Clinical and Economic Considerations of Vaccination Against Varicella

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We evaluated the medical and economic literature pertaining to varicella vaccine in healthy children in an effort to provide perspective for both clinicians and those responsible for making payment policies. Chickenpox is relatively mild in most immunocompetent children; however, disease-related direct and indirect medical costs have been estimated at approximately $400 million/year. A vaccine effective in preventing the disease is now available in the United States and may offset some of these expected costs. Universal vaccination for patients older than 12 months of age without history of varicella infection or other contraindication is recommended by the American Academy of Pediatrics. It is estimated that it would save $0.90/dollar spent and $5.40/dollar spent from payers' and society's perspectives, respectively. Thus varicella vaccination is cost-beneficial only when considered from a societal perspective.
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Chickenpox results from primary infection with the varicella-zoster virus (VZV). It is highly contagious, but for most people the resulting disease is relatively mild. In the United States the incidence of chickenpox is approximately 3.9 million cases/year,[1] and disease-related direct and indirect costs are estimated at about $400 million/year.[2]

An attenuated live-virus vaccine to prevent chickenpox was first used in Japan in 1974[3] and became available in the United States in 1995. It is unclear how long it protects against VZV infection, and the need and optimal timing for booster doses to provide continuous protection have not been determined.

Although vaccination is recommended by the American Academy of Pediatrics for all healthy children at age 12 months without a history of varicella, the economic consequences of such a policy have not been completely defined.[1] In addition, relatively few published studies are available in the peer-reviewed literature on this topic. An important question pertaining to the vaccine is its possible effect on the frequency of herpes zoster and the resulting economic impact.

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Epidemiology and Disease Considerations

The VZV is a herpesvirus. It is able to establish latent infection.[4] The first time infection occurs, the result is chickenpox, or varicella. Herpes zoster (zoster, shingles) results from reactivation of VZV from dorsal nerve ganglia[5] and may occur in immunocompetent patients starting around the fifth decade of life. The VZV appears to cause clinical infection only in humans and is considered to be a common disease of childhood. Chickenpox affects both sexes and all races equally.

Transmission of VZV is by direct and respiratory contact. It is estimated that 90% of all cases of chickenpox occur in children 3 years

old or younger.[5] Incubation of infection is about 14–15 days, but the disease may appear from 10–20 days after exposure. Infection may be transmitted from 2 days before rash eruption until all blisters have crusted and are dry. Among household contacts, 70–90% of susceptible individuals may become infected. Pediatric mortality previously was estimated at less than 2/100,000 cases,[5] however, in 1992, 100 varicella-related deaths were reported to the Centers for Disease Control and Prevention.[6]

Immunocompromised patients are thought to be at high risk for complications and extra-dermatologic involvement, which occur approximately 30–50% of the time in this group.[5] Other populations at higher risk for varicella-related complications are otherwise healthy adolescents and adults, and people with respiratory illnesses.

Efficacy of the Varicella Vaccine

Numerous published studies and unpublished manufacturer's data estimated the protective efficacy of the varicella vaccine,[7–11] and *The Medical Letter* evaluated its clinical effects.[12] Despite these reports, description of clinical efficacy remains incomplete; for example, the potential need and timing for booster doses is unclear. The package insert from the United States manufacturer describes the duration of protection as unknown.[11] Postmarketing studies are currently under way to determine an optimum revaccination strategy.

The vaccine is safe and effective in preventing primary varicella infection. The duration of protection remains unknown. The recommended dose for healthy children ages 12 months–12 years is 0.5 ml, containing at least 1350 plaque-forming units (PFU) of the virus, injected subcutaneously in the outer aspect of the upper arm or the anterolateral thigh.[11] Adolescents age 13 years and older and adults should receive two 0.5-ml doses by subcutaneous injection 4–8 weeks apart.

