrace the opportunity for mass adoption of low cost vaccination solutions to mitigate risks due to public health catastrophes. POV represents a lifestyle practice similar to use of neem tree twigs for cleaning teeth (*Azadirachta*[52] *indica*). Instead of the elusive quest for alms, developing nations with ~7 billion people may prefer ***bold approaches*** rather than waiting for 'blessings' from FDA, CDC, ECDC for POV solutions for healthcare.

Pandemic Regulatory Capacity.*

Country	Regulatory Authority	Maturity Level	Scope of Products
China	National Medical Products Administration (NMPA)	3	Vaccines (producing)
Egypt	Egyptian Drug Authority (EDA)	3	Vaccines (producing)
Ghana	Food and Drugs Authority (FDA)	3	Medicines; vaccines (nonproducing)
India	Central Drugs Standard Control Organization (CDSCO)	3	Vaccines (producing)
Indonesia	National Agency of Drug and Food Control (BADAN POM)	3	Vaccines (producing)
Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)	3	Medicines; vaccines (nonproducing)
Saudi Arabia	Saudi Food and Drug Authority (SFDA)	4	Medicines; vaccines (producing)
Serbia	Medicines and Medical Devices Agency of Serbia (ALIMS)	3	Vaccines (producing)
Singapore	Health Sciences Authority (HSA)	4	Medicines; vaccines (nonproducing)
South Africa	South African Health Products Regulatory Authority (SAHPRA)	3	Vaccines (producing)
South Korea	Ministry of Food and Drug Safety (MFDS)	4	Medicines; vaccines (producing)
Tanzania	Tanzania Medicines and Medical Devices Authority (TMDA)	3	Medicines; vaccines (nonproducing)
Thailand	Food and Drug Administration (FDA)	3	Vaccines (producing)
Turkey	Turkish Medicines and Medical Devices Agency (TITCK)	3	Medicines; vaccines (producing)
Vietnam	Vaccine regulatory system involving the Drug Administration of Vietnam (DAV); the Administration of Science, Technology, and Training (ASTT); the National Institute for the Control of Vaccines and Biologicals (NICVB); and the General Department of Preventive Medicine (GDPM)	3	Vaccines (producing)

Table 3: Nations preparing for pandemic readiness are ignoring or ignorant about transgenic POV. Cartoon: Genetically Modified, Bio-Engineered and Transgenic are terms representing the *elephant in the room*[53] preventing global adoption of useful plants/crops. Phobia, resistance and irrationality among rational humans are holding ~7 billion people hostage by depriving them of access to health/healthcare.

The global need for vaccines is the fuel to pursue plant-based oral vaccines (POV). But one must add and admit that there will be errors and missteps in the process, even if the benefits vastly outweigh the problems. Almost nothing in science is always absolutely perfect, even the best solutions may present unexplained problems which may temporarily plunge the effort in a quandary, agnostic of how precisely it was planned, executed and/or implemented. POV may not be a panacea for all ills, it is expected to experience growing pains and it will expose gaps in our multi-disciplinary knowledge or even overwhelm us with unknown unknowns. Are these sufficient reasons to asphyxiate the pursuit of scientific solutions?

Despite the anticipated and unanticipated shortcomings of POV, let us use the Pareto principle and proceed to hypothesize that POV may be effective in preventing healthcare disasters 80% of the time for 80% of the ~7 billion people in less affluent nations. Is saving 80% of the world not worth the effort?

If the positivism of the 80% optimism is too sugary for Pareto pessimists, let us consider *what if* POV may be effective in preventing healthcare disasters for only 20% of the ~7 billion poor people. The pessimists of POV should reflect whether we can discard or bypass or scoff at the ability of POV to help 1.4 billion people (i.e., current population of India [~1.4 billion] or China [~1.4 billion]). In other words, are the *nay-sayers* of POV prefer to ignore scientific rationale and choose to be oblivious of the preventive health of ~1.4 billion poor people? Do POV pessimists "believe" that they are "protecting" poor people by their opposition? In reality, inaction about POV makes *living a dying art*.

The **20th** century scientific research results, ***re***-presented in this discussion, may become catalytic to save the world from public health cataclysms in the **22nd** century. How common is resistance to reason?

In the 18th century, for sailors, disease during long sea voyages was often more dangerous than enemy action. One British expedition to raid Spanish holdings in the Pacific Ocean in the 1740's lost 1,300 of an original complement of 2,000 men to illness. That illness was scurvy. In 1747, on board HMS Salisbury, James Lind (1716-1794) carried out the first controlled clinical trial in medical science[54]. He took 12 men suffering from similar symptoms of scurvy, divided them into six pairs and treated them with remedies suggested by previous observers/writers (in 1622, explorer Richard Hawkins[55] recorded that "sower lemons and oranges" were "most fruitful"). In 1747, the results from James Lind's "clinical trial" demonstrated that oranges and lemons were indeed a cure for scurvy. "Treatise of the Scurvy" appeared[56] in 1753, but it was not until 1795 (42 years later) that the British Admiralty issued an order for distribution of lemon juice to sailors. Apparently, James Lind did not possess sufficient *clout*.

In the 19th century, John Snow (1813-1858), an anesthesiologist in London, conducted an epidemiological study of water supply from the Broad Street Pump in 1854. Results indicated that cholera was a water-borne disease. But, the "germ" theory was ignored by the *Miasma* theorists. It was not until the epidemic of cholera in Egypt in 1883 that Snow's findings were *re-discovered*. The germ theory gained acceptance based on Snow's observation[57] that cholera was a water-borne disease. The means to prevent cholera had been identified by Snow ~30 years before the cholera epidemic. It wasn't used as a preventive solution to save lives due to prevalent scientific ignorance which failed to grasp Snow's scientific thinking and scientific insight, at least three decades ahead of the cholera epidemic, which was preventable.

In the 19th century, Ignaz Semmelweis (1818-1865) made a discovery by comparing a highly qualified clinic (death rate ~10%) with a clinic operated by midwifes (~2.5% death rate). Semmelweis observed[58] that simply by washing hands, the death rates dropped (to ~2.5%). The news spread. Doctors thought it was too mystic, despite the results. Semmelweis, in his next job, did the same thing. Dropped the death rate just by washing hands and equipment. Semmelweis pioneered the habit of washing hands in hospitals, published[59] papers about it but was rejected, had a mental breakdown and was sent to an asylum where he was beaten to death by the guards, in 1865. Merely two decades later, Louis Pasteur[60] proved Ignaz Semmelweis was correct. In the 21st century, the medical profession may perish if sepsis[61] was uncontrolled and medicine may struggle to exist without hand hygiene[62].

POV will remain a bright light obscured behind a bushel unless the less affluent nations are bold (***audentes fortuna iuvat*** [63]) enough to focus on science as a service to society and people in need, first, of course with caution, but not excessive caution resulting in paralysis due to analyses. The interpretation of the "bold" *(fortune favors the bold)* approach advocated for POV means acknowledging that perfect is the enemy of good, rapid acceptance of promising results to save lives must take precedence over need for more data/results from the next experiment (*in praise of imperfection*) and prioritizing common sense of science that serves the people in that community. The "bold" approach does not exclude being careful to do no harm ***(primum non nocere)***. The "bold" approach is less enthusiastic about the trend of repetitive studies fueled by bureaucratic see-saw[64] or to re-consider, re-evaluate and re-validate (with even more platitudes) the initial results to re-confirm what we already know or wait for adverse effects to surface, sometime, somewhere, to placate politicians. Less affluent nations must not blindly mimic but adapt the protocols, procedures and processes in US/EU but find leaders who may possess the humility, knowledge and wisdom to inspire trust and responsibly shoulder the challenge of renewing that golden braid[65] of choice, chance, and character with civilization (even in face of constraints and consternation).

The *"hidden"* 20th century science, re-presented in this discussion as POV (plant-based oral vaccines), may become catalytic to save the world from public health cataclysms in the 22nd century. If one must profit from "cottage industry of vaccines" then we suggest 1% net profit limit. For example, a charge of $10 or $100 / year / person (for all vaccines) for 80% and 20%, respectively, of the 7 billion market, generates $196 billion per annum (pa) revenue from less affluent (poor) nations. Charging the affluent 1 billion people $1,000 or $10,000 / year / person, for 80% and 20%, respectively, translates to $2.8 trillion pa. 1% net profit from $3 trillion from a market of 8 billion is $30 billion pa. Even if this **naïve** optimistic *what if* scenario is **1% true**, the *net business profit* from POV could be about $0.3 billion or $300 million pa (***"enough for human need but not enough for human greed"*** – M. K. Gandhi[66]).

> *"It sometimes feels as if I had shouted a deeply cherished message out into an empty chasm and nobody heard me."*
> Douglas R Hofstadter, Gödel, Escher, Bach: An Eternal Golden Braid
> Download - https://www.physixfan.com/wp-content/files/GEBen.pdf

In the short-term, creating and implementing the distribution of fast growing transgenic plants for rapid immunization from known culprits with pandemic potential (Ebola, Marburg, Lassa, etc.) is a wise path, as discussed thus far, in this call for action. The key elements in this approach is removal of the purification protocols and the cold supply chain logistics. These two elements are rooted in the industrial complex of affluent nations and are holding the less affluent world hostage.

