A Model for Estimating the Impact of Changes in Children's Vaccines

ABSTRACT

Objectives. To assist in strategic planning for the improvement of vaccines and vaccine programs, an economic model was developed and tested that estimates the potential impact of vaccine innovations on health outcomes and costs associated with vaccination and illness.

Methods. A multistep, iterative process of data extraction/integration was used to develop the model and the scenarios. Parameter replication, sensitivity analysis, and expert review were used to validate the model.

Results. The greatest impact on the improvement of health is expected to result from the production of less reactogenic vaccines that require fewer inoculations for immunity. The greatest economic impact is predicted from improvements that decrease the number of inoculations required.

Conclusions. Scenario analysis may be useful for integrating health outcomes and economic data into decision making. For childhood infections, this analysis indicates that large cost savings can be achieved in the future if we can improve vaccine efficacy so that the number of required inoculations is reduced. Such an improvement represents a large potential "payback" for the United States and might benefit other countries. (*Am J Public Health.* 1995;85: 1666–1672)

Kit N. Simpson, DrPH, Andrea K. Biddle, PhD, and N. Regina Rabinovich, MD, MPH

Introduction

Childhood infectious diseases still represent a grave threat to our nation's children. Efficacious vaccines for some of those diseases have been available for a number of years, yet a relatively large number of children are not vaccinated and, consequently, are at risk of contracting the diseases. While the vaccination rate of children enrolling in school is greater than 95%, vaccination rates among preschool-age children in some areas are relatively low. In two retrospective surveys of schoolchildren in nine inner cities and other localities, the proportion of 2-year-olds who were up-to-date with immunization ranged from 11% to 61%.[1,2] Among the reasons for these low rates are providers missing opportunities for vaccinating children when those children are seen for other reasons, the increasing number and complexity of vaccine schedules, the cost of vaccinations, publicity about alleged adverse reactions, and perhaps the perception by parents that childhood diseases are not serious threats to health.[3,4]

Various efforts are being undertaken to improve the level of vaccination among children; notable among them is the Children's Vaccine Initiative. The primary goal of this global program is to support the development of safe, affordable, and heat-stable vaccines that can protect children against the major infectious childhood diseases with a small number of doses given orally early in life. As part of this effort, the National Institute of Allergy and Infectious Diseases (NIAID) has augmented its role as the lead Public Health Service agency for vaccine research. As might be expected, the Children's Vaccine Initiative entails a complex technical and scientific agenda with a large number of components, including the improvement of existing vaccines (e.g., enhancement of efficacy, reduction in vaccine-related adverse events) and the development of new vaccines. There are important ethical and safety reasons for improving selected characteristics of vaccines. However, in an era when funds for research and development are scarce, if they exist at all, it is also important to understand the potential cost implications of improving selected vaccine characteristics.

Research toward initiative goals is being conducted in both the public and private sectors. For decisionmakers within both sectors, strategic planning concerning which research projects to fund is important, and may be improved by knowledge about the effectiveness and costs associated with vaccine programs and about how certain vaccines may affect the incidence and cost of childhood disease. In particular, policymakers must first consider how the "best" value for research investment can be obtained. Is the impact and/or savings greater if a vaccine's efficacy is improved so that one less inoculation is required for immunity, or are benefits and savings greater if the adverse event rate is improved? They

Kit N. Simpson and Andrea K. Biddle are with the Department of Health Policy and Administration, School of Public Health, University of North Carolina at Chapel Hill. N. Regina Rabinovich is with the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Md.

Requests for reprints should be sent to Kit N. Simpson, DrPH, School of Public Health, University of North Carolina at Chapel Hill, Campus Box 7400, Chapel Hill, NC 27599-7400.

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must then consider whether these decisions are interactive. In the case of a multicomponent vaccine (e.g., diphtheria–tetanus–pertussis [DTP]), if one component can be improved so that fewer doses are required, can the other components confer immunity in fewer doses? If not, what types of improvements can maximize immunity for all components in the vaccine?

