Edible vaccines

Biology term paper by Masha Streiff, 4F
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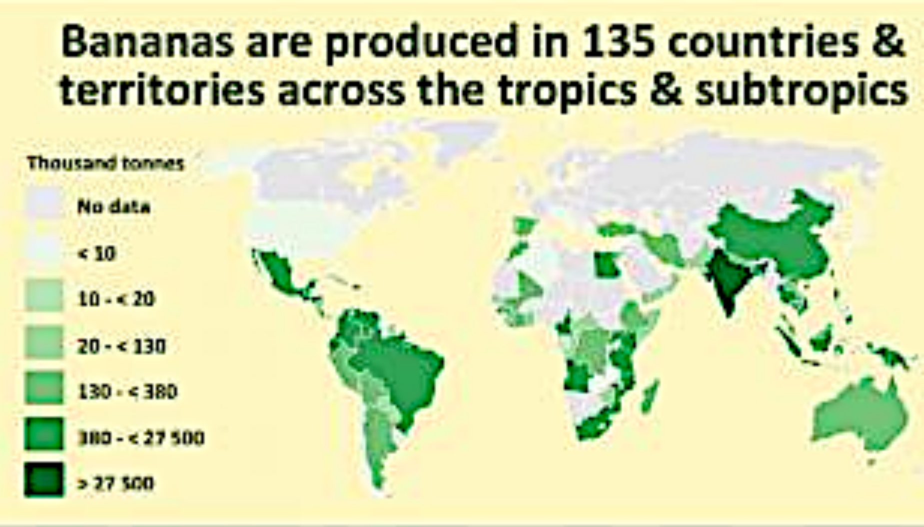
1.1 Personal motivation for this topic

The people in Switzerland are some of the "lucky few". Vaccines and other treatments are readily available to all of the population, unlike in third World countries, where the education toward these diseases is missing, hygiene is usually non-existent and money is scarce enough without having to buy expensive medicine for each child. The notion of creating vaccines that are available even to the poorest people and that would most probably be accepted, due to their familiar look, is terrific, I think. And so, I chose this topic so that I could also inform myself about the state of this invention.

1.2 Especially Interesting facts



As one of the cheapest foods in tropical regions, bananas are well suited for the distribution of vaccines as they are available to almost all of the population. If unopened, a banana offers a "sterile" environment for sensitive proteins, like the added vaccines. They are protective against outer influences as well as bacteria, viruses, fungi etc.

Growing one portion of an edible vaccine for HBV(Hepatitis B virus) is estimated to cost $0.005 - compared to using needles that, without including the doctor's service, sterilising materials and the actual vaccine, cost about $0.12.

HBV (Hepatitis B Virus) attacks and destroys the liver. 2 Billion people are infected, and many don't know until it's too late and they have transmitted it to another person. The vaccination of this disease is the key-problem: The vaccine requires refrigeration, needs to be administered intramuscularly 3 separate times, with the cost ranging from $100 to $150 or more. This is why the hope of a cheap and sustainable edible vaccine, the banana as a carrier, would have solved many problems, first and foremost the price.

1.3 Central questions

- Are edible vaccines a real prospect in preventing and/or eradicating epidemics?
- What is the process and how do edible vaccines work (focus on the Hepatitis B vaccine using bananas)?
- What is the future for this type of vaccine?

2.1.1 Historical importance

The first experimental uses of vaccines were documented to be between 1774 and 1796, when Edward Jenner infected a boy with cow pox, and several weeks later with the "real" pox. The boy

showed immunity and thus Jenner concluded that he had found a safe way of inoculation.
With molecular biology came the first vaccine of this type: In the mid- to late 1970's scientists developed an HBV vaccine.
A polio vaccine, in use since 1955, had already proved successful- polio was eradicated in the U.S. by 1979. Case numbers also decreased dramatically all over the world, but it is not eliminated. Occasionally, wild polio will cause infections, but the bigger problem are vaccination myths, like in Pakistan - one of the remaining three countries where polio is an endemic disease. Radical Muslims have been spreading the word that these vaccines are a way of sterilising Muslim children, and will readily use the children as a shield against military intervention (mostly by the U.S.).
The science toward edible vaccines started out in the 1990s, when Charles Arntzen began experimenting with using potatoes against the Norwalk virus (causing inflammation to stomach and intestine that results in diarrhoea. In developing countries this is dangerous as sufficient rehydration is usually not possible.) He went on to using tomatoes, and finally bananas, the latter of which he used for carrying the HBV vaccine.
Pharming(genetically modifying plants for the use in medicine), as it is sometimes called, was also developed as a security against bioterrorism.
This was because of the Anthrax spores that were delivered to government officials after 9/11. This was also when the development of an antidote against Ebola began.

