

The Varicella Vaccine

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The United States of America became the first country to implement a mandatory, universal, childhood varicella vaccination program. This program specified a single dose for children between the ages of twelve months and twelve years. However, two years ago, the vaccination program was changed to a two-dose regimen because the efficacy of the varicella vaccine in producing immunity decreased noticeably with time. Concerns regarding the effectiveness of the vaccine, the potential for fewer, but more severe cases of varicella, and the increasing incidence of herpes zoster not only exist but also are especially serious. The potential for adverse effects brings attention to an important question addressing the implementation of any vaccination program: whether the taking of risks incapable of being calculated is worthwhile if there is clear potential for adverse events.

The United States of America became the first country to implement a mandatory, universal, childhood varicella vaccination program on May 1, 1995.⁶ This program specified a single dose for children between the ages of twelve months and twelve years.^{13, 15, 9} Two years ago, the vaccination program was changed to a two-dose regimen because the efficacy of the varicella vaccine in producing immunity decreased noticeably with time.¹⁵ Concerns regarding the effectiveness of the vaccine, the potential for fewer, but more severe cases of varicella, and the increasing incidence of herpes zoster not only exist but also are especially serious.^{15, 6, 12}

The potential for adverse effects brings attention to an important question addressing the implementation of any vaccination program: whether the taking of risks incapable of being calculated is worthwhile if there is clear potential for adverse events. Andrew Farlow, a research fellow at Oxford University notes that the decision to implement obligatory childhood immunization for varicella depends on many complex factors that affect each other including societal attitude, political atmosphere, economic state, scientific understanding, and individual interest.⁴ One must ask to what point is it even acceptable to implement a vaccination program without knowing the long-term consequences of the vaccine. A vaccination regimen should be implemented when the vaccine can have a positive impact on the overall health of society both immediately and in the future.

One of the most common communicable diseases in the world, varicella, commonly referred to as chickenpox, is caused by the varicella-zoster virus (VZV).^{2, 5} Most individuals over the age of sixteen remember chickenpox “as a normal passage of childhood.”¹ Before the vaccine program, it was estimated that four million cases of varicella occurred every year in the United States. Most of these cases occurred with individuals under the age of fifteen years, with children between the ages of four and ten years having the highest rate of incidence.¹⁰ This high incidence among young individuals correlates with the age at which children begin to attend school and daycare in the United States. Furthermore, the peak age of incidence of the primary infection is less than five years of age, suggesting that the increased use of day-care and playgroups lead to greater exposure at a younger age.² VZV is extremely contagious and can easily spread to others. Therefore, it is recommended that an infected child be sent home from school

until the symptoms subside, usually about seven days after the appearance of the rash.¹⁵ Generally, a child infected with varicella would not need any additional treatment beside rest and maybe some ointment to alleviate the itch caused by the rash.² Thus, varicella is a common disease that in nearly all cases not life-threatening.

While the symptoms of most cases are alleviated within two weeks, there exist serious complications from varicella. The most frequent complications include infected skin and soft tissue, dehydration, pneumonia, and encephalitis.¹⁰ These complications usually require professional medical attention. From 1987 to 1995, it is estimated that 10,632 individuals were hospitalized each year as a result of infection with varicella. Children under the age of five years accounted for nearly half of these hospitalizations, and adults at least twenty years old accounted for about thirty percent. It is paramount to note that “compared with varicella-infected children aged 5 to 9 years, infants aged < 12 months and adults aged ≥ 20 years had 6- and 13-fold higher risks, respectively for hospitalization.”¹⁰ More than two thirds of the patients who were hospitalized were otherwise healthy, and “only 11% had immunocompromising conditions.”¹⁰ Moreover, from 1970 through 1994, an estimated one hundred five patients died annually, and varicella was a contributing factor in at least forty more deaths per year. During the four years prior to the implementation of the varicella vaccine in 1995, individuals of at least twenty years of age “had a 25-fold higher risk for death from varicella compared with children aged 1-4 years,” and “89% of varicella-related deaths among children and 75% among adults occurred in individuals who were not immunocompromised.”¹⁰

It is clear that the varicella-zoster virus is a highly contagious disease responsible for at least one hundred deaths each year in the United States and that the cost of the hospitalizations due to complications arising from varicella is tremendous. However, knowing that there always exist serious risks in deliberately altering the epidemiology of a disease, one must ask whether there is a real need for a vaccine. Moreover, it has been proven that “recovery from the primary infection results, in most people, in life-long immunity to exogenous