In the long term, plant-based oral vaccines may explore tools from the food industry to convert the plant material (e.g., leaves from the transgenic plants producing the antigen in their leaves for oral immunization) into a dry packed form factor in dose-adjusted supplements (e.g., turmeric[67]) or sachets (e.g., dehydrated[68] seaweed or vegetables included with Ramen[69] and Miso[70] as shown in Figure 6) with a long shelf life at room temperature to facilitate rapid distribution, in case of a public health emergency.

Figure 6: Can processing (e.g., dehydration, storage, etc.) affect the efficacy/immunogenicity of antigens? POV as sachets can be sold in retail stores, petrol pumps, vending kiosks, to optimize global access.

Molecular immunologists must address whether food technology processed (post-FTP) antigen conserves sufficient number of epitopes to remain viable as an antigen (efficacy of immunogenicity). Food technologists must explore post-processing *dosage issues* which could differ between the untreated transgenic leaves and post-FTP leaves in sachets, after periods of storage (low efficacy due to degradation during storage). We must investigate if expressing the whole antigen (e.g., EBOV-1, SARS-CoV-2 Spike) is necessary or do we create GMO/transgenic plants expressing a number of epitopes[71] for each antigen? Natural changes in epitopes due to genetics of virulence[72] and antigenic drift[73] may make universal[74] epitopes useful. A "first" dose of "universal" epitope may induce immunization to decrease the acuity of infection from specific variants if new epitopes are not covered by the universal dose. Research on epitope integrity, structure, function and post-FTP immunogenicity will transform GMO/ transgenic plant-based oral vaccines as effective, efficient, safe, and accessible preventive public health solution. Food industries may reap ~$30 billion in annual net profit as a POV supplier if focused on PAPPU[75], i.e., earning 1 penny / day / person (1 US penny as **net** profit / day / person) from ~8 billion global users.

EPILOGUE – ANALYSES OF SCIENTIFIC FACTS IN SCIENTIFIC RESEARCH PUBLICATIONS

The anti-GM (genetically modified / transgenic / bioengineered) movement and its anti-science propaganda ignores pre-existing scientific knowledge and is responsible (albeit, partly) for the trials and tribulations of ~7 billion people who are deprived of global public goods but shares an increasing burden of healthcare due to their inability to access affordable preventive public health measures (vaccination).

What if we knew that a plant or crop may resemble canonical cancer or a cancerous form (if the same criteria were applied to humans and animals)? Should we eat "cancerous" plants or plant products?

The truth, hidden (deliberately?) in plain sight, is that ***we eat***, ***we crave*** and we will be in trouble without that specific plant. Acknowledging the science (genetics) of our daily bread[76] made from wheat (*Triticum-Aegilops* group) reveals that chromosomal multiplication (polyploidy) in wheat is a fact known to science[77] for ~100 years. Chromosomal aberrations (ploidy[78]) are a natural phenomenon in *many* edible plants. Genomic[79] changes and ploidy are associated with cancer[80] in humans (pathological somatic aneuploidy[81]) or indicates risk[82] of cancer[83] (neosis[84] leading to PGCC[85] or polyploid giant cancer cells). Hence, it appears that human cancer related chromosomal aberrations also occur in wheat. The obstreperous raconteurs (anti-GM / anti-science cults) are unconcerned about the state resembling "cancer" of the wheat in our daily bread-basket. *Is it willful ignorance or just garden variety hypocrisy?*

Therefore, the science of genetic modifications behind the evolution of wheat "cancer" is of no consequence (required edible food) for the anti-GM and anti-science aficionados. But, the same "anti" socialists are up in arms to burn, kill, and prevent access to healthcare, if transgenic plants (e.g. golden rice) may serve as vaccines for the ~7 billion poor people, who are forgotten and often down-trodden.

Evolutionary[86] dynamics[87] uses many tools to address "fit" with chaotic[88] non-binary outcomes due to punctuated equilibria[89]. Ploidy-based "cancer" of the wheat is a *positivism* quintessential for our civilization. Exploring[90] ploidy in humans reveal ploidy as a diagnostic[91] tool for cancer prognosis but it also offers certain protective[92] functions and may help in stress response for plants[93] and humans[94].

The ill-informed pseudo-science driving the anti-GMO collusion is laden with misgivings and replete with incomplete information arbitrage designed to selectively suppress scientific facts. Transgenic plants created by humans use tools which *mimic* natural genetic processes to insert/delete/amplify genetic material (e.g., discovery of transposons[95] by Barbara[96] McClintock[97] in the 1920's and restriction endonucleases by Werner Arber, Daisy Dussoix[98] and Ham Smith[99] in the 1960's as well as *"cut and paste"* application of restriction endonucleases by Kathleen Danna[100] and Dan Nathans[101]). Plants, naturally, *amplify/alter/exchange* genetic material with *foreign (non-plant) genes* (see **APPENDIX 1**). It will be an irremediable and egregious error of leadership if we fail to overcome the obstructionists. Science must serve societies and communities chronically underserved and under severe economic constraints. One tiny contribution in this context is this science-based solution for preventive global health, but only if we can *implement* the proven value of plant-based oral vaccination (POV) to improve the health of nations.

The potential of plant-based antibodies was unleashed 30 years ago[102] but its promise[103] for global health was muted[104] by diabolical[105] groups[106] and inhuman individuals[107] who would not even help to prevent blindness[108] in children (due to lack or reduced dietary intake of Vitamin A). Scientists[109] genetically supplemented *Oryza sativa* (rice) with phytoene synthase, an enzyme from daffodils (*Narcissus pseudonarcissus*), which leads to the accumulation of phytoene, a precursor in the pathway of Vitamin A biosynthesis. Consumption of *golden rice*[110] provided phytoene, the precursor for Vitamin A, as a measure[111] to reduce preventable morbidities due to xerophthalmia. But, asphyxiation of science[112] reduced adoption[113] and implementation[114] (but increased fake rice products instead of Golden rice[115]). It remains to be seen whether plant-based oral vaccines can chart a better path to global implementation.

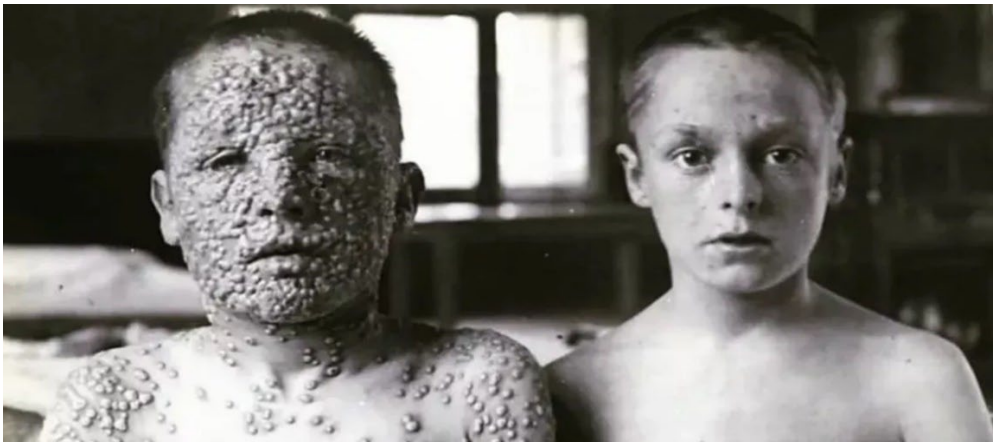


Figure 7: Moving the boy[116] on the L to the state of boy on the R takes a massive amount of ***preparation***.

AMAT VICTORIA CURAM - Is this the message?

Could you and your scientific network help to convert the suggestion in this article (in principle, proven. published) into practice? Can you be a leader-catalyst-scientist to create and help implement plant-based oral/sublingual vaccination? Seven steps (outlined here) could help 7 billion people. Do you think you can be the "hand" and the "brains" that can transform this idea into reality? Scientists can help to source recombinant antigens (plasmids) to transfect and produce the transgenic plants.

Do you have what it takes to drive this science for social good? It requires convergence. It will be difficult to accomplish. It can save ~7 billion people. Can you become an instrument of global goodwill to usher hope for billions who are hopeless about their ability to access preventive public health and global public goods in terms of healthcare? You and your effort can empower ~7 billion people, forgotten and downtrodden, to find a reason to believe, that they, too, can be a constructive economic contributor to the wealth and health of nations. You and your effort can give voice to ~7 billion voiceless people. You and your effort, should you decide to pursue the opportunity, requires you to possess that moral, ethical and visceral fiber which represents an eternal braid of chance, choice and character.