Among 147 children immunized with doses of 500–5000 PFU, 5 developed varicella, for an efficacy rate of 96.6% at least 7 years after vaccination.[7] In a placebo-controlled, double-blind study, vaccine efficacy was evaluated for 9 months after a dose of 8700 PFU in 914 initially seronegative children between ages 1 and 14 years.[8] None of the 468 vaccine recipients developed varicella during the first 9 months, whereas 38 in the placebo group did. After 7 years of follow-up of the original group of recipients, 23 cases had occurred, for a reported protection rate of 95%.[9] In 4042 children and adolescents given 1000–1625 PFU of vaccine between 1987 and 1989, the first-year protection rate was 98%, and in the second year was 96%.[10]

By comparison, the measles vaccine has an estimated efficacy rate of at least 90–95%.[13] The mumps vaccine was 95% effective in clinical trials ranging from 75–91% in outbreak studies.[13] Rubella vaccine is estimated to be protective in at least 90–95% of recipients.[13]

Effect of Vaccination on Herpes Zoster

It is not known whether vaccination against varicella would lead to a change in the frequency or severity of herpes zoster. Currently, about 15% of unvaccinated, naturally infected, otherwise healthy people are expected to experience herpes zoster at some time, usually in late adulthood, as a long-term complication of latent VZV infection.[12] A change in the occurrence or severity of herpes zoster and related complications (e.g., postherpetic neuralgia) would be expected to have significant clinical, economic, and quality of life implications. The risk of herpes zoster after vaccination of immunocompetent children has not been evaluated.

Herpes Zoster in Immunocompromised Patients

The incidence of herpes zoster is thought to be high in immunocompromised patients.[5] The effect of the varicella vaccine on the incidence of herpes zoster in healthy individuals is not known. As a proxy for its effects in healthy patients, it may be reasonable to consider the influence of the vaccine on herpes zoster in immunocompromised patients. In one large study to evaluate this question over 5.5 years, 346 children with acute lymphoblastic leukemia (ALL) in remission for at least a year were given a dose of about 1000 PFU of vaccine.[14] Eighty-four children in this group were matched with controls by disease, geographic location, and chemotherapeutic protocol. No statistically significant differences in herpes zoster occurrence were found between vaccinated children and those who experienced natural varicella infection. Within the matched group of 84 pairs, no significant differences were found, even in controls who became infected with varicella after being diagnosed with ALL.

A smaller study also evaluated this question in

Table 1. Summary of Varicella Vaccine Economic Impact Models[a]

Age (yrs)	Perspective	Treatment Groups	Direct Costs (millions of $)	Indirect Costs (millions of $)	Total Costs (millions of $)	Total Benefit:Cost or Cost-Effectiveness Ratio
0–30	S, P	v, nv	16.9 nv 48.6 v	383 nv 89 v	400 nv 137.4 v	6.9:1 S, 0.3:1 P, benefit:cost ratio only[2]
15 mo–30	S	v, nv	1.77 nv 4.9 v	10.3 nv 0.5 v	12 nv 5.4 v	Not reported[16]
0–30	S, P	v, nv	90 nv 98 v	439 nv 48 v	529 nv 146 v	0.9:1 P, 5.4:1 S, 4.20/varicella case prevented, 10,000/life-year saved[17]

S = societal; P = payer; v = vaccination; nv = no vaccination.
[a]All costs are in U.S. dollars.

240 patients with acute leukemia given 1000–2000 PFU of vaccine.[15] The incidence of herpes zoster was 0.4% compared with 11% in control subjects over an observation period of 4–50 months.

To summarize, the varicella vaccine is safe and efficacious in preventing chickenpox, but its effect on the frequency of herpes zoster in otherwise healthy patients is not known. In patients with acute leukemia or other malignancy, it appears to produce either no effect or a decrease in the frequency of herpes zoster disease. To use this information in making clinical and payment decisions, the economic consequences of vaccinating healthy children to patients, payers, and society must be considered.

