Rice: vaccine of the future?

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Vaccinations have become an essential necessity within our public health system. In some cases they have even eradicated diseases. Unfortunately, vaccines are not readily available to everyone in need. With the recent cholera epidemic in Haiti, finance and logistics were among the limiting factors in supplying the entire population with an adequate vaccine. Overall, accessibility of vaccines is especially limited in developing countries where various problems are encountered. Could edible vaccines be the solution to these problems?

Problems with current vaccines
Because of the fragile nature of some of the currently available vaccines, they need to be transported and stored at a certain temperature, which requires refrigeration. Preserving the so-called ‘cold chain’ of a vaccine costs an estimated € 145 to € 218 million annually and stresses the necessity of electric facilities. The use of needles increases the risk of secondary contamination and requires a careful way of dealing with waste products. In order to overcome these problems, researchers are working on new concepts of vaccinations.

Oral Vaccines
The problem of contamination of needles could be overcome by developing vaccines that can be taken orally. At the moment, oral vaccines against selected diseases such as cholera and polio are available. This kind of vaccine is easier to use and does not require needles, but they still need to be refrigerated. Incorporating a vaccine into an edible substance, which does not require such stringent storage measures and can easily be disposed of seems therefore an attractive idea. Experiments have been performed in Europe and the United States using potatoes, wheat, banana, and tobacco leaves, but so far none of these products were successful enough to be brought on the market. More recently, Japanese researchers have been working on the concept of incorporating a cholera toxin B (CTB) subunit into the genome of a food product. The food product the researchers selected was rice.

The benefits of oral vaccinations
Edible, and thus oral, vaccinations have an advantage over their parenteral counterparts; the induction of a mucosal immune response in addition to a systemic response. A systemic immune response is activated only after the pathogen has crossed the mucosal barrier, while a mucosal immune response could prevent the pathogen invading the host all together. Due to exposure of the antigen in the gastrointestinal tract, rather than solely in the circulation, the host can produce secretory IgA, as well as systemic IgG. Therefore, oral vaccines can be produced to protect against pathogens that enter the body through the gastro-intestinal system, like *V. cholerae*, *E. Coli*, *Hepatitis B* and *H. pylori*.
Preventing the use of needles for vaccines is beneficial for several reasons: it is less stressful for patients, secondary contamination is avoided, and there are less health specialists required and the costs of waste management are more contained. However, there are already oral vaccinations available, even for cholera. What then, is the advantage of producing the cholera vaccine in rice? It all comes down to the cold-chain.

**Avoiding the cold-chain**

The problem of the existing oral vaccinations for cholera is the need for cold-chain maintenance. An important question is whether edible vaccines would be able to withstand higher temperatures and thus facilitate different storage measures. Research has shown that the CTB-rice can be stored at room temperature (25°C), for 18 months without the vaccine becoming ineffective. This fact makes cold-chain storage for the rice-vaccines unnecessary. Since these vaccines are needed most in the developing world, the impact of this finding is huge. The costs of storing the vaccines could be lowered dramatically and because the antigen-producing rice plants can be grown locally and the rice does not need extensive purification or processing, the production costs might also remain low. These low costs might allow developing countries to produce and distribute these kinds of vaccines themselves. This would bring the immunization of entire populations one step closer.

However, while the possibility of local production and storage seems an advantage, at the same time it could be a drawback. Pharmaceutical companies may not be willing to invest in such a vaccine when there is so little profit to be made. However, local governments could tackle this problem by applying for funding from organizations such as the Global Alliance for Vaccines and Immunization.

**Are edible vaccines effective?**

So far, the use of edible vaccines sounds promising, but do they actually work? To be effective, the antigen in question must reach the gastrointestinal tract without being digested in the stomach. Furthermore, in order to induce both the specific mucosal and systemic response mentioned before, antigens in the foodstuffs must be absorbed at a specific location in the small intestine, the Payer’s patches. A Japanese research group found that 75% of the CTB in rice remained...
intact after simulating the acidic conditions of the stomach, due to unique protein storage organelles in rice that can withstand the acidic environment and digestive enzymes of the gastrointestinal tract. Also, excitingly, a specific IgA (mucosal), in addition to an IgG (systemic) response was found in mice and macaques that were fed powdered CTB-induced rice, with CTB being found in specific Payer's patches cells. This shows that rice has definite potential for being a vessel for active immunisation against CTB, and hopefully even other antigens.

**Rice allergies**

Another problem that must be taken into account is the risk of inducing an immune response against the substance used to contain the antigen, in this case the rice, which could cause food allergies. Although the research group did not find antibodies directed at the rice itself, it is a possibility that requires further attention. Creating rice allergies in developing countries would of course cause a whole new array of problems.

**Daily dosage**

According to the Japanese research, the amount of expressed CTB in each rice grain could reach up to a maximum 30 µg. The necessary dosage for effect was not mentioned. However it might be inconvenient if a large amount of rice would have to be consumed in order to reach the correct amount. An experiment was completed on macaques, and to immunize the animals they were fed 667 mg of CTB-containing rice-powder. An equivalent dose for human use would be around 1000 mg. This is the amount a capsule can contain, meaning there should be no problem with administration. The exact dose regimen is not yet known, but most likely it will take a few doses to elicit a significant level of immunisation, similar to every other vaccine. The effects and measures of an over-dosage of CTB were not studied, but would have to be part of future research before making rice vaccines available.

**Gray area**

Finally, if this technique is to be used on humans in the future, jurisdiction on the crops in question would have to be addressed. Currently, these ‘plant vaccines’ are not considered to be medicinal and thus might not be treated accordingly. With the amount of marketed biotechnological products increasing, clear legislation for such substances has to be provided. Growing the crops locally means that local food and drug regulations would apply. As safety measures differ per country, this could cause problems for foreign investment or the distribution among various populations. Also, as production of plant-derived vaccines cannot just be completed in a laboratory, it must be clear how the quality checks can be done and who will be held responsible.

**Rice vaccines: a reality?**

We have yet to wait for this type of edible vaccines to become available for common
Vaccination Facts

Vaccine-preventable diseases are responsible for nearly 20% of the 8.8 million deaths occurring annually among children < 5yrs.

Worldwide 82% of children <1yrs are vaccinated against Diphtheria, Tetanus and Pertussis.

Immunization is responsible for averting between two and three million deaths each year.

An estimated 24 million children <yr1 were not vaccinated in 2008.

Further reading

- Nochi et al. A rice-based oral cholera vaccine induces macaque-specific systemic neutralizing antibodies but does not influence pre-existing intestinal immunity. J. immunol. 2009. 183; 6538-6544

About three quarters of unimmunized children live in ten countries: Chad, China, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Iraq, Nigeria, Pakistan and Uganda. (WHO)

use. The technique sounds promising and could solve some important problems. However, several practical issues still need to be addressed and international agreements would have to be made before it is possible to implement such a large-scale vaccination method. If all of these challenges will be overcome, we will soon look at our daily plate of rice in a completely different way.

About the authors

Annelien de Kat and Esther Bot have both obtained a Bachelor in Pharmacy and are currently enrolled in the second year of the Selective Utrecht Medical Master of the University of Utrecht (SUMMA).