The Vaccine Against Varicella

Do We Have the Optimal Vaccine?

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The live-attenuated vaccine has been the object of many recent reviews\(^1,2\); therefore, the focus here is an attempt to reconsider whether this vaccine is the optimal means of preventing the disease complex of varicella-zoster virus (VZV) infection. In addressing this question, it will review the accrued knowledge of strategies in vaccine development, and how these vary depending on the nature of the infection to be prevented, along with technical advances in vaccine production that potentially allow us to achieve the goal of prevention of varicella infection, as opposed to reduction of disease symptoms.

DISEASES WITH AN ACUTE PHASE ONLY AND DISEASES WITH BOTH AN ACUTE AND A CHRONIC PHASE

The majority of infectious diseases prevented by immunization have only an acute phase and therefore to be successful such a vaccine needs only to prevent disease. A common feature to these vaccines is that they do not prevent infection—exposure or a subclinical infection in the form of natural infection to the disease may remain a risk. Vaccines need to prevent infection. The vaccine against varicella presents an additional problem of a live vaccine against a chronic disease. The varicella-zoster virus (VZV) infection in humans. The live vaccine against varicella on the other hand presents both shortcomings of not preventing latent infection and of causing latent infection.

The vaccines against hepatitis B (HBV) and human papilloma virus (HPV) infection are the proof-of-concept that vaccines can prevent infection. The vaccine against HBV has accomplished its primary aim, that is, to prevent HBV infection in infancy and young children that leads in a vast majority of cases to a chronic infection and later in life to cirrhosis and cancer. The vaccine against HPV has not yet been shown to prevent cancer, but because it prevents the persistent infection that the immune system is unable to clear it is reasonable to assume that it will prevent the ensuing cancer development. The active component of both vaccines is virus-like particles, which represent empty, nonreplicating, particles expressing major viral surface protein(s), suggesting this is at least one route to creating successful vaccines against chronic viral infections.

Live vaccines against diseases with a chronic phase are more problematic. The Bacillus Calmette-Guérin vaccine will prevent acute disease(s) when given to infants but will not prevent infection (latent tuberculosis) or will do so for a very short period of time. However, the Bacillus Calmette-Guérin vaccine does not seem to have the additional problem of a live vaccine against a disease with a chronic phase, that is, to cause latent infection by itself. This may be either because of the intradermal route of administration or the attenuated strain not being based on Mycobacterium tuberculosis but on Mycobacterium bovis, a bacterium known to be able to cause acute disease but not latent infection in humans. The live vaccine against varicella on the other hand presents both shortcomings of not preventing latent infection and of causing latent infection.

THE MECHANISM OF ACTION OF THE LIVE-ATTENUATED VARICELLA VACCINE

The vaccine against varicella is the same kind of live-attenuated vaccine as those against measles, mumps and rubella. These vaccines consist of clinical isolates that have been attenuated by serial in vitro passages with the aim to induce a genetically stable virus that no longer causes clinically significant disease but will induce immunity. The amount of virus in these live vaccines is very small, in the thousands or ten thousands, compared with the many millions of virus particles in inactivated viral vaccines so the multiplication of the virus will occur during the asymptomatic systemic infection.

Based on the mechanism of action of live vaccines and the nature of VZV infection, it is to be expected that the varicella vaccine will also invariably give rise to latency.\(^3,4\) The Japanese pioneers in the field have in recent years advanced the hypothesis\(^3\) that the vaccine would not infect every child but only those who develop a rash after vaccination. The hypothesis is neither supported by mechanistic considerations nor by a follow-up study by the Center for Disease Control in the United States, which stated “it should be noted that herpes zoster has also been reported in vaccine recipients in whom no previous vaccine-related varicella-like rash was identified.”
VACCINES AGAINST SHINGLES (HERPES ZOSTER)

The reactivation of the latent infection caused by the live vaccine seems to be lower than after natural infection. This advantage is however likely to be counterbalanced by the foreseeable demographic changes. The Office of National Statistics in the United Kingdom predicts that of children born in 2012 one-third will live to 100 years of age. With shingles being a disease that becomes both more common and more severe with increasing age, it is clear that future generations are facing a formidable challenge. Repeated vaccinations of the elderly are likely to be necessary even with inactivated and/or subunit vaccines—and in the future we are talking of the very old for whom vaccine responses are likely to be attenuated—which would not seem to be the optimal immunization strategy if alternatives are available.

The current zoster vaccine to prevent reactivation is moderately efficacious and efficacy decreases with age at immunization. Efficacy against the most severe form of postherpetic neuralgia has been shown to wane in a 7-year follow-up every year postvaccination and is not significant after 5 years. There are efforts being made to develop killed or subunit vaccines as booster vaccines against shingles, and these might be more efficacious than the live zoster vaccine. The most promising indication was provided by a study of an inactivated vaccine based on the OKA strain in hemopoietic cell transplant patients. The study showed 62% efficacy in preventing herpes zoster, as good as the best results for the live vaccine in healthy elderly individuals. Whether such an inactivated vaccine would be immunogenic enough to also prevent varicella (varicella) infection is not known.

THE CORE OF THE PROBLEM AND A WAY FORWARD

Early cost-effectiveness calculations included only the costs for vaccination against varicella and showed that it would meet cost-effectiveness for prevention of the disease. However, VZV infection differs from other childhood diseases because it is a disease complex, where a change at one end (varicella) need to include possible effects at the other (shingles). Introduction of varicella vaccination of children is predicted to increase herpes zoster for the first 40 to 60 years when the natural boosting of adults from the virus circulating among children ceases. When the total costs were modeled, varicella vaccination was not considered cost-effective in the United Kingdom.

Nobody would question the merit of preventing varicella in children, but there seems to be a need for a major gain in sight at least for future generations for both varicella and shingles. Perhaps the most convincing argument for our generation that could lead to universal acceptance to take the costs— economical and human—would be the vision of eradication of the whole complex of VZV infection. With eradication of an infectious disease one generation takes the costs for the benefit of future generations. The current vaccine does prevent varicella but leaves the problem of shingles forever for future generations to handle.

Varicella vaccine is unique, in that it establishes latent infection and it is very unlikely that such a vaccine would be developed today. The relative success of the live vaccine seems however to have given research funding bodies the impression that the problem has been solved. Research into the VZV infection complex has been given little support, and this prioritizing would need to be reconsidered. The experience gained with HBV and HPV vaccines has proven that we now have the technical tools to tailor-make the vaccines that we would like to have. They also point towards the type of vaccines that could prevent infection. We would only need to rethink our strategies and to recognize that the eradication of varicella and of shingles is inseparable entities.

REFERENCES