To assist in this strategic planning process, we have developed an economic model that estimates the potential impact of vaccine innovations on the incidence of childhood illness and the total cost associated with vaccination and illness in the United States. In its current formulation, this model has been tested with three vaccines—DTP, *Haemophilus influenzae* type b (Hib), and measles–mumps–rubella (MMR).

There are several potential uses for the model. It may provide data to inform planning and policy decisions at various levels of the federal government. It also may serve as an organizing framework for comparing and discussing seemingly unrelated vaccination efforts and as a basis for evolving a standardized framework for the analysis of vaccination programs. Selected examples of such uses include the following:

1. Estimates of "payback" from research efforts that contribute to different types of improvement (e.g., disease specific vs generic)
2. Estimates of how the use of potential new vaccines may affect costs and outcomes, given a specific set of epidemiological assumptions
3. Examples of how the use of funds for current vaccination programs and/or vaccine research programs may affect overall costs and outcomes in the short- vs long-term horizon
4. Information needed for price-setting discussions or other negotiations with vaccine manufacturers

Methods

Process of Model Development

The model developed for this project is the result of a multistep, iterative process of extracting and integrating data from the literature and NIAID documents, and of combining these data with expert assistance from NIAID staff. The first step in the modeling process was a comprehensive review of the literature for each of the seven childhood diseases and the three vaccine combinations: DTP, Hib, and MMR. The purposes of this review were (1) to obtain sufficient information to develop a model of the immunization process for each vaccine, and (2) to determine parameters for inclusion in the model.

MEDLINE was used to identify all papers published between 1986 and 1992. From these articles, all major studies and summary reports published prior to 1986 were identified and retrieved. Rather than reintegrating all individual study results as part of the modeling process, our search focused on reviewing articles that summarized the state of knowledge for each vaccine/disease. While this approach left us open to accepting erroneous interpretations made by others, it made the model reflect currently accepted data in the field. This literature review was supplemented by NIAID documents and information received during the initial meeting with our NIAID project officer. At this meeting, the basic assumptions of the model were discussed, and the analytical perspective was selected.

A prototype model of the vaccination process was then developed. This model incorporated information from the literature review, and used the principles and techniques of clinical decision making and operations research.[5] After the initial model was formulated, it was presented to NIAID staff for review and comment. Of particular interest was whether the model accurately reflected the flow of children through the vaccination process from the first inoculation through the final or booster inoculation and whether the parameters that had been chosen from the literature review were acceptable, up-to-date figures.

The pertussis model was developed first; it then served as the basis for the other diseases. NIAID staff with expertise in each of the disease entities reviewed a written and graphical summary of the model along with tables with model parameters and their sources. Queries and comments were forwarded to us, and the model assumptions/parameters were adjusted as needed. The conceptual model, assumptions, and parameter estimates were then presented to a group of NIAID staff and invited experts. The model was further refined based on the discussion at the meeting. This sequence of written reports and face-to-face discussions was repeated for each disease/vaccine component. The process lasted 18 months and involved three sets of written reports, eight group meetings, and 10 to 12 telephone conferences before the current edition of the model was finalized. (Further modifications and additions to the model presented here are planned.)

The comments and insights thus generated were incorporated in the final model, which was then adapted to seven diseases and modified to accommodate the combined vaccines. Several scenarios were developed, and the number of cases of disease and adverse events and the costs savings associated with these scenarios were estimated.

The Conceptual Model

The construction of the model was based on a simplification of the knowledge and understanding of how public investment in vaccine research will eventually influence the mortality, morbidity, and costs related to infectious diseases and vaccination programs. The model severely telescopes reality in that it assumes we can invest today and reap the health benefits and economic improvements tomorrow. This is done to illustrate for the decision maker the impact of a change using familiar practice conditions; it is easier for decision makers to grasp the impact of their choices if those choices are shown in terms of the current costs and problems. All diseases are treated identically in this regard. This simplification allows us to avoid the difficult task of predicting the morbidity and mortality states that may exist many years in the future. The model does not attempt to identify the amount or type of investment needed to achieve an improvement; rather, it identifies the potential improvement in terms of current information. The basic conceptual framework used in designing the model is shown in Figure 1.