ACKNOWLEDGEMENTS

Idealism is rarely rewarded in a capitalist society, especially when a country can be bought. It is easy to see why the amanuenses to whoever is in power among the ultra-wealthy may think this article to call attention to the situation facing global health is *quixotic*. "I have a dream" was an idea and idealism that was crushed like a red rose on white snow. If we don't have a dream then how can dreams come true?

Hence, this re-presentation of scientific facts inspired by many, including the herculean Hypatia of Alexandria[117], Brahmagupta[118], Tycho Brahe[119] and Gregor Mendel[120] followed by the 20th century icons Marie Curie[121], Rosalind Franklin[122], Dorothy Hodgkin[123], Barbara McClintock[124] and the living legends Lydia Villa-Komaroff [125] and Mary-Claire King[272], to name a few of the *founding mothers* of modern science and molecular biology. Research in the West (UK, US, EU) saved billions of lives, worldwide (vaccines), and will improve more lives in future (e.g., GLP-1[126]). POV is an outcome of basic science. POV can help ~7 billion poor[127] people but needs scientific contribution from the West. Without the magnanimity of (starving) scientists in wealthy nations we may not be able to help the less affluent nations in their plight to implement POV. One would think that a nation with ~300 million people which spends ~$5 trillion[128] for healthcare will be benevolent enough to help ~7 billion poor people to live!

The message here (>50 years old) may begin[129] with Ingo Potrykus[130] and the "golden rice" which continues to save countless children from xeropthalmia (blindness). The benefits are vastly outweighed by the irrational resistance to transgenic/GMO crops. (See **APPENDIX 1**, a discussion of facts about the science behind the safety of transgenic/GMO plants for human use and consumption as food items).

Suggestions here are due to a few labs, including Roy Curtiss, Charles Arntzen and Carol Tacket. The opinions and commentaries (but *not* the research) are due to the author and does not reflect the views of reviewers or affiliated institutions. The scientific evidence re-presented in this article was reviewed by erudite scholars (list below). The published scientific results indicated a grand potential for plant-based antigens in the POV approach. The proposal here is to transform POV into practice for mass oral vaccination, and as a cottage industry for less affluent nations.

Kathleen Hefferon, Cornell University	https://cals.cornell.edu/kathleen-hefferon
Micah Samuels, Former US Navy	https://www.linkedin.com/in/micah-samuels-0ab439/
Andrew Fire, Stanford University	https://med.stanford.edu/profiles/andrew-fire
John Carr, Cambridge University	https://www.plantsci.cam.ac.uk/directory/john-carr
Anahita Dua, MGH, Harvard	https://www.massgeneral.org/doctors/20714/anahita-dua
Elliot Meyerowitz, Cal Tech	https://www.bbe.caltech.edu/people/elliot-meyerowitz
Katalin Karikó, UPenn	https://www.pennmedicine.org/providers/profile/katalin-kariko
Robert S. Langer, MIT	https://langerlab.mit.edu/langer-bio/
Sanjay Sarma, MIT	https://meche.mit.edu/people/faculty/sesarma%40mit.edu
Roy Curtiss, UF	https://www.vetmed.ufl.edu/profile/curtiss-roy/

Updated version of the article is available from MIT Library https://dspace.mit.edu/handle/1721.1/145774

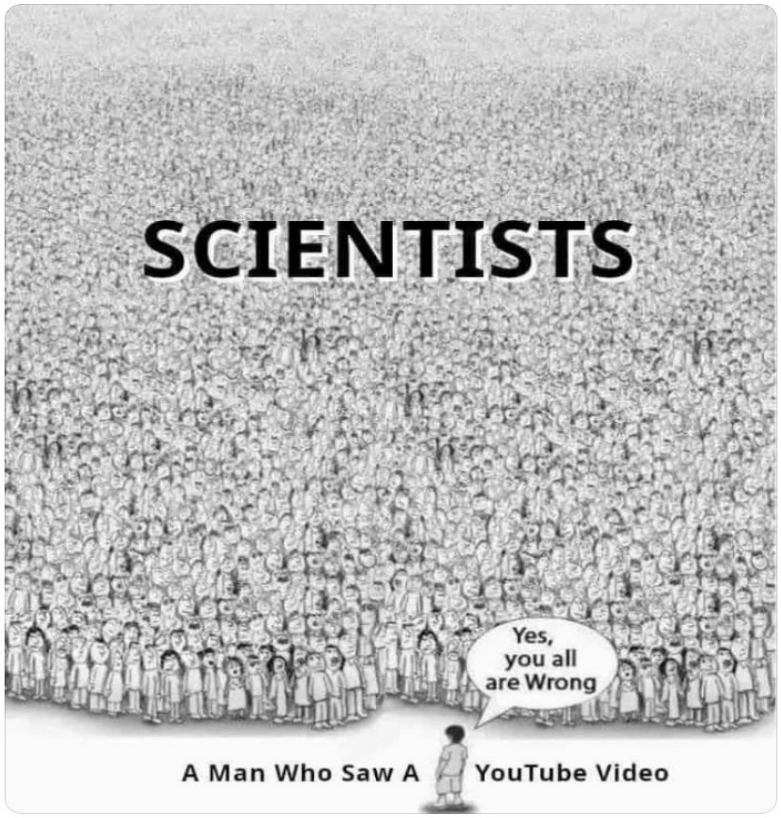
APPENDIX 1 ● Elephant[131] in the Room vs Scientific Facts from Credible Published Research Papers

Are genetically modified (GM)/transgenic/bioengineered plants safe for human consumption as food?

Yes.

But, being dogmatic about dogmas is unscientific[132]. Nature can prove us, our knowledge and our collective wisdom, to be insufficient, incorrect or inappropriate, in instances. It is not impossible that there may be a non-zero probability that the answer 'yes' should be qualified with the stipulation that it is "yes" for >99.99% of cases we are likely to encounter. Scientists generally refrain from making absolute decrees. This reflects neither the weakness of ethics nor a lack of wisdom but exhibits strength based on the notion that science must offer room for questions in our plight to pursue the facts and the truth.

APPENDIX 1 (supplemental information) contains scientific fact-based explanations which may be comprehensible, hopefully, by individuals with a basic science education, who is respectful of science and possesses an open, analytical mind which applies reason, factual logic and if needed, rational extrapolations. We offer a guided tour of the science behind the "yes" if individuals are more likely to abhor fanaticism fueled by quackery and prefer to evaluate outcomes from credible scientific research.



Cartoon 1: In this discussion, we may fail to include those who exhibit irrational exuberance in ignoring scientific facts and are prone to transmogrify tabloid fodder into veritable truth, at any cost to humanity and society[133]. Ignoring public views[134] as well as scientific[135] institutions[136] providing evidence of GMO food safety[137] is apparently considered a badge of honor among those who are committed to being a rebel without a cause or purpose. Government reluctance[138] based on beliefs[139] rather than actual research-based scientific evidence is further adding insult to injury and is an anathema to progress.

In simple terms, the bio-engineering / transgenic modification involved in this discussion of plant-based oral vaccines (POV) calls for insertion of a gene for a foreign antigen in the plant to be biologically expressed in the plant (e.g., in leaves). The simplest and perhaps basic questions are:
[1] whether genes (generally in the form of pieces of DNA) are ***naturally*** dynamic (mobile) in organisms, specifically in plants (in order to provide evidence that we are not engaging in any **unnatural** process)
[2] whether genes (generally in the form of pieces of DNA) are ***naturally*** inserted (or deleted) by the organism, i.e., plants (in order to provide evidence that we are not creating an **unnatural** process)

In the "epilogue" section, we provided scientific evidence of ***massive movement of genes*** and chromosomes in plants, as a natural part of evolution, which resulted in wheat, a staple food, globally. Even after thousands of years of wheat consumption, humans do not seem to suffer from detectable physiological dysfunctions due to wheat, which resembles a "cancerous" state (ploidy of chromosomes).

Figure 8: The discovery[140] of transposons in maize by Barbara McClintock[141] demonstrated how genes "jump" from one genome to another, naturally (variation in kernel color[142]).

Genomes of plants (and animals) are dynamic elements which are evolving through natural processes of genome editing which includes gene insertions/deletions/modifications. The "edits" may not be based on "self" content but introduce/exchange nucleic acids (DNA and RNA, hereditary material) with other organisms. Food crops (plants) use a (fascinating) cross-kingdom and cross-species immunity strategy to protect food (as in food crops). Of particular interest is the **bi-directional** cross-species[143] and **cross-kingdom** RNA interference[144] tools. Pathogens and pests deliver small RNAs (fungal sRNAs) into host (plant) cells to modify host (plant) immunity. On the other hand, hosts (plant) transfer sRNAs into pathogens (fungus) to modify their virulence[145] (disabling the fungus from infecting the plant, hence protecting the food crop).