Economic Considerations

With the introduction of the vaccine, the question of preventing chickenpox as a cost-effective strategy has come to the forefront, whether from society's, the payer's, or the consumer's perspective. Current debate focuses on whether medical resources should be used either to prevent or treat varicella in immunocompetent patients. A rational social policy for universal vaccination has not been consistently defined by local communities, health plans, or government at all levels.

One reason for not providing the vaccine is its cost relative to perceived benefits, where cost is defined as all health care resource units required to administer the vaccine. To make a rational policy decision, regardless of the perspective, all applicable costs and benefits must be studied simultaneously. To solve this problem, it is necessary to review what is known about the economic consequences of varicella vaccine in otherwise healthy children.

Perspective

A key to understanding economic analyses of medical technology, including drugs, is perspective. Perspective refers to the choice of which costs to include in an economic analysis of medical technology. A payer's perspective includes direct and indirect medical costs such as drug acquisition, hiring additional staff, and constructing new facilities to support a new program. It is the point of view most often adopted by insurers, health maintenance organizations, and other third-party payers. Society's perspective accounts for all costs attributable to the choice either to use or forego use of the technology. Included are direct and indirect medical costs, time lost from work, and changes in productivity due to illness.

The choice of perspective is critical for public health strategies such as immunization. It is also important to note that payers may sometimes choose to adopt a societal perspective. This is particularly true in considering problems that potentially affect large numbers of people, such as communicable diseases.

Economic Studies

Several studies are summarized in Table 1. In the first study of its kind examining a hypothetical cohort of 3.5 million individuals, from birth to age 30 years,[2] several assumptions were made in order to estimate economic impact. Ninety-five percent of the nonimmunized cohort would be infected. Only one dose of 90%-effective vaccine would be necessary, given at age 15 months to 90% of the cohort at the same time as combined measles-mumps-rubella immunization. The vaccine would provide immediate protection, with no decrease of immunity over

time. Herpes zoster epidemiology would be unaffected. One physician visit would be made per 10 cases, patients with encephalitis and Reye's syndrome would require an extra prehospitalization office visit. For patients who see a physician, nonprescription antipruritics would be purchased at $2/purchase by 25%, 10% would receive prescriptions for antipruritic drugs costing $5, and 2% would receive an antibiotic prescription costing $6. One case per household would occur at a time. Fifty-four percent of families would experience time lost from work. Vaccine cost would be $15/dose. No additional administration costs would accrue due to dosing at the same time as measles-mumps-rubella vaccine. Ninety-four percent of unvaccinated people would become infected with varicella at some time between birth and 30 years of age. Direct medical costs were physician visits, drugs, hospitalization, and long-term disability. Lost time from work by a caregiver was included as home care costs.

From a payer's perspective, the overall benefit:cost ratio of this base case is 0.3:1, or 30¢ saved/dollar invested in an immunization program. From the societal perspective, the ratio was $6.90 saved/dollar invested.

Sensitivity analyses were performed for the base case, as well as best and worst cases. In the best case, healthy individuals were assumed to account for 99.9% of varicella cases, vaccine efficacy was 95% instead of 90%, encephalitis cases increased by a factor of 10, and Reye's syndrome cases rose by a factor of 3 over the base case. In addition, the vaccine cost was $10/dose. In this view, vaccination saved $11.40 for each dollar invested from society's perspective, and 80¢ for each dollar invested from a payer's perspective.

The other sensitivity analysis assumed that vaccine coverage was 70% with 85% efficacy, varicella-related hospitalizations were 20% lower (to account for possible misidentification of varicella as the reason for admission), one-third fewer families incurred home care costs (to account for several cases occurring in a household simultaneously), nothing was spent for antipruritics and half as much for antibiotics, and vaccine reactions, including encephalitis, increased by a factor of 10. The worst case also assumed that minor vaccine reactions required twice the time spent on a physician visit and that the vaccine cost $30/dose. This view saved $2.20/dollar invested from the societal perspective and 10¢/dollar invested from that of the payer.