2.1.2 Recent events in the scientific history

The epidemic that is probably freshest in our minds is Ebola. It seemed to be spreading uncontrollably and it was fatal to nearly every individual that contracted it. Nine missionaries from the U.S. were among the unfortunate that were infected. Though untested for humans, a new treatment called ZMapp was administered to them - under the "compassionate use" guidelines, only applied in absolute emergencies, when there is only a small chance of survival without treatment. Seven of the nine treated survived, thanks to ZMapp that was created in a tobacco plant.
ZMapp is now in use in clinical trials, and the development of several other types of plant-based vaccines and treatments has been fired up, like using the green algae *Chlamydomonas reinhardtii* against Malaria and cancer.
However many edible vaccines never get to the stage for testing on humans. And if they do, the amount of paperwork and security facts before it is approved for use usually makes it come to a grinding halt. No Edible vaccine has been approved (without limitations, i.e. outside of a strictly controlled clinical or field trial) for use on humans yet.

2.2 Areas and Reasons of Utilisation

Edible Vaccines were developed primarily for third world nations. Many of the diseases that were considered for edible vaccines predominantly occur in those regions due to the lack of hygiene, low incomes preventing treatment and missing education, that would prevent it spreading as easily.
Just like scientists are using genetic modification to create "Superfoods", like crops resistant to pests or environmental influences (like temperature extremes) or crops that carry additional essential materials for people's health (e.g.: Golden Rice, which

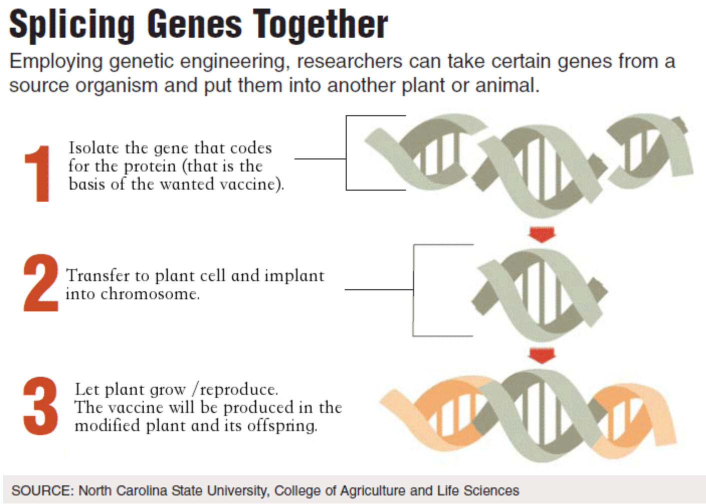
carries Vit. A to fight the often fatal deficiency of it in Asia. It is not in use yet, due to approvement issues.), they are using this modern technology for pharmaceutical reasons (thus the name "pharming"). By using vegetables and fruit that are a main source of income and or easy to grow in large quantities in a specific region, it was supposed to be a way of making it available to all families, irrespective of their financial situation.
As it would be delivered in form of a (dried) piece of fruit or vegetable, or maybe as a powder for a drink, even children would be easily vaccinated and probably even like it.
The biggest potential reason, I think, is because there is no trained medical staff needed, nor is there any (expensive!) equipment that has to be handled with care. This minimizes cost and risks involved in the whole procedure.
This means even countries with no trained doctors or nurses, or regions far from settlements with clinics or hospitals a life-saving vaccine can take place.
Even though it is not an active reason today, we should not forget that edible vaccines would be cost-effectively produced and easily administered for entire countries in case of a bioterrorist attack.

2.3 Alternatives for this type of treatment

Alternatives to edible vaccines are "conventional" ones, like the HBV vaccine developed through molecular biology in the 1970s .
It's what we know today as a vaccine - liquid in a small syringe is administered directly into your muscle. Depending on the type of vaccine, it is vital a second and maybe even third dose is re-administered after a certain period of time.
Another alternative is a different type of edible vaccines. This time, it may look like either type (i.e. syringe or food).
The vaccine, however, is a purified form of plant antibodies to a specific disease. ZMapp is an example of this.

3. Description of engineering technique

I am going to describe the technique used to create a vaccine from a plant(e.g.: ZMapp) and the vaccine implanted into the vegetable / fruit (e.g.: Banana vaccine against HBV) based on those two examples. The first step in making tobacco plants create antibodies is to use bacteria. Specific bacteria, able to infiltrate the plants, are able to transport genes in with them that create the recombinant proteins that will act as medicine. After only a few days, the plants will start producing this protein, thus "making" the antibody.
For the Ebola medicine, the bacterium *Agrobacterium tumefaciens* was used. By mashing the leaves up and filtering the obtained juice three times, three "sets" of antibodies are won. These are combined to create the medicine. To make the vegetable or fruit become a carrier of the wanted proteins that form the vaccine, the process of splicing together is used.



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4. Interview Charles Arntzen

1. Is the banana vaccine against HBV in use today?
No approved vaccines for humans have been made in plants.

2. If yes, in which regions?
As I said, no edible vaccine has been approved for humans, but they were intended to be used in third world countries.

3. Are there strong advantages or disadvantages for edible vaccines?
The advantage that was the most alluring to myself was the low cost of production and of the end product. However, I later realized that I had only estimated a fraction of the cost. Plant-to-plant variations require exact analytical controls to determine the dosage if unpurified. Last but definitely not least is the cost of testing it extensively and getting past the official approval costs a lot more than I was expecting when I started developing edible vaccines.