The model estimates events and costs occurring during one calendar year for all US children under age 5. In the current practice scenarios, the selected risks of disease and adverse events are applied to the age distribution of children presented in the 1990 US Census.[6] Vaccine coverage rates are not assumed to be 100%; the actual value depends on survey reports[1,2] for the specific disease/vaccine.

The number of cases and the disease costs estimated in the model are driven by two sets of probabilities: (1) that of being successfully vaccinated, and (2) that of contracting disease given the lack of immunity. Vaccination program costs and benefits are influenced by the number and cost of inoculations required, the probability of adverse events, and the unit cost of these events. The costs and benefits

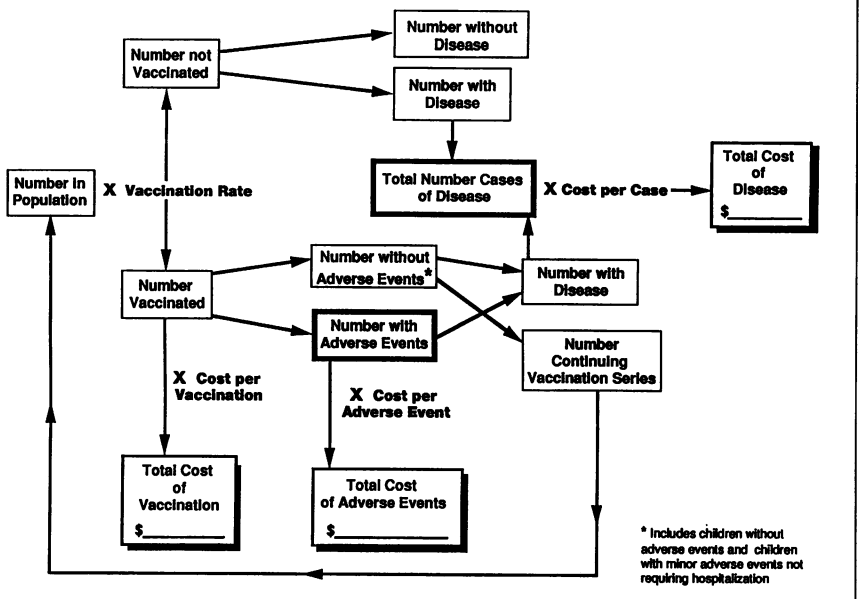

FIGURE 1—Schematic vaccination model.

estimated by the model are those that would be expected for a calendar year if a change in vaccination practice occurred at the beginning of the year.

All costs provided are total costs for vaccination, disease, and adverse events. The benefits and costs included in a scenario are assigned to the respective vaccine component according to the distribution of events. Costs related to the administration of a trivalent vaccine are assumed to be distributed equally between the components. The scenarios examined in this paper assume that the three components in a combined vaccine are improved so one dose is avoided while protection remains the same. All costs and benefits in the model are for 1 year only and are reported in 1991 "present value" using a discount rate of 6% per annum for any required adjustments of dollar and life expectancy values.

Assumptions

The assumptions made in the development of the conceptual model attempt to err on the conservative side but will ultimately depend on the scenario estimated. Thus, the results of the base model can be considered a lower bound on, or minimum expectation of, the costs and health impacts of implementing a specific improvement in vaccine technology. It was assumed that the baseline for any improvement is current practice in the United States, and that vaccinations are given as specified by the Immunization Practices Advisory Committee. Related to this assumption is the use of marginal analysis; that is, the marginal costs or cost savings associated with moving from current practice to the implementation of some improvement in technology (e.g., a reduction in the number of inoculations required to fully immunize a child) were examined. Marginal analysis allows the policymaker to evaluate the relative value of investments in vaccine research-related changes in technology compared with the status quo. The analyses have been limited to children 4 years of age and younger because immunization for universally used pediatric vaccines occurs during this period.