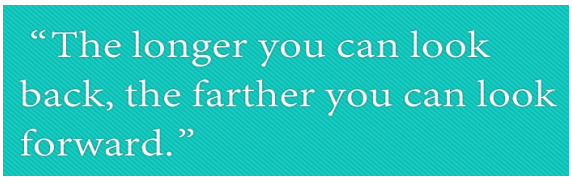
Thus, plant host-induced gene silencing (HIGS) is a bi-directional transfer of genetic material between plants and fungus (they are taxonomically[146] in distinct kingdoms) which is a *natural* event. Cross-species and cross-kingdom immunity is a strategic genetic tool and a gift from evolution to food crops to protect the plant (producing the food that humans consume and have been consuming for thousands of years without any detriment either to individual health or health of nations or civilizations).

Bi-directional HIGS (B-D HIGS) is not unique to plants and is available from the evolutionary playbook for plants, insects, worms[147] and humans. *Wolbachia pipientis,* an intracellular endosymbiont bacteria confers host resistance[148] against RNA viruses in insects. In mosquitoes[149] the presence of *Wolbachia* can inhibit the transmission of certain viruses, such as Dengue, Chikungunya, Yellow Fever, West Nile, as well as the infectivity of the malaria-causing protozoan, *Plasmodium* and filarial nematodes which causes filariasis[150] in humans. Fecal microRNA (miRNA) present in extracellular vesicles (EV) mediate inter-species gene regulation[151] by entering *Fusobacterium nucleatum* (an oral bacterium, indigenous to the human oral cavity, which plays a role in periodontal disease*)* and *Escherichia coli*, to regulate bacterial gene transcripts, a potential strategy for manipulating the human microbiome.

Indeed, small non-coding clustered, regularly interspaced short palindromic repeat (CRISPR) RNAs (crRNAs) have gained great attention as a tool[152] for targeted genome editing[153] and crRNAs are almost ubiquitous as tools for cross-species immune regulation. However, CRISPR tools for adaptive immunity are not invincible. Anti-CRISPR genes[154] which can resist bacteriophage infection were identified in *Pseudomonas aeruginosa* and is nature's "off-switch" for CRISPR gene editing. *Pseudomonas aeruginosa,* a gram-negative opportunistic pathogen that primarily infects immunocompromised hosts, uses outer membrane vesicles[155] (OMVs) to transfer sRNAs to human airway epithelial cells[156] (*in vitro*) with the intent to target host mRNA function and/or stability which may reduce host immune response (immunosuppression in humans).

Hence, genome editing in plants, bacteria, worms and animals (including humans) is a natural process. In this discussion of POV and elsewhere, we mimic Nature and adapted the modifications for our (human) use, for example, to create a plant which will produce the Ebola Virus antigen (EBOV-1) in its cells (leaves). The latter (leaves), if administered orally (sub-lingual) will deliver the foreign antigen in the human bloodstream and trigger immune response to the foreign antigen. Thus, immunization via POV has the ability to offer humans immunity from Ebola infection. What we have accomplished and trying to implement through POV is exactly what we have learned from Nature and natural processes from the evolutionary tool kit which are used by plants for protection of food crops.

In terms of science, supported by an opulence of credible scientific evidence, are there any known "monsterization" processes or outcomes GMO antagonists claim are harmful to humans and human food?



Cartoon 2: The core principle[157] of future proofing?

Plants are made useful[158], not harmed, in the process of bio-engineering plant products to serve humans. One reason why Nature endowed plants with the ability to photosynthesize[159]. Transgenic modification by selective insertion/deletion of one or few genes is ***not a systemic change***. In other words, the plant "as a system" remains almost the same after its genetic modification.

The broad question in this context is whether modification of one gene or modification as a result of one change (one nucleotide, one amino acid) is capable of dysfunction in an organism? The answer to this question is weighted because through these single-change events (point mutations[160]) we have delineated functions attributable to elements in nucleic acids (DNA, RNA) and proteins. The bulk of molecular structure-function relationships in nucleic acids and proteins were untangled one mutation at a time. Such systems evolved over geological time scales and were first described in bacteria (lactose operon[161] and the concept of allostery, applicable to humans[162]) and mutations in human diseases are well documented (sickle cell anemia[163], cystic fibrosis[164], LDLR-hypercholesterolemia[165]).

One change in a plant (during the process of genetic modification) can, theoretically, lead to (?) a problem. Will that problem become a human burden of disease, dysfunction and disaster? Rational extrapolation of the scientific facts from thousands (millions?) of years of crop plant evolution (ploidy in plants resembling "cancerous" state due to amplification of chromosomes) suggests that plants and plant physiology are unlikely to be affected by humans modifying single gene insertion/deletion for purposes of using plant products to benefit humans and human physiology (e.g., immunization of humans and animals). Beneficial outcomes from plant products[166] in human[167] therapy are widely documented.

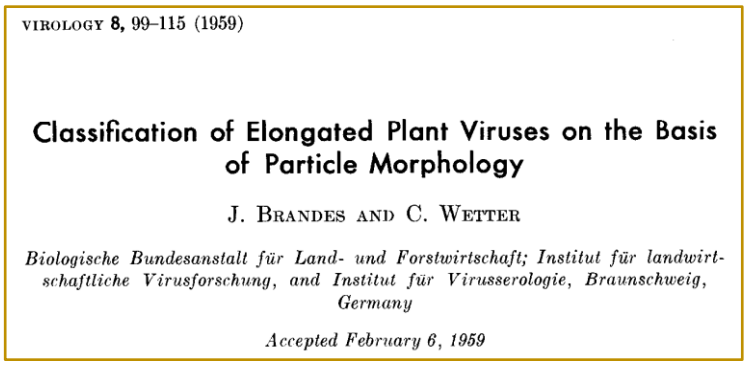
A reader asked to include an extremely oversimplified example of what is a "system" aimed at children in elementary/middle school (whose analytical ability and science[168] education is pivotal to our collective future). Let us consider a bedroom. One expectation from a "bedroom system" is a good night's sleep. The bill of materials (BOM) for a "bedroom system" includes walls, bed, mattress, pillows, duvet, decorations, side tables, table lamps, desk, posters on walls, ceiling art, chandeliers, lights, ceiling fans, rugs, carpets, dresser/drawer, wardrobe, spot heater, a/c, TV, etc. (as a point of reference think about a "car system" which may include engine, wheels, transmission, brakes, seats, a/c, TV, etc.). In Emma's bedroom she has an "upgrade" in the form of a coffered ceiling made of real timber. Emma's school friend Siena visits her and while chattering away she (Siena) notices that Emma does not have a humidifier in her room. Siena insists that she gives a humidifier to Emma because Siena's house has two. Siena and Emma goes to Siena's house and brings the humidifier. Emma's *bedroom system* has a new "insert" – the humidifier contributed by Siena. Emma's bedroom remains unchanged except for a change in available floor place (because the humidifier now takes up a small space on the floor next to Annie's cushion). Emma's sleep objective (good night's sleep) is still unchanged. Emma sleeps well, anyway.

Plants modified genetically to "insert" a foreign gene in the process of implementing POV remains unchanged in almost all physiological/biological attributes. But, the transgenic (GMO) plant now offers leaves (and other tissues) carrying the antigen (in its cells), which could (oral route) help trigger immunity against that specific antigen. Wouldn't you choose POV for immunization?

The idea of "jumping genes" sparked a comment from a reader with respect to transgenic plants harboring Ebola Virus antigen (EBOV-1). On contact, could the virus jump out of the plant to infect a human? It is a logical question in view of the "spillover" genes[169] reported from animals to human (for example, the recent outbreak of Marburg virus in Rwanda[170]). If a transgenic plant is expressing the Ebola Virus protein (antigen) EBOV-1 (as an immunogen for POV), then the most comforting note of safety is that the EBOV-1 protein from Ebola Virus is just that – one protein – it is ***not*** the virus. Therefore, the virus cannot jump or infect because the virus is not there (only one viral protein is there).

What if there was an actual plant virus in the plant? Can that plant virus jump from a plant to infect a human or domestic pets? As a scientist one should not say "no" unequivocally but the taxonomic distance between plants and humans (very distant "kingdoms") are significantly different in terms of our biology which may make it almost impossible for a plant virus from a plant (or plant product) to directly jump/infect a human or animal and cause a viral disease (or even bodily discomfort). In recorded history, we have been glorifying and living with plant viruses in our living rooms and bedrooms for more than a thousand years. Thus far, we have not yet recorded a "jump" from any plant to human, in order to cause an infection by the plant virus (or even an annoyance). It is quite appropriate to elaborate on this excellent question (from a middle school student in RAAS[171]) by digressing into the history of humans co-existing with plant viruses in our homes (without any known infection).