Despite these sensitivity analyses, the strength of the assumptions included in this model is questionable. It is likely that, between birth and 30 years of age more than 95% of a nonimmunized cohort will become infected with varicella. Some individuals require more than one dose of vaccine to become seropositive; seropositivity is used as a surrogate for immunity. Duration of vaccine-induced immunity and the potential need for booster doses have yet to be determined. The same is true for any effect of the vaccine on herpes zoster epidemiology. Household contacts are more likely to result in transmission of disease than are casual interactions, and therefore families with more than one susceptible child may have more than one case of varicella at a time.

Use of the 1981 U.S. Bureau of Census data to estimate the percentage of women working outside the home, as well as hourly wage rates, may result in an underestimation of costs. In addition, nonprescription drug costs may be higher than assumed. This is supported by the findings of another study that found an average cost for nonprescription drugs of $12.50/case.[18] Other costs for prescription drugs are most likely underestimated in 1996 terms. Vaccine cost to pharmacies and physicians in 1995 was approximately $39/dose.[12]

Although assumptions varied among the cases, the authors of this study concluded that vaccination saves costs from a societal perspective and that the main factors driving the analysis are costs of the vaccine and of home care. Although their overall conclusions appear reasonable, and this model appears to be robust with regard to the assumptions subjected to sensitivity analyses, other potentially important assumptions remain untested. The degree of cost-benefit reported here is questionable.

A study examined a hypothetical cohort of 100,000 children.[16] In this model, the direct cost from an unvaccinated cohort was estimated at about $1.8 million, with estimated work loss costs of $10.3 million, not including the cost of nonprescription drugs. In a vaccinated cohort, almost all of the $4.8 million would be for vaccine acquisition and administration, representing a savings of about $7.3 million.

To test the robustness of this model to certain assumptions, the authors performed several sensitivity analyses.[16] The base case consisted of giving one dose of a 95%-effective vaccine at age 15 months. The vaccine's efficacy rate was tested

at 80% and 100%, costs of treating chickenpox were raised and lowered by 50% relative to the base case, a second dose of vaccine at age 12 years was added, and the costs of work loss were decreased by 50%. As vaccine efficacy increased, net costs of medical care decreased. Addition of an booster dose nearly doubled net medical costs. Increasing the costs of treating infection resulted in lower net medical costs, and lowering the cost of work loss produced no effect on net total costs compared with the base case. All changes resulted in a net decrease in total costs.

The strength of the included assumptions bears examination. Vaccine efficacy has not been categorically determined; it is thought to approximate 95%. The authors assumed a vaccine price of $35; as previously noted, the 1995 acquisition cost of the vaccine was approximately $39/dose for physicians and pharmacies.[12] The value of a lost day from work was obtained from 1991 average weekly earnings for women and may underrepresent the 1996 value. This model is the only one for which the effect of adding a second dose of vaccine was reported.

In another model of this type, a hypothetical birth cohort of 4 million individuals over a 30-year period was examined to project cost-effectiveness of routine vaccination in otherwise healthy, American, school-age children.[17] The authors estimated that a vaccination program would save $0.90 and $5.40 for each dollar spent from payers' and society's perspectives, respectively.

In this model, sensitivity analysis was done for three main assumptions: vaccination coverage rates, vaccine efficacy, and vaccine price and administration strategy.[17] Other assumptions, including those pertaining to a two-dose strategy and a combination varicella-measles-mumps-rubella vaccine, were tested but not reported. The base case primary assumptions were one dose of 90%-effective vaccine would be given to 97% of 6-year-old children and its price was $35. As the level of coverage reached in the target population by the age of 6 years increased, the cost of each year of life saved dropped from $7400 at the 50%-coverage level to $2900 at the 70% level and $2500 at the 97% level. The 70%-coverage level was slightly more cost effective than the 97%-coverage level. When coverage was assumed to be 97%, the net medical cost/case increased linearly by 58¢ and the cost/life-year saved increased by $683 for each dollar increase in vaccine price. Efficacy varied from 95–83% of recipients, with complete protection 6 weeks after vaccination. At the base case coverage rate of 97%, benefits, costs and cost-effectiveness ratios were all insensitive to changing assumptions of vaccine efficacy.