The costs of vaccination were examined from the perspective of the health care system rather than from that of society as a whole. Accordingly, only the direct costs of physician and hospital care required to treat childhood illnesses and vaccine-related adverse events were examined. For children who sustain conditions that require lifetime medical or custodial care as the result of either illness or vaccination, the costs of this additional care have been included. However, neither the costs of pain and suffering that might be incurred as the result of disease complications or adverse events, nor the costs associated with productivity lost by society as the result of premature death were incorporated. Since costs were defined from the perspective of the health care system, any costs associated with work loss for parents as a result of illness or adverse events were also omitted. Readers should note that such costs could be substantial; Bloom and colleagues[7] found that family out-of-pocket expenses added 50% to the total cost of care for children with cancer. Consequently, our model underestimates the benefits of vaccination and the costs of illness to society as a whole.

Finally, where available, the cost of actual resources utilized rather than the charges for these resources were applied. Because of difficulties in identifying "true" costs in some cases, only approximations of costs based on current reported charges could be used. However, the most important costs in the model, those for the vaccine dose and its administration, are based on our estimate of the resources lost to other uses by the health care system as a result of vaccination efforts.

Sources of Parameters

Parameter values were derived from several sources. The literature reviewed during the initial stages of the project yielded data on vaccine efficacy and effectiveness,[8–14] vaccine coverage rates,[1] and rates of adverse events[14–16] and disease complications.[15,17–22] Rates of adverse events for the seven diseases were supplemented with information from the 1993 Institute of Medicine report.[23] Age-specific disease incidence rates for all diseases except measles were calculated with case data from the annual *Summary of Notifiable Diseases,*[24] population size estimates from 1990 US Census data,[6] and an estimate of underreporting.[25] The incidence of measles was assumed to be the average for the years 1984 through 1992 (6621 cases for ages newborn to 4 years). This figure was chosen because our base year, 1990, was an epidemic year for measles.

The costs of adverse events and disease complications were based on published studies of the cost–benefit/cost-effectiveness of the specific vaccine, whenever possible,[15,17,26] and from vaccine injury compensation awards[27] provided through the Vaccine Injury Compensation Program. These data were validated and/or supplemented with data on the costs of hospitalization from an analysis of Maryland hospital discharge data[20] for 1985 through 1989, and with data on visit charges for Medicaid and Medicare populations.[28,29] The cost of a vaccine is defined as the dose cost less the surcharge

collected for each dose; this is because the surcharge is a transfer of funds from the vaccine manufacturer to the Vaccine Injury Compensation Program to cover the risk of vaccine-related adverse events. Vaccine dose costs (bulk purchase and catalogue) were obtained from the Division of Immunization at the Centers for Disease Control and Prevention (CDC) (personal communication, Robert Snyder, September 1992). Published vaccine administration cost estimates[4] were adjusted for inflation with the medical care component of the consumer price index.[30] Vaccination and disease rate estimates from published documents were reviewed with NIAID staff, and the final model estimates were chosen after group discussions of the strengths and weaknesses of the available data. The case frequencies assumed in the model are provided in Table 1; other disease-specific parameter estimates are on file with the first author.

TABLE 1—Expected Disease Cases for the Model and Reported US Cases for 1991, 1992, and 1993[a]

Disease	Aged Newborn to 4 Years Model Cases[b]	Reported Cases: All Ages[a] 1991	1992	1993
Diphtheria	6	5	4	0
Hib	3126	2764	1412	1419
Measles	6049	9643	2237	312
Mumps	1109	4264	2572	1692
Pertussis	6391	2719	4083	6586
Rubella	112	1401	160	192
Tetanus	5	57	45	48

[a]From Centers for Disease Control and Prevention.[37]
[b]Assumes 50% underreporting of cases to the CDC.