Around 1593-1594, Carolus Clusius, (Charles de l'Ecluse, 1526-1609) a botanist, begun a botanical garden at the University of Leiden (NL), to cultivate tulips[172] in Netherlands[173]. Originally a wildflower, tulips were cultivated in the Ottoman Empire (Turkey, *-stan* states), as early as 1,000 AD and later imported to Holland in the 17th century, where they became a formidable economic force. It was the first economic bubble to explode[174] circa 1637. Tulips were a key element of the Dutch economy[175] in the form of auctions. *Tulipmania* coincided with the formal establishment of the Amsterdam Stock Exchange in 1602. Tulip trade was a catalyst for the Dutch economy, which achieved a high standard of living in Europe by the middle of the 17th century. The newly found affluence spawned a Golden Age, for the Dutch, typified by the great artist Rembrandt van Rijn (1606–1669). The bursting of the bubble of the tumultuous tulip economy may have been evident from the price of *Semper Augustus*, a variegated tulip with distinct striations on its petals. Around 1636, the price of the bulb of *Semper Augustus* was ~$34,584 and as high as $97,200 (based on other forms of valuation). These colorful patterns are caused by potyviruses[176] which are plant viruses with positive-strand RNA genomes, which alters distribution of pigments in the petal due to virus replication. A specific potyvirus, the tulip-breaking virus, causes successive generations of the bulb to shrink until it can no longer flower. Hence, the incredible price[177] of the *Semper Augustus* bulb. Tulipmania was brought to its knees by the potyviruses (1636-1637) and it contributed to the destruction[178] of the Dutch economy. These viruses still circulate, transmitted by aphids. The decline of the Dutch economy due to potyviruses, coincided (?) with the bubonic plague. It ravaged the nation, a 5th of the population dying in Amsterdam (1635-1636).



VIROLOGY 8, 99–115 (1959)

Classification of Elongated Plant Viruses on the Basis of Particle Morphology

J. BRANDES AND C. WETTER

Biologische Bundesanstalt für Land- und Forstwirtschaft; Institut für landwirtschaftliche Virusforschung, and Institut für Virusserologie, Braunschweig, Germany

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Figure 9A: (LEFT) Colorful striations of *Semper Augustus* caused by infection due to the potyvirus, tulip-breaking virus. Fig 9B: (TOP) Identification[179] of potyvirus was a triumph in the age of tulipmania.

Tulip cultivation since circa 1000 A.D. in Turkey lead to turbulence within the economies of Europe in the 17th century but it was not due to healthcare. The Dutch flower markets made "auction" a household name. It continues today at Aalsmeer, NL and also online (**eBay**, since 1995). Neither in reality nor in cyberspace (online) there are any evidence of tulips harboring potyviruses (tulip-breaking virus) causing harm to humans even though potyviruses are mobile[180] between and within plant cells. Flowering plants (rose, marigold, tulip) are woven into the fabric of our daily lives and some petals (especially rose) are edible. In this context, it is appropriate to mention how edible petals and virus-like particles (VLP) may converge as yet another approach (but distinctly different from POV and may not be low-cost).

In 2007, HIV[181] and influenza[182] virus-like particles (VLP)[183] were followed by vaccine candidates (influenza virus[184]) including SARS-CoV-2[185] related advances[186]. Imagine, if, VLPs are introduced in roses (rose rosette virus, fimovirus[187]; rose yellow mosaic virus, potyvirus[188]) or tulips (tulip-breaking virus[189], potyvirus). Using RRV[190] or RYMV[191] as vectors, perhaps we could create roses specifically expressing VLPs for Ebola (Rose Ebola). We could create a rose specifically expressing VLPs for SARS-CoV-2 and variants as well as flu and variants. If VLPs are expressed in the sap or in the petals, then a teaspoon of crushed petals from rose/tulip will contain millions of impotent virions (VLPs) as antigens for sublingual administration. By extending this hypothetical *modus operandi* to other plants as vehicles for VLPs, imagine the inclusion of tomatoes[192] (*Solanum lycopersicum*), basil (*Ocimum basilicum),* tulsi (*Ocimum tenuiflorum)* and neem[193] (*Azadirachta indica*). Almost 30-years ago, an epitope derived from VP1 of foot-and-mouth disease virus (FMDV) was cloned into the CPMV (cowpea mosaic virus) genome encoding the small (S) coat protein. Chimeric S protein produced in plants infected with the insertion reacted with FMDV-specific antiserum[194]. Plant virus vectors and VLPs[195] represent new[196] mechanisms for disease control using diverse ideas[197] from different domains[198] if we are not afraid to stop lying[199], discard roadmaps (use a compass) and even try inserting square pegs in round holes.

If we are not afraid to "push the envelope" forward, scientists should not be afraid of push back, either. The origins of "push back" in science is rooted in humility. Science can be strenuously complicated if we acknowledge the fact that both living and non-living forms are connected "systems of systems" with boundaries which are immersed in a quagmire of unknown unknowns. Submarines have millions of parts which are configured into thousands of sub-systems which are integrated as systems in the design. When completed, we call it a submarine[200]. Man-made machines are complicated but a submarine or a space station, with its millions of sub-systems (which generally produces deterministic outcomes), pales by comparison to what we *think* we know in terms of ***system of systems***[201] in bacteria[202] or about what we *do not know* about the now defunct dogmatic view[203] of the "central dogma" in biology.

Let's start with information flow in the simplest model systems in biology: unicellular bacterium E. coli. Its genome was sequenced more than 25 years ago, yet we still don't understand how most of its genes are regulated, leaving many open questions about its general physiology and evolutionary history. It is one thing to have the gene sequence, and it is quite another to understand what the gene and its protein product do and how they are regulated. Amazingly, only 30% of the expected transcription-factor-gene regulatory interactions in this organism have been characterized. Similarly, more than half of all operons of this organism's genome lack any annotated transcription factor binding sites. The methods to rectify this sorry state of affairs are understood, and it should be only a matter of time and willpower to sort it out. We should not believe that we have "solved" E. coli, even in this very narrowly defined sense. In the case of multicellular organisms, the situation gets even worse[204].

If we suffer a catastrophe (e.g., earthquake, tsunami, pandemic) and if we lost scientific research data about what we know about multicellular organisms, then, after we recover from the disaster and account for losses, we will realize that it wasn't such a loss after all because we almost do not know anything except a few nuggets about bacteria. After more than a quarter century: [1] we know little about the ***meaning*** of the human genome sequence[205], [2] the human genome codes for thousands of non-conventional open reading frames[206] (ncORFs) but we know almost nothing more, [3] the seminal discovery of RNA interference[207] (dsRNAi) has resulted in a few FDA-approved siRNA therapies[208], and [4]the genetics of virulence (Fields and Byers, 1985) is beyond human grasp. Far from these specifics, on an evolutionary level, we are clueless about the mechanism/reason/significance of lessons[209] from LRP6[210] (LDL Receptor Related Protein 6[211]), CCR5[212] (chemokine receptor type 5 or CD195) and the conserved angiotensin converting enzymes[213] gene in subkingdom Eumetazoa (see Figure 8[214]). The latter relates to ACE2, the receptor for entry[215] of SARS-CoV-2 virus[216]. Our genocentricity[217] overshadows the fact that the ***unit of life is the cell*** not genes (or nucleic acids). *Life manifests* through ***cells.*** We are creating atlas[218] of cells and cancer[219] cells but do we understand[220] the syntax and semantics of cells or activities[221] of cells? The latter is one reason why the promise of mucosal[222] immunity[223] is still a mirage. At the most elementary level, even blood cells (CBC, complete blood count) may not reflect a "standard" range but likely to be patient-specific[224] (may serve as a risk stratification[225] tool).

For system of systems in worms[226] or insects[227], our science is at a loss to explain mechanisms, network, connectivity and the non-linear dynamics of weighted dependencies between their system of systems involved in an incessant push-pull quest for homeostasis within and between internal closed-loop systems versus the environment (external open-loop sub-system of sub-systems). In terms of humans, with billions of publications from trillions invested in research, we have not yet scratched the surface of even one disease sub-system (e.g., cancer[228]) in terms of "understanding" mechanism of action. In living organisms, all sub-systems and systems are intra-/inter-dependent and inextricably connected to events both near and far at the molecular/subcellular level (DNA sequences and transcription[229]), meso-level (Gram-negative bacteria, ankylosing spondylitis, autoimmunity, molecular mimicry, HLA-B27[230]) and macro-level (sleep and atherosclerosis[231]; oral microbiome and risk of Alzheimer's disease[232]). After 75 years of longitudinal epidemiological study (Framingham Heart Study, 1948[233]) we have islands of information[234] about cardiovascular health[235].

This *ad infinitum* tsunami of unknown unknowns ***which cannot be adequately explained is the only explanation*** which antagonists of GMO and POV can offer to threaten the march of reason (Fig 10). Our perpetual chasm of knowledge about living systems (plants, animals, humans) leaves room for "what if" scenarios which will persist in eternity as long as there is life on earth. Is the "fear of the unknown" and our lack of knowledge a sufficient reason to hinder the progress of civilization?