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infection.”² After an individual is infected with VZV, the virus remains inactive in the dorsal root ganglia.⁵ Studies have also shown that re-exposures to varicella-zoster throughout life aid in the maintenance of effective immunity.² VZV causes both varicella and zoster, commonly known as shingles. This secondary infection, usually occurring when immunity has been weakened “is believed to result from reactivation of latent VZV, latency having developed during a prior attack of chickenpox.”⁷ Epidemiological data from the Brisson study in 2002 has confirmed that prior exposure to varicella builds immunity against successive zoster infection.² Thus, it remains debatable that the varicella vaccine is necessary if infection from the natural virus causes life-long immunity. Moreover, serious concerns that a significant decline in the incidence of varicella will put previously infected individuals at a much greater risk for serious complications due to a reactivation of VZV.

However, in May of 1995, the Food and Drug Administration (FDA) approved Varivax® (Oka/Merck), and the live attenuated varicella vaccine became commercially available.^{6,3} The vaccine strain was developed by Michiaki Takahashi at Osaka University in Japan in the 1970s.^{1,8} The initial varicella strain was taken from a Japanese child named Oka who was otherwise healthy. The virus was then passed through human embryonic lung fibroblasts, after which the strain was passed through guinea pig embryo cells. The virus underwent a total of about thirty-five passages.⁷ Since there is no animal model acceptable for the testing of VZV, the vaccine strain was initially tested in healthy children susceptible to varicella.⁷ Upon testing, no skin lesions appeared on those who were injected, but antibodies that develop with the natural virus developed with the vaccine strain as well as cell-mediated immunity.⁷ Following the testing on children with healthy immune systems, immunocompromised Japanese children were vaccinated because they were at higher risk for complications from VZV. The results demonstrated that the vaccine was safe and effective in inducing the production of anti-bodies and cell-mediated immunity in both immunocompetent and immunocompromised individuals.⁷ With these major developments, controversy arose as the risks and benefits of the vaccine began to be scrutinized, and “investigators who believe that the potential benefits of this vaccine outweigh its potential risks have continued to test the vaccine in the United States since the late 1970s.”⁷

The Oka/Merck strain of the varicella vaccine went through clinical trials in the United States, and in 1995 experimental data demonstrated the vaccine more than eighty percent effective in preventing the development of and immunizing from varicella with the potential for adverse events next to none.³ In 1995, the Advisory Committee on Immunization Practices (ACIP) recommended a single dose of Varivax® for children twelve months to twelve years of age.¹⁵ Even though the vaccine was not proven to eradicate the incidence of varicella infection, the vaccination program was implemented in the United States. Those who were vaccinated but developed symptoms of varicella generally had milder symptoms.³

The American Society of Health-System Pharmacists recommends the vaccine for the following reasons:

“It causes a rash, itching, fever, and tiredness. It can lead to severe skin infection, scars, pneumonia, brain damage, or death. The chickenpox virus can be spread from person to person through the air, or by contact with fluid from chickenpox blisters. A person who has had chickenpox can get a painful rash called shingles years later...about 11,000 people were hospitalized for chickenpox each year in the United States...about 100 people died each year as a result of chickenpox in the United States.”¹⁶

Before the vaccine, millions cases of varicella had occurred annually. The fact that the mortality rate is about one hundred out of millions presents varicella as extremely benign.

Estimates of the economic impact are shown in “cost-benefit studies, which include both direct medical costs and the indirect cost of a parent’s lost wages, show that there would be a return of \$5.40 in benefits for every dollar spent on the vaccine.”³ That means that spending thirty-nine dollars on a single dose of Varivax® will produce an estimated return of two hundred ten dollars and sixty cents. In addition, at the time the vaccine was licensed, the economic situation practically dictated that men and most women with children work full-time and simply “could not afford to stay home for a week with a sick child even if they wanted to.”¹ Indeed, economic factors affected the decision to license the vaccine.