Source of Scenarios

For each of the vaccines examined, at least one scenario (i.e., an assumed improvement in vaccine technology resulting in a change in the recommended vaccine schedule) was analyzed. For example, a scenario may involve a change in the formulation of the vaccine (e.g., the use of an acellular pertussis vaccine), an improvement in the vaccine such that the full immunity can be achieved with fewer inoculations (e.g., DTP, Hib), or an improvement that allows the inoculation to be given at an earlier age (e.g., MMR). These scenarios were developed jointly with NIAID staff who have expertise with particular childhood vaccines. The scenarios are not exhaustive of the possibilities for future vaccine improvement; their purpose is to demonstrate the potential impact of improvements and thus help focus strategic discussion.

Sensitivity Analyses

Sensitivity analysis using the pertussis part of the model was employed to test the consequences of changes in model parameters and assumptions. Of particular interest were the effects of changing both the vaccine administration cost estimates and the incidence of pertussis hospitalizations and deaths. Our final model for both scenarios used $8.33[4] as an estimate of vaccine administration costs. Because estimates of administration costs in the literature are relatively scarce or of questionable validity, the model was then recalculated with administration costs ranging from $5 to $44 (the approximate cost of a physician visit). However, these variations were found to have a surprisingly moderate effect on the results of the model because the baseline and scenario costs change together when administrative costs are varied. That is, while the costs of each inoculation are important, they influence total costs much less than the frequency with which inoculations are given. Also examined was the sensitivity of the model to changes in the incidence of disease. The model was found to be somewhat responsive to variations in diseases with high incidence and much less affected by low-incidence disease, as expected. This variation is important in light of recent studies of the completeness of disease reporting for pertussis[25] and measles,[31] for epidemics of measles in 1989 and 1990, and for pertussis in 1993.[32]

Results

Some estimates from the model are presented in Table 2. Change scenarios are described separately for each type of vaccine to illustrate the data generated by the model.

DTP Vaccine

Current practice[33] assumes that children under 5 years of age receive inoculations at 2, 4, 6, and 15 to 18 months, and just prior to fifth birthday, with the recently approved acellular formulation used for the fourth and fifth inoculations.[34] The first scenario illustrates the impacts expected if the acellular vaccine, a significantly more expensive formulation, is used for *all* inoculations. At a cost of $118 million annually, which includes the costs of inoculations, disease, and vaccine-related adverse events for children under 5 who would receive their shots during that year, we reduce adverse events associated with vaccination by about one third from the current level. Implicit in this scenario is the assumption that the acellular formulation can be modified to be given to children under 15 months of age and still achieve the same level of immunity observed in older children. The second scenario moves us incrementally from a world where children are given five acellular inoculations, with three required for the same or a greater level of protection, to one in which children are given only four inoculations, with two needed (at 2 and 4 months) to achieve full immunity. Such an improvement (other things held constant), in the conditions specified in scenario 1, would result in approximately 800 fewer cases of diphtheria, tetanus, or pertussis; an additional decrease of 13% in vaccine-related adverse events; and savings of $90 million annually.

Hib Vaccine

The current Immunization Practices Advisory Committee inoculation schedule for Hib recommends that the vaccine be administered as two to three doses beginning at age 2 months and then as a booster at 12 to 15 months.[13] Under this schedule, our model predicts a total of 3126 cases of Hib, including 131 fatalities, and $506 million annually in total direct costs of vaccination and medical care (Table 2). If the vaccine is improved so that the inoculation at 6 months is no longer required to achieve immunity (scenario 3), the model predicts 493 fewer cases and 20 fewer fatalities than would be expected under current practice. In addition, total costs associated with vaccination and medical care would decrease by $105 million annually.