Returning to the known reality about the health of civilization, it is helpful to understand that POV, transgenic plants and GMO crops ***are edible*** (***were*** edible plants). The plant bio-engineering process may introduce one or two genes into the edible plant. The plant ***still remains edible for humans***. POV is not a gene editing approach to change or optimize any plant function (which is, in most cases, harmless to humans[236] for plants and animals[237]). Antibodies to allergens in milk, wheat[238] and rice[239] proteins are detected in humans, naturally. Of the ~7 billion poor people in the world, more than half (~4 billion) are in Asia (half of the world's ~ 8 billion population), which is the predominant rice-eating continent of the world (the Indian subcontinent ~1.9 billion[240], SouthEast[241] Asia ~700 million[242], and China~1.4 billion[243] constitutes the continent of Asia). Scientific literature indicates cases related to rice allergens[244]. One individual suffered from anaphylaxis[245] after consumption of rice (*Oryza sativa*). In a related vein, recreational use of tobacco[246] also induces immune reactions (antibodies) in humans, naturally.

The gastrointestinal tract limits the ability of external food, including GMO plants, to enter our body (blood). POV (***edible plants***) recommends sub-lingual administration to prevent degradation[247] of the POV immunogen (the antigen POV aims to deliver to the bloodstream). However, oral delivery (ingestion) of uncooked plants and vegetables were shown to be immunogenic (Fig 3 & 4; Table 2). It may not be unwise to state that ***edible*** plants suggested in the POV approach may not pose any significant or unusual/unknown mortality risk[248] with respect to human consumption (ingestion or via sublingual administration). Morbidity due to allergic reactions are anticipated to follow established food related trends (milk, wheat, rice, etc.). These occasional biological discrepancies cannot justify vile and vicious actions deliberately inflicted on vulnerable poor people by well-funded irrational organizations[249].

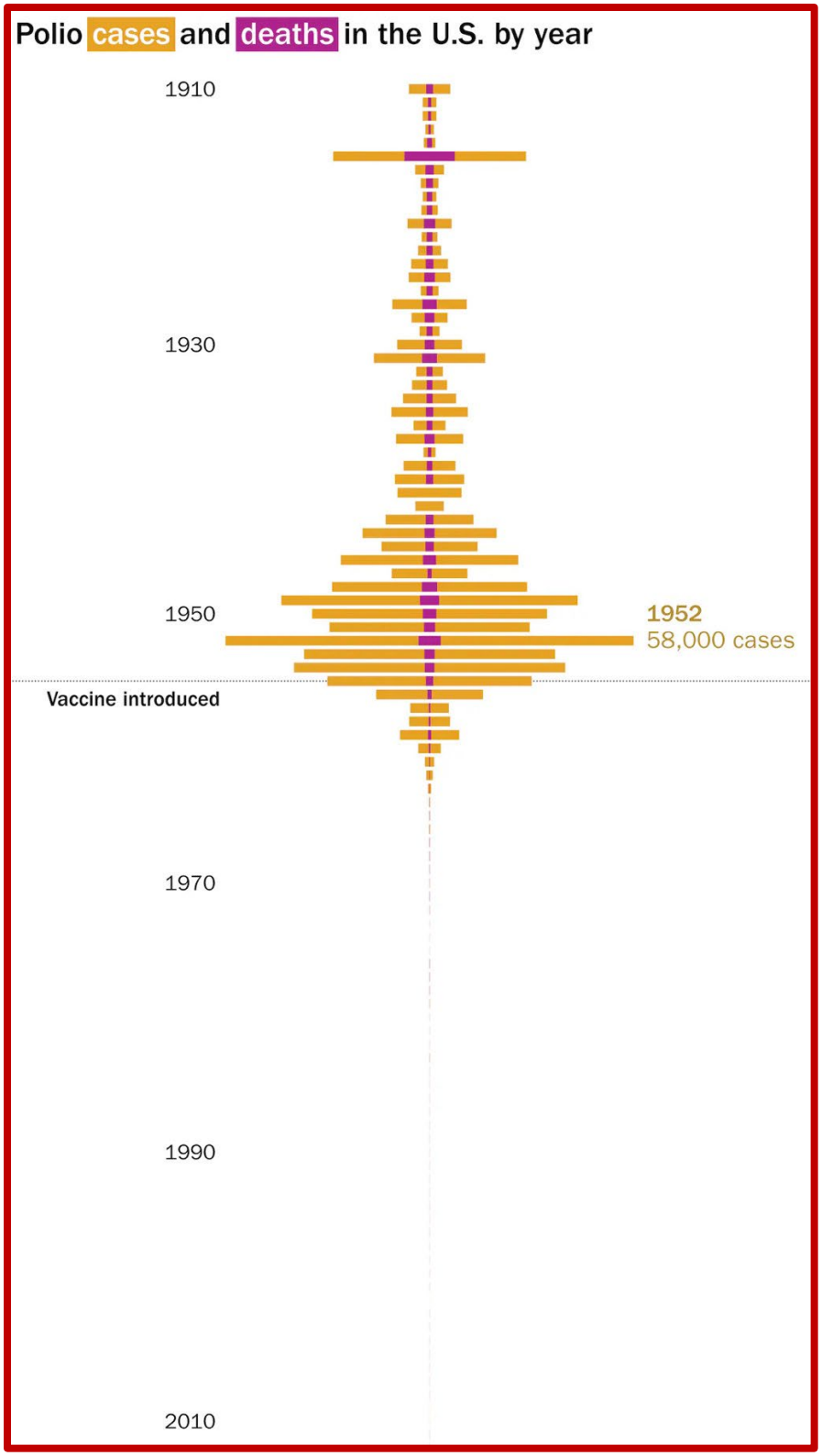


Figure 10: The March of Reason – vaccines[250] do more good[251] than harm – beyond reasonable doubt.

Ardent supporters of sublingual[252] POV implementation will be innately pro-active human instruments of goodwill united by the zeal for finding new ways to help the world (in an unrelated example, using mosquitoes[253] to *bite people on purpose*, not to deliver parasites or viruses but to *prevent infection by delivering antigen through the mosquito bite for the purposes of mass immunization*). These individuals are naturally endowed with creative abilities to foresee how anastomosis of history[254] of science[255] with human values[256] may be catalytic in our plight to *apply* the fruits[257] of science as a service to society. If knowledge is credible, it leads to the haphazard evolution[258] of more credible knowledge. This layer-cake of knowledge may even create an Einstein[259] and sow seeds of wisdom to prevent the decay[260] of civilization as well as shape seismic shifts to restore civilization's path toward the desired trajectory of greater good. The "path" is in a continuous flux due to the incessant oscillation between the many ways for punctuated[261] equilibrium[262] (Eldredge, Niles and Stephen Jay Gould (1972), ref 89) to influence progress versus the pendulum of disequilibrium infecting global harmony through the wrath of disenfranchised and diabolical humans. The lack of principles[263] and the practice of politics[264] with international aid[265] will not help *poor economics*[266]. Unearthing[267] the "old" science of POV will offer pragmatic help for the health of poor people, ***now***, rather than queuing for charity or new vaccines[268].

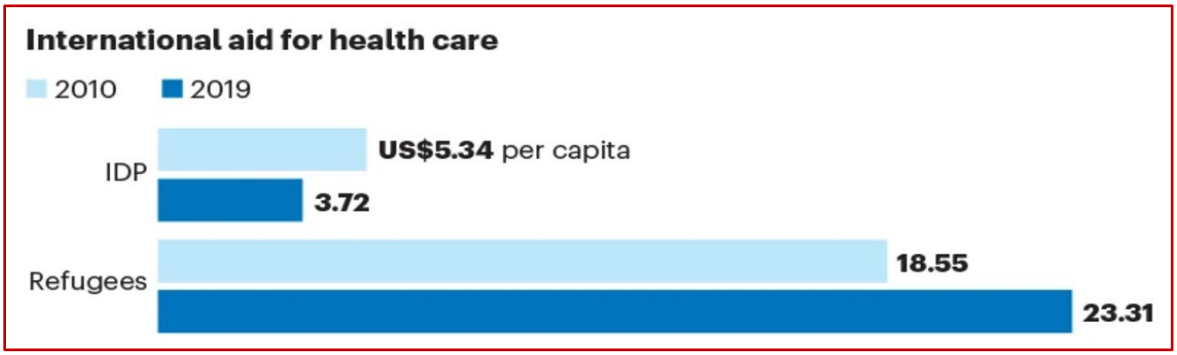


Figure 11: Policies for pittance: playing politics with the lives of poor people. International aid for health care does not care for poor people (ref 265). The science of POV will help poor people, albeit only in one dimension (ie., access to vaccines for preventive public health practices in remote corners of the world).

Whether POV implementation will become a preposition on a *post-it* note or a pebble in the pond will depend on the personal ethos of one visionary or a small group of leaders. POV protagonists will possess an ethical approach to pecuniary polarization[269], a sense of dignity, preference[270] for the scientific[271] rationale rather than succumb[272] to hand-waving ideology. They understand the value of innovation, they are pro-active catalysts yet cognizant of the need for caution and accountability. They are passionate about cultivating science to improve lives of people (science[273] as a service for global[274] society). They are forever optimistic with a profound sense of the future[275] which embraces the principle of ***audentes fortuna iuvat*** and exemplifies[276] the adage through science[277] and actions in their own lives[278].