However, in 2006, the ACIP augmented its decision with the presentation of new evidence about the efficacy of the single-dose regimen. From its implementation in 1995 to 2006, eighty-nine percent of children nineteen to thirty-five months old had been vaccinated, and “varicella-related morbidity and mortality were dramatically reduced.”¹⁰ The United States observed a reported decline of eighty-eight percent in the rate of hospitalizations and associated costs as a result of the varicella-vaccine. Direct inpatient and outpatient medical expenditures declined over sixty million dollars.¹⁰ Adverse events occurring in those who had been vaccinated were reported 16,683 times to Merck & Co. More than fifty-five million doses of Varivax were distributed throughout the world.⁶ Although the coverage of the vaccine is high and the economic impact significant, the single-dose regimen was proved incapable of the complete prevention of varicella outbreaks.¹⁵ A review of the effectiveness of the varicella vaccine determined that “a higher degree of effectiveness is needed in order to interrupt transmission and to prevent outbreaks in settings with high contact rates.”¹³ Compared with those vaccinated with a single dose, individuals vaccinated with two doses developed significantly more antibody titers and had a “3.3-fold lower risk for breakthrough disease and higher vaccine efficacy.”¹⁰ Thus, in 2006, the ACIP recommended the implementation of a two-dose varicella vaccine regimen.¹⁰

The United States is one of the few countries in the world that have adopted the varicella vaccine in the program for universal immunization. Andrew Farlow presents major concerns regarding the implementation of universal immunization, beginning that “childhood immunization for varicella

zoster virus may shift the burden of disease to adults.⁴ The consequences of such a shift in the incidence of VZV would cause major problems since the mortality rate in adults is almost thirty times greater.⁴ In addition, “getting varicella as a child confers life-long immunity, but it is not yet clear how long vaccine induced immunity will last.”⁴ While the vaccine was licensed in Japan and Korea in 1988, “doubts about the vaccine’s long-term effectiveness delayed its entry in the U.S. market.”¹ Data from early trials suggested that immunity from one dose would last no less than twenty years; however, the one-dose regimen was determined insufficient in this capacity. Analysis of clinical observations demonstrated that only partial immunity lasted for “at least 8 years.”⁸ Moreover, it was not even eleven years after the implementation in 1995 that the ACIP altered its recommendation to a two-dose regimen. Thus, it is obvious that serious concerns for the efficacy of extended immunity to varicella are evident.

Understanding the relation of herpes zoster (HZ) to varicella is fundamental in determining the value of universal childhood immunization.⁴ Zoster affects an estimated one million individuals in the United States annually¹¹, and about fifteen percent of human beings have an episode of zoster in their lifetime.⁵ Zoster can be a result of a broad spectrum of factors, notably from a “natural decline in VZV-specific cell-mediated immunity”¹¹ and is caused by “reactivation of the varicella-zoster virus (VZV) after primary VZV infection.”¹² Herpes zoster, more commonly referred to as shingles, usually begins with “pain, itching, paresthesias (numbness or tingling), dysesthesias (unpleasant sensations), or sensitivity to touch (allodynia)”¹¹ and causes “acute and chronic morbidity.”¹² The most common complication related to zoster is postherpetic neuralgia (PHN)^{5,12} is experienced by about forty percent of zoster patients over the age of sixty.¹¹ Characterized by “constant, severe, stabbing or burning, dysesthetic pain that persists...sometimes years after resolution of rash,” PHN has no universally accepted treatment.¹¹

Reynolds et al. have concluded that “in theory, universal varicella vaccination has the potential to change the epidemiology of HZ. However, to date, the data available in the United States do not provide conclusive evidence that such a change is occurring.”¹² On the other hand, studies have given evidence that zoster develops by “retrograde transport of virus from ganglia to skin in a host partially immune to VZV.”¹¹ Moreover, studies have reported that “exposure to people with varicella disease is associated with a lower risk of HZ.”¹² Nevertheless, accurate calculation of the impact of the vaccine is extremely difficult because separating the effects of the

varicella vaccine on the epidemiology of HZ is next to impossible. However, until these factors can be accounted for “we cannot adequately assess the possibility of additional effects from a varicella vaccination program that are due to changes in opportunities for external boosting.”¹² It is entirely possible that “given that exposure to VZV boosts natural immunity, the decreased circulation resulting from a mass vaccination could potentially result in an increased number of cases of zoster.”⁵ When Merck & Co. was asked to comment on this theory, Dr. Gordon Douglas, a senior physician at Merck, maintained that “it was not known whether the vaccine also protected against shingles (herpes zoster).”³ As the incidence of HZ may significantly increase over the next fifty years, “the burden of the increased incidence of HZ may counteract most or all of the benefits of varicella vaccination.”¹² Thus, this theory that the incidence of varicella is inversely related to the incidence of zoster is definite cause for concern and must be carefully evaluated.

