Varicella is a highly infectious disease that caused more than 4 million cases, 11,000 hospitalizations, and 100 deaths each year in the United States before the availability of a varicella vaccine [1]. Since 1996, the Advisory Committee on Immunization Practices has recommended routine childhood vaccination to prevent varicella. The subsequent impact of a childhood vaccination program has been dramatic in the United States, with significant decreases in deaths, hospitalizations, and ambulatory visits in all age groups, including adults [2–4].

The optimal approach to varicella vaccination in adults is uncertain. Adults are more likely than young children to experience severe morbidity and mortality from varicella disease. However, population seroprevalence estimates for varicella in the United States performed before 1996 suggested that 96% of 20–29-year-old adults and 99% of adults ≥30 years old were immune to varicella [5]. Thus, the usefulness of a routine vaccination program for adults would likely be limited. Another possible approach would be to perform serological testing for adults to determine the presence of immunity to varicella and vaccinate only susceptible adults. However, serological testing requires that an initial blood sample be obtained and assumes that individuals will return for vaccination if they are susceptible to varicella, resulting in potential missed opportunities to vaccinate those who do not return for a second visit.

In this issue, Merrett et al. [6] conducted a cost-effectiveness analysis to determine the optimal approach to vaccination of adult immigrants and refugees arriving in Canada. This population of adults is particularly interesting, in that immigrants and refugees are disproportionately susceptible to varicella, compared with adults from industrialized countries. This paradoxical finding has been postulated to be attributable to the higher ambient temperature of tropical climates (which perhaps inactivates varicella zoster virus in cutaneous lesions), epidemiologic interference caused by the high prevalence of other childhood viruses and rural living conditions, which may be a marker for the degree of social interaction within and between communities [7–9].

Merrett et al. [6] do an excellent job of including primary data available to them regarding the seroprevalence of varicella in their immigrant and refugee population in Montreal, Canada, on which much of this analysis is critically dependent. By focusing on this high-risk adult population, they found that selective serological testing followed by vaccination of susceptible 30-year-old adults was cost-saving in the base-case analysis. Other strategies were either more costly and less effective or had cost-effectiveness ratios that exceeded $100,000 per quality-adjusted life-year, a commonly used benchmark for cost-effective interventions. Selective serological testing and immunization also prevented one-half of congenital and neonatal varicella cases.

However, as with all cost-effectiveness analyses, the results of the model depend on the baseline estimates chosen, and bias may be introduced in this way. To understand what is inside the black box, we must take a critical look at the sensitivity analyses performed. In the model used by Merrett et al. [6], the results were critically dependent on 2 parameters: the annual varicella attack rate and the rate of varicella susceptibility. If the annual varicella attack rate was ≥3.8% among susceptible adults or if ≥5% of the population was susceptible to varicella (i.e., if >95% of the population had varicella antibody), then selective serological testing was no longer cost-saving.

A closer look at these assumptions highlights their uncertainty. The annual attack rate among susceptible adults was assumed to be 7%, which seems quite high, particularly in the post-vaccine era. This estimate was based on the force of infec-
tion from another published study [10]. However, varicella transmission dynamics are likely to be different in the era of universal childhood vaccination. On one hand, the circulation of varicella in the population may be lower, resulting in fewer opportunities for exposure and perhaps a lower risk of contracting varicella, even among susceptible adults. On the other hand, there is concern about the possible accumulation of young adults with partial or complete primary vaccine failure occurring in conjunction with reduced opportunities for natural boosting from the community. This growing pool of susceptible individuals may place young adults at higher risk of disease from outbreaks, because it is unlikely that varicella will be eradicated anytime soon.

The results are also dependent on varicella susceptibility rates. Selective serological testing followed by vaccination appears to be cost saving or cost-effective for younger adults, who are less likely than older adults to be immune to varicella. This age dependency was also seen in several other cost-effectiveness analyses, supporting the need for empirical data regarding the population being studied [11, 12]. Another parameter that was not fully explored in sensitivity analyses was vaccine cost. Merrett et al. [6] assumed a cost of Can$26.75 per dose, compared with current US private and public sector prices of US$71 and US$57 per dose, respectively. Finally, the inclusion in the model of productivity costs attributable to death is of concern. By definition, mortality is incorporated into the denominator of quality-adjusted life-years as the effectiveness measure [13]. Thus, including a monetary value for lost life in the numerator as well as loss of quality-adjusted life-years in the denominator effectively counts patients who have died from varicella twice, which is a significant limitation of this study.

So, what can we conclude? First, cost-effectiveness analysis is a helpful tool when making decisions about programs or policies for large populations. On the basis of this and other analyses, selective serological testing of adults with a negative or uncertain history of varicella, followed by vaccination of those who are found to be susceptible, appears to be a reasonably cost-effective and perhaps even a cost-saving approach for younger adults, immigrants, and refugees. Second, cost-effectiveness analysis can highlight areas of uncertainty to which future research efforts should be directed. For example, further work is needed to understand the impact of a childhood vaccination program on the transmission of varicella in the population and the potential for an increased pool of susceptible adults to further inform the optimal approach to vaccinating adults. Finally, this work highlights the growing need to strengthen the infrastructure of adult immunization programs, especially given the addition of tetanus, diphtheria, and acellular pertussis vaccine and herpes zoster vaccine to the list of recommended vaccines for adults in the United States. The current vaccine financing system relies on a patchwork of private and public funding, and many gaps exist, particularly for uninsured and underinsured adults. Additional resources are needed to implement and strengthen vaccination programs for all adults to overcome these barriers; otherwise, many individuals will be left unvaccinated, despite the rational development of vaccination policies.

Acknowledgments

Financial support. Agency for Healthcare Research and Quality (K-08 HS013908-01 A1).


References