In the base case, vaccine efficacy was assumed to be 90%.[17] This has not yet been shown definitively, but, as previously noted, is thought to approximate 95% in clinical trials.[7–10] It is probably unnecessary to vaccinate 97% of 6-year-olds. Unless mandated by law, it is also probably unlikely to occur. The assumed vaccine acquisition price is lower than the current amount.[12]

Discussion

Evaluations of the economic consequences of varicella vaccination have been done in several populations and in comparison with serotesting.[19–22] In addition, evidence from three such evaluations in healthy children indicates that primary prevention is cost-beneficial from society's, but not a payer's, perspective. In populations at high risk for complications, such as immunocompromised patients, it is cost-beneficial from both perspectives.

In determining costs and benefits of vaccination against varicella, perspective is critical. Most projected varicella-related costs are not due to treatment, but rather to time spent by caregivers away from the workplace, or in terms of the opportunity costs of not being able to pursue productive activities at home. In these terms, avoidance of missed work or, more frequently, missed school may be expected to result in decreased varicella-related costs.

Caregiver and patient preference is an important consideration that has yet to be examined in the published literature. Benefits of the vaccine include avoidance of infection and potential sequelae, and decreased or no time lost from work. However, the potential severity of primary infection and the chance of sequelae increase with age, so a person may be at increased risk if the disease occurs because the vaccine does not confer lifetime immunity, or if booster doses are not given appropriately. It may be reasonable to give one or more booster doses at well-defined intervals throughout a person's life, as this may prevent primary and, possibly, secondary varicella infection, but this has been described in only one published study to date.[16]

The difficulties associated with this course of action are many. An optimally beneficial interval

between immunizations has not been determined. Thus if the actual interval is too long, the costs to society and payers would be expected to increase due to unforeseen varicella infections and possible sequelae in adolescents and adults. In addition, not all people will adhere to revaccination recommendations.

Costs directly attributable to vaccination make up the primary component of direct medical costs. Changes in dosing recommendations would be expected to affect the cost effectiveness and benefit:cost ratios; however, it is not clear to what degree they would change with administration of one or more additional doses. Although total costs would increase, one investigator found that a vaccination program with one booster dose would still result in savings from a societal perspective. It is not known what would happen if more than one booster dose were necessary.

Some investigators attempted to forecast costs for a period of 25–30 years. This presents at least two problems. One is that predicting the behavior of economies is inherently difficult. Techniques such as adjusting for inflation and discounting, controversial in themselves are widely applied to try to improve estimates.[23] They are not foolproof, but they are the best tools currently available. The other conundrum is that, although long-range forecasting may produce impressive looking results, payers and individuals want to know how adopting a particular program will affect them in the short term. This is particularly important when considering that it is in the early phases of a vaccination program that the largest share of expenses is incurred, including hiring new staff and providing new facilities, if necessary.

Conclusion

Current data indicate that the varicella vaccine is cost-beneficial from the perspective of society but not from that of the payer. Considerable uncertainty remains and will not be eliminated without significant clinical experience and additional research. At present, however, it is reasonable to adopt a societal perspective with regard to varicella vaccination specifically and to immunization in general. Otherwise, the payment decision favors no vaccination despite strong clinical evidence of safety and efficacy. Vaccination against hepatitis B virus (HBV) is an example of this. Although HBV disease is relatively uncommon even in high-risk groups, it may result in serious public health and individual consequences. In varicella as well, decreased societal costs due to vaccination outweigh the decrease in costs expected with no vaccination.[24]

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