In most studies, it is reported that potential risk factors for vaccine failure have been identified, but findings remain inconsistent. Most pediatricians were skeptical about the efficacy and the potential for adverse events of the vaccine.¹⁴ Dr. Arthur Lavin’s query presents a major debate involving the decision to implement the vaccination program: “How can our profession accept a tremendous intervention in the epidemiology of an overwhelmingly benign disease, with little idea as to whether more harm than good will result in the long-term?”¹ Farlow poses the dilemma: “must we always wait for all the evidence we need before acting so that we will be judged, with hindsight, as having made the right decision? What if we can only know by taking actions that give us the natural experiment that will tell us the best policy?”⁴ The decision to implement the vaccination program pivots on “a complex mix of society’s attitude towards different risks, politics, and scientific understanding.”⁴

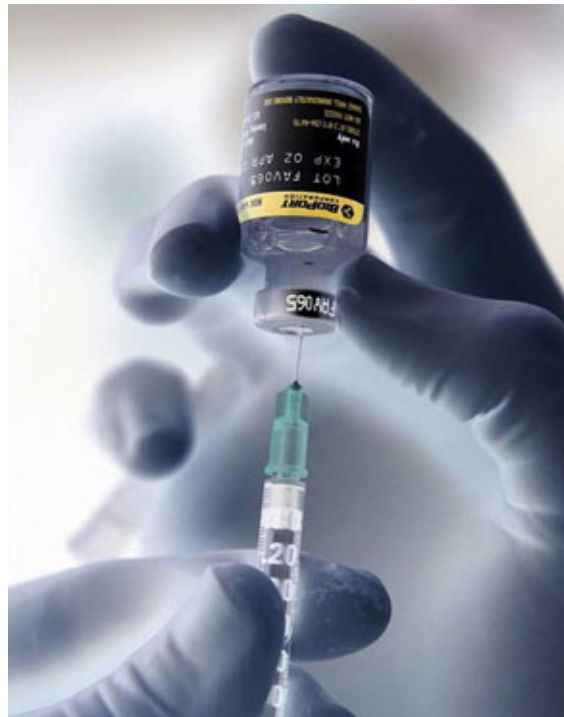


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Notes on Healthcare Reform

The 2009 – 2010 healthcare debate left an extensive paper trail in its wake. Volumes of articles, news stories, and blog posts were created to follow the daily developments that led to the passage of the Patient Protection and Affordable Care Act. It will take years for health policy scholars and historians to digest the full impact of the legislation. In the meantime, *TuftsScope* offers its annotated guide to the articles and multimedia presentations that the journal editors believe to be of lasting value:

General Articles

The Cost Conundrum

Dr. Atul Gawande tells the story of McAllen, Texas and the strange disparity in costs between the town and its neighbor, El Paso. This article became required reading in Washington, DC and promoted discussion of regional cost disparities in healthcare.

Gawande, Atul. “The Cost Conundrum.” *The New Yorker*. June 1, 2009.

Available online at: http://www.newyorker.com/reporting/2009/06/01/090601fa_fact_gawande

Making Healthcare Better

David Leonhardt recounts the efforts by Intermountain Healthcare (Utah/Idaho) to implement evidence based medical protocols throughout all of their hospitals. A struggle to realign medicine with its scientific roots.

Leonhardt, David. “Making Healthcare Better.” *The New York Times Magazine*. November 3, 2009.

Academic Works

The Obama Administration’s Options for Health Care Cost Control: Hope Versus Reality

A discussion on the options for cost-containment and a prescient picture of how far politicians were willing to go on reform.

Marmor T, Oberlander J, White J. *The Obama Administration’s Options for Health Care Cost Control: Hope Versus Reality*. *Annals of Internal Medicine*. 2009;150:485-489.

Available online at: <http://www.annals.org/content/150/7/485.full>

The Social Transformation of American Medicine

The seminal history through the 1970s on the origins of the modern American healthcare system.

Starr, Paul. “The Social Transformation of American Medicine.” USA: Basic Books. 1984.

Documentaries and Media

Frontline: Sick Around the World

T.R. Reid’s documentary on PBS travels to Japan, Germany, Taiwan, Great Britain, and Switzerland to examine how the rest of the world organizes its healthcare systems.

Reid, TR. “Frontline: Sick Around the World”.

Available online at: <http://www.pbs.org/wgbh/pages/frontline/sickaroundtheworld/>

Wendell Potter on Profits Before Patients

Wendell Potter, a former CIGNA executive, shares his experiences in the insurance industry and relates some of the tactics used by the insurance industry to oppose healthcare reform.

Bill Moyers Journal. “Wendell Potter on Profits Before Patients” July 10, 2009.

Available online at: <http://www.pbs.org/moyers/journal/07102009/profile.html>