4. After many years of research, is the banana still the best-suited carrier for the HBV vaccine?
We abandoned the idea of using the banana as an edible vaccine fairly quickly. Of all the fruit or vegetables in the experiment the banana was the one with the lowest expression of antigens. Also, it took several years to grow a fruiting plant, which is what we needed for this.

5. Are there different types of processes to add the vaccine to a fruit/vegetable?
I no longer am attempting to produce vaccines in edible plant tissue. We have switched to focusing on purified vaccines and drugs from plants — the most successful has been ZMapp.

6. Is there a future for these vaccines?
At the moment, there is no vaccine near approval. So even if there are still scientists trying to create edible vaccines, they won't be on the market any time soon.
Not to mention that even if one would be eventually approved, they would have to wait for the FDA to create guidelines on plant-based / edible vaccines as they don't exist yet. The rules just haven't caught up with genetic engineering yet.

Personal remark: All research facilities that I have found in regard to my topic are located in the U.S. and therefore not possible to visit. In addition, I have realised that my topic is not active in the way I was hoping it would be. Though creating vaccines from plant-material is very much an on going project, creating them in edible plant tissue is not.

[1] Original by NC State University, edited by Masha Streiff

5.1 Progress made with the application of the chosen technique

Though no edible vaccine has been approved, the research on the topic has paved the way for the future. Instead of creating a source of food carrying the vaccine, using plants or plant-material as a base for cheaper and in some cases better vaccines has become the main focus in that area of research.
Had the extensive research on genetically modifying plants for medicinal purposes not happened, the way of purifying antibodies from plants would not have become such a success.

5.2. Future research steps

Based on the success of ZMapp, I think this process for vaccines and in general treatments will be continued and enhanced with the many facts that will be acquired during this process.
As several other vaccine / medicines from purified plant-material have been announced to be tested, there will be a wide range of information with the intensive research of the different plants, research and reactions in the test subjects (i.e. first animals and - if successful - even humans.)

5.3.1 Ethical aspects: Advantages

- Lower cost of production solely for the vaccine
- Only light, water, soil and nutrients needed - no bioreactors, expensive lab-equipment and chemicals needed
- using plant-material reduces risk of contamination of the vaccine
- plant-material is hardier than most mammalian, that of yeast or bacterium
- ecological: easier reproduction(collect seeds, not starting over after every generation.)
- No trained clinicians needed
- No sterile environment and materials needed for injection - no needle, disinfectant or gloves
- Two-way bonus: food and vaccination combined in one.
- Absorbing the vaccine orally means it has direct contact with mucosal lining, therefore guaranteeing a dual-effect protection.

5.3.2 Ethical aspects: Disadvantages and dangers

- edible vaccines are GMO and not accepted widely (yet)
- GMO crops for production of edible vaccines could spread pollen (for this, some researchers created pollen- and seed-free variations. This increased production cost and difficulty, i.e. the positive aspect of generations creating the next is eliminated), thus destroying or transforming endemic species.
- Approval is not possible at the moment: there are no guidelines for safely offering GM- plants as vaccines.
- Conformity (of dosage) is not guaranteed in each plant
- Dosage needed unclear, as not purified inside the fruit/vegetable
- Transportation of fresh fruit/vegetable problematic (if the fruit spoils, so does the vaccine it's carrying)
- Storage in third world country problematic or impossible (problem of spoiling)
- Further processing, i.e. drying, grinding etc. necessary to prolong "shelf-life".
- Long-term affect of GMO not yet studied extensively

6. Summary

- Are edible vaccines a real prospect in preventing and/or eradicating epidemics?
No, as there is no approval (possible) yet and the research has not given answers to crucial aspects(conformity of each dose in a plant). In addition, there are several "design-flaws" still present in all edible vaccines. (e.g.: shelf life not optimal, further processing raises price)

- What is the process and how do edible vaccines work?
There are two different processes: Inducing the plant to create antibodies, which are then purified to win the medicine or, using the process of "splicing" to make the plant itself produce a certain protein(=vaccine). In the latter, the plant itself is the carrier - eat it and the vaccine gets into your body.

- What is the future for this type of vaccine?
At the moment, only the first type of processes described above (and 3. on p. 5) is still in use. The scientist who first started developing edible vaccines, using fruit/vegetable as carriers, has transferred to researching plant-based antigens, purified foremost from tabacco plants at the moment.
According to an expert in this field, Charles Arntzen, edible vaccines, where you "eat your vaccine", are not part of the future.

The answers to my central questions I wanted to answer for myself during this work say it all: Research using plants to create vaccines, or ailments of all kind, is still a big part of science - Even though using the plants as carriers just did not work out for several reasons. Financial(higher costs than estimated would make the price go nearly as high as a "normal" vaccine), biological (fruit is not hardy enough to fly around the world and endure extreme influences) and scientific (you cannot supply people with a vaccine that is not uniformly dosed.).

7. References

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Pictures (in order of appearance)

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- Found on: https://realtruth.org/articles/223-gefwtc.html
Originally from North Carolina State University, College of Agriculture and Life Sciences. Edited by Masha Streiff