APPENDIX 2 ◦ **FAILURE IS NOT AN OPTION** (informed objectivity and ethical access to vaccines)

Thus far we have harped on success of POV and explained why it can succeed as a global plant-based vaccination/immunization solution to usher in preventive public health for ~7 billion poor people. It is well-nigh impossible to "claim" success for POV vaccination/immunization in a discussion paper irrespective of seminal past research outcomes and other positive[279] trends. The critical scientific clue for success of POV as a global plant-based solution for very-low cost oral immunization is the initial human test (key R&D milestone). Can it confirm oral route of plant-products containing foreign antigen induces significant antibody (IgG) titers? While the focus is on induction of immunogenicity by B cells (IgG), it will be important to determine if T cells are immune responsive, at all. Plant-based antigen delivers the protein antigen perhaps as a whole(?) or in pieces (epitopes) which induces IgG response. mRNA[280] vaccines are taken up by cells, the mRNA is *translated inside the cell* and the antigen (epitopes) are displayed on the cell surface (MHC), which induces T-cells to confer cellular immunity, in addition.

Key R&D Milestone on the Path to POV Implementation (Induction of Immunity through IgG)

We commence with two targets: SARS-CoV-2 (Spike) and Ebola (EBV1). To get to the "plant" stage we will need to successfully transfect plants. After sufficient growth of the leaves in the transgenic plant, we will duplicate Fig 2 from Mason et al, 1992[281] in triplicate. Results are expected to confirm that we have plant-produced viral antigens in the transgenic plants created with SARS-CoV-2 and Ebola virus.

Control POV using SARS-CoV-2 (BNT162b2[282] mRNA 1273) may demonstrate plant based antigens can induce neutralizing antibody titers (WHO[283]) to ***reasonably*** signal potential for "immune" status (if normal[284] humans were challenged by an infectious agent, i.e., virus). It will be necessary to note the distribution of neutralizing antibody titers induced by antigens from different types[285] of vaccines[286] as well as different communities[287], demographics[288] and variants[289]. ELISA and other tests for SARS-CoV-2 antibodies are available and published. This step is essential as a proof of concept milestone for the new beginning of POV because we now know what form of "immunity" to expect for SARS-CoV-2. Also, it is necessary to document any adverse[290] effects from consumption of plant-based antigens for POV and relevant null/placebo controls.

For n=10 human test, only seronegative humans will be selected (who test negative, i.e., not immuno-positive for SARS-CoV-2 RBD [Spike] and Ebola antibodies, in blood). It may be quite difficult to find seronegative humans uninfected with SARS-CoV-2 but perhaps easier to find seronegative humans for Ebola. Human testing can be done in Asia, Africa, US, UK, EU (depending on the location of the lab).

10 humans (sero-ve)	10 humans (sero-ve)	10 humans (sero-ve)
POV with SARS-Spike	POV with Ebola EBV1	POV with null plasmid
Expect: Spike ab (+ve)	Expect: EBV1 ab (+ve)	Expect: -Spike/-EBV1

Titrate [1] Antigen Dose: 0.5µg – 50µg protein and [2] Duration: Kaputsa, 1999

Positive outcome from key R&D milestone signals forward progression. In this phase of POV, antibody (IgG) titers from seronegative humans may be compared to titers demonstrated after injecting mRNA vaccine for SARS-CoV-2 (mRNA vaccine is the mRNA for pike protein of the SARS-CoV-2). The CoVID-19 antibody is the antibody a normal human (who is not immunocompromised) should produce in response to the antigen (protein) introduced in the human (as mRNA vaccine). CoVID-19 antibody (IgG) titer may be the "gold" standard for claiming *induction* of the immune system in humans. If we claim POV is working then we must be able to show antibody titers ~50% of what was achieved by the mRNA vaccine. Immunogenicity is also a function of duration and dosage (in addition to pre-conditions in humans). Dosage and duration can be titrated for POV induced antibody titers (Kaputsa et al, 1999) to reach ~50% of the antibody titers induced by CoVID-19 mRNA vaccine (Kariko, 2005; Kariko, 2008).

Documenting this data (~50% IgG titer levels) from human tests (n=10) may reflect a modest confirmation of success. It recognizes the fact that the immune system in the test humans responded to plant-produced antigen in the POV approach, at least for the IgG antibody isotype. Determination of mucosal immunity (IgA[291]) may be useful but IgA, IgD, IgE and IgM titers may be excluded, initially.

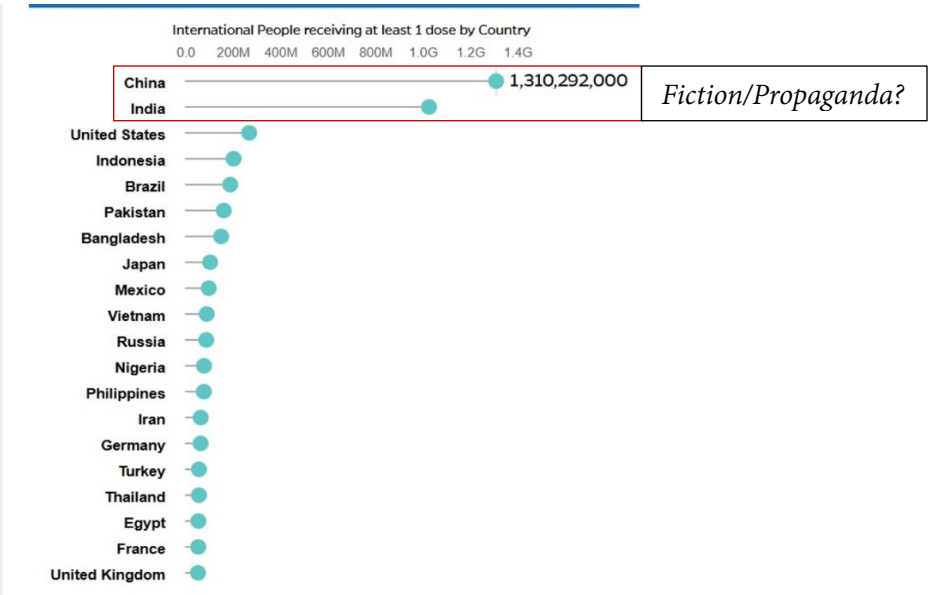
If we cannot successfully accomplish this key R&D milestone then the promise of POV may suffer a temporary pause. Perhaps more work on the molecular nature of the recombinant antigen may be necessary to optimize transcription initiation (other[292] gene expression issues) of the antigen in plant tissue and/or re-visit Kozak's[293] consensus[294] to optimize translational efficiency. The basic science research includes a few exciting[295] challenges worthy of analyses. For non-scientists and critics, these biological "hiccups" may be discouraging or an impediment to *faster and cheaper positive results*. Non-scientists (funders) may not be interested in unraveling the molecular biology of antigen gene/protein related transcription/translation (and post-translational modifications, i.e., glycosylation) issues for plant-specific optimization or other unknowns (e.g., plant tissue tropism[296] of transcription initiation and/or translation elongation factors with differentiated specificity between root, stem, leaf, petal). The complexity of the biological machinery and its molecular elucidation could be germane to producing sufficient antigen in plant tissue (to maximize *bio-availability* in the human system) in order to induce immunogenicity in humans at levels approaching the concept (principle?) of sterilizing immunity.

Any temporary science related failure to implement POV may be a systems level failure to determine standard principles and practices in plant science, plant molecular biology and plant-based applications, as a service to society in the context of the five foundational pillars necessary for the survival and growth of modern day civilization, i.e., FEWSH (food, energy, water, sanitation, health/healthcare). To set the context of this incessant *emphasis* on very low-cost plant-based oral vaccinations in terms of the scientific strides pioneered mostly by the Western world, it could be useful to note that the author's insistence on "plant-based" global vaccination/immunization solution is fundamentally rooted in the economic perspective that health of nations could be proportional to wealth of nations. In other words, the focus on "plant-based" is entirely a pecuniary consideration. The focus on plant-based immunization has nothing to do with any "tree-hugger" conscience or that plant-based approaches are "green" for earth.

Fleming-Florey-Chain antibiotics, Enders-Weller-Robbins polio virus and Salk-Kariko-Langer vaccines are revolutions to be embraced. It is only moral, ethical and humane to share the fruits of these life-changing biomedical discoveries from UK and US with the rest of the global population, rich or poor.

Pecuniary priorities[297] and opportunistic profit[298] raking has rained on that parade. In LIC (low-income) and LMICs (lower-middle-income countries) less than 10% of the population[299] may have received one dose of CoVID-19 vaccine (perhaps by combining made for TV video releases of country-specific photo-op converged with 1 dollop of fiction and 1 dose of "*How to Lie with Statistics*" [300]).

Figure 12: Irremediable Injustice? The reach of "single dose" of CoVID-19 vaccination by country[301].



The only thing necessary for the triumph of anti-science is for scientists to do nothing.

Raison d'être

The time-sensitive need for alternative very low-cost (VLC) vaccinations/immunizations for citizens of less affluent nations and a few of the OECD[302] nations is due to the harsh reality that >80% of the global population and/or their national health services cannot afford vaccines from for-profit corporations. Primary targets are citizens of Africa and Asia. The broader population must include anybody earning <$20 per day (84% of the global population[303]). ~7 billion people need VLC vaccines (87% of the world) for pathogens likely to evolve/emerge from Africa and Asia, sooner or later.

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic.[1] After genomic sequencing of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, messenger RNA (mRNA)-based vaccines were developed by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2).[2,3] In December 2020, both vaccines were authorized by the US Food and Drug Administration for Emergency Use Authorization (EUA).[4] A third COVID-19 vaccine, an adenovirus vector vaccine manufactured by Janssen Biotech, was also granted EUA on February 27, 2021.[5]

On July 22, 2020, Pfizer announced an agreement with the U.S. government for an initial order of 100 million doses of its mRNA vaccine for $1.95 billion with a possibility of acquiring up to 500 million additional doses [9]. On August 11, 2020, Moderna, Inc., announced that the U.S. government committed up to $2.48 billion for early access to 100 million doses of Moderna's mRNA vaccine, with the option to purchase up to 400 million additional doses [10]. According to an article published on Nov. 17, 2020, Pfizer has set the initial price at $19.50 a dose ($39 per patient), and Moderna has set its vaccine price to $25 per dose ($50 per patient) [11]. Schwartz et al. [12] report the price of the Moderna vaccine as $30 for the two-dose regimen.

Distribution of the mRNA vaccines is a serious challenge due to the need for ultra-cold storage. The Pfizer and Moderna vaccines require different storage temperatures: −70 degrees Celsius for Pfizer and −20 degrees Celsius for Moderna [13]. Moderna's vaccine can be stored in a regular freezer, making its distribution less costly. Pfizer has provided several ultra cold freezers to store and distribute their own vaccine [14].

Figure 13: (top) Vaccines were produced/approved[304] with a prohibitive price[305] tag (bottom) which made vaccines inaccessible to less affluent nations. In an age of air travel, transmissibility of infection is not a risk but a ***fait accompli***. It is in the interest of wealthy nations to invest in the success of POV to safeguard their home, hearth and wealth. The risk of ~7 billion unvaccinated infectious people will mathematically overpower any sense of a safety quotient for the affluent ~1 billion. Another reason to root for success of POV is the fact that POV is useful for *any disease with a target (neo) antigen*, e.g., cancer[306].

The penchant for implementation of plant-based oral vaccination (POV) for immunization:
[0] *is **not** aimed at* ideological paradigm shift to "green" public health or any such social reform agenda
[1] *is **not** aimed at* any effort to out shine conventional vaccines (attenuated whole virus, recombinant protein-based) or mRNA vaccines or discourage vaccine innovations (multivalent nano-vaccine design)
[2] *is **not** aimed at* second guessing the necessity for the painstaking process and minutiae of vaccine approval based on repeated series of rigorous tests and multi-phase clinical trials for vaccine safety
[3] *is **not** aimed at* the essential requirement of precision standards and accuracy of SOP involved in the end-to-end process engineering required for manufacturing efficiency of high efficacy vaccines.
[4] *is **not** aimed at* any form of competition whatsoever but only as an alternative source of reasonably effective very low-cost affordable immunization to partially provide preventive public health for the poor.

The yearning for global implementation of plant-based oral vaccination (POV) ***is driven by*** a simple and fundamental desire to strengthen global economic growth. The latter, in turn, may improve social cohesion and gender-agnostic access to education (to sow/reap the harvest of science as a service for society). Education and economic growth is the bread and butter to fuel freedom and development. Hence, POV is an enabler for the less affluent nations and its market of ~7 billion consumers. POV aids in the fortification of public health which translates to improved productivity of nations. Robust health of nations absorbs more people into the economic engines generating effective and assiduous participation. Health of nations helps to create wealth of nations and perhaps even the wisdom to create an equitable infrastructure to structure equity in the distribution of and access to global public goods. In the toolbox of ethical civilization, POV is an instrument akin to a catalytic converter with the potential to transform the principles of "liberté, égalité, fraternité" into social practice. POV is an essential attempt to inculcate global harmony. POV will reduce the risk of affluent nations suffering public health disasters and socio-economic meltdown due to infectious agents (transmitted by air travel) emerging from Africa and Asia.

Preventing the global implementation of plant-based oral vaccination (POV) is a passport to continue the irremediable injustices that plagues the world through diabolical actions perpetrated by the few who constitute the bombastic billionaire's bureau in certain nations. The failure to translate the credible science of POV into global solutions for the less-affluent world may be a crime against humanity. The latter may have become a laughing matter. Crimes, today, are often rewarded by the electorate immersed in fake information arbitrage and convicted felons may remain unpunished, legally (?).

To conclude - there is a non-zero probability that this initiative (in this instance) for plant-based oral vaccination (POV) may fail (temporarily) for credible scientific reasons and/or post-immunization medical reasons related to patient safety (widespread hospitalization due to major dysfunctions in a statistically significant percentage of vaccinees). For the greater good, the failure to try and the failure to execute a test implementation (pilot scale) may be a cataclysmic failure of science as a service to society.

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Misguided cancer goal. *Nature* **491**, 637 (2012) https://doi.org/10.1038/491637a **Editorial**: *Nature* dismissing cancer vaccines as a "goal science cannot deliver" (*naturally*, sixpence short of a shilling!).

Cancer prevention vaccines on trial

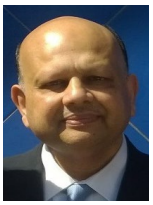
Planned and in-progress clinical tests of vaccines to prevent cancer include the following:

TARGET CANCERS	Participants	Number of participants	Start date	Antigens	Vaccine type
Breast, ovarian, prostate	People with *BRCA1* or *BRCA2* mutations who have never had cancer or are in remission	44	April 2021	hTERT, PMSA, WNT1	DNA
Triple negative breast	People in remission after treatment for triple negative breast cancer	24	October 2021	Alpha-lactalbumin	Protein
Pancreatic	People with an inherited mutation or family history that puts them at high risk for pancreatic cancer	25	May 2022	KRAS	Peptide
Colon, endometrial, others	People with Lynch syndrome who have never had cancer or are in remission	45	June 2022	Suite of 209 frameshift neoantigens	Viral vector

The Last Word – Plant based oral vaccination (POV) can also deliver cancer vaccines to humans (IgG)
Source: Kaiser, J. (2022)
https://www.science.org/content/article/new-generation-cancer-preventing-vaccines-wipe-tumors-form

BRIEF BIO

Shoumen Datta



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Affiliated with MIT Auto-ID Labs, Department of Mechanical Engineering, Massachusetts Institute of Technology (Cambridge, MA) and MDPnP Labs, Department of Anesthesiology, Massachusetts General Hospital, Harvard Medical School (Boston, MA). He obtained his PhD in molecular biology from Rutgers University School of Medicine (NJ, USA) with help from Department of Molecular Biology at Princeton University (NJ, USA). He was a Research Fellow in Medicine (Thyroid and Neuro-Endocrine Labs, Endocrinology, Molecular Oncology) at Massachusetts General Hospital and Instructor in Medicine at Harvard Medical School. He was a Research Associate at the Whitehead Institute at MIT (transcription, yeast genetics) and a founding member of the MIT Human Genome Project. He was a Research Scientist in Molecular Parasitology at UCSF (University of California UCSF School of Medicine, San Francisco, CA). In the 20th century, he was involved with local, state and federal government agencies to improve US public education and technology. He served as a Special Assistant to the Mayor of the City and County of San Francisco, California; Science Education Partnership at UCSF School of Medicine; Berkeley Pledge initiative at the University of California, Berkeley and Chair of the US National Task Force on Education, Economy, Workforce, Technology sponsored by Information Technology Association of America, US Dept of Commerce, Dept of Labor and White House Council of Economic Advisers (1998-1999). As a former Research Scientist in ESD (Engineering Systems Division), MIT School of Engineering, he explored technology innovation, RFID, IoT, digital supply chain, data, analytics and econometrics in decision systems. He taught and teaches Strategy & Management, Supply Chain Innovation at the MIT Sloan School of Management, Chalmers University (Sweden), ESSEC and KEDGE (France), Cambridge University (UK), NTU & NCKU (Taiwan), TUS (Japan) and continues to serve as an advisor to start-ups, corporations, global organizations and government agencies (foreign and US). In the 21st century pandemic years, he was an advisor to various NIH funded CoVID-19 research groups (for developing ACE2 and aptamer-based nano-biosensors for low-cost diagnostics of SARS-CoV-2 for infection/transmission control).
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