TABLE 2—Annual Outcomes and Costs Estimated for Current Vaccination Practice for Children under Age 5 Years, and Changes from Baseline in Events and Costs Resulting from the Hypothesized Vaccine Improvement Scenarios

Baseline/Model Scenario	Cases of Disease	Adverse Events	Deaths	Annual Base Costs and Increases/(Savings)
Current practice: DTP[a] estimates	6402	142 325	9	$343 536 253
Scenario 1 (DTP): use DTaP for all 5 inoculations	No change	Reduced by 47 368	No change	$117 790 530[d]
Scenario 2 (DTP): use 4 DTaP inoculations but achieve similar levels of immunity	Reduced by 804	Reduced by 18 646	Reduced by 1	($90 019 450)[e]
Current practice: Hib[b] estimates	3126	0	131	$505 876 690
Scenario 3 (Hib): inoculation at 6 mo no longer required to achieve immunity	Reduced by 493	No change	Reduced by 20	($105 235 417)
Current practice: MMR[c] estimates	7270	87	14	$185 566 669
Scenario 4 (MMR): inoculation at 4 y no longer required to achieve immunity	Reduced by 300	Reduced by 41	Reduced by 1	($85 964 953)
Scenario 5 (MMR): change that allows children to be vaccinated with one dose at 6 mo	Reduced by 3817	Reduced by 7	Reduced by 7	($11 963 056)[e]

Note. DTP = diphtheria–tetanus–pertussis; DTaP = acellular vaccine; MMR = mumps–measles–rubella.
[a]Three whole-cell DTP doses at ages 2, 4, and 6 months, with two doses of DTaP at 18 months and 4 years.
[b]Four doses of Hib vaccine at 2, 4, 6, and 18 months.
[c]Two doses of MMR at 18 months and 4 years.
[d]Figures in parentheses denote cost savings.
[e]Figures are marginal or incremental costs from those associated with the previous scenario.

MMR Vaccine

Current guidelines for MMR vaccine recommend that children receive a total of two doses, with the first administered at age 15 months followed by a booster dose given just prior to school enrollment.[35,36] As seen in Table 2, the model predicts that under current immunization guidelines, nearly 7300 cases of measles, mumps, or rubella would occur annually, resulting in 14 deaths, with nearly 90 children experiencing vaccine-related adverse events. Currently, the model predicts an annual total cost of $186 million for inoculations, vaccine-related adverse events, and medical care associated with measles, mumps, and rubella cases. If the MMR vaccine is improved so that we achieve current levels of immunity with only one inoculation given at 15 months (scenario 4), then 300 cases of measles, mumps, or rubella are avoided and adverse events and annual cost decrease by nearly 50%. If the vaccine is further improved so that immunity is achieved with one dose at 6 months (scenario 5), then disease cases and deaths are reduced to approximately one half of current levels and a small cost savings is found.

Discussion

In the process of defining and discussing this model, we gained insight into some important aspects of interactions between children's vaccination schedules, disease and adverse event incidence rates, and the related costs of medical care. The dynamics between these factors and the variables that influence outcomes and costs were not obvious prior to the modeling effort.

For example, we expected to find that an increase in vaccine efficacy and safety would improve both costs and outcomes greatly. The model clearly suggests that efficacy changes should not be expected to result in significant cost reductions unless they enable us to diminish the number of inoculations. Furthermore, a reduction in adverse events might not influence current costs. It seems that the major economic impact of a change in risk might be more long term, with much of it related to a reduced need for funds to support cases that come before the Vaccine Injury Compensation Board and thus a decrease in the vaccine surcharge over time.

The importance of pricing policy for new products is illustrated by the pertussis scenarios. An improvement in vaccine safety (e.g., the change from using whole cell vaccine to acellular preparations) may decrease vaccine-related adverse events by one third. Because the current price for the acellular preparation is nearly 2.5 times the price of the whole cell preparation, the cost increase is only partially offset by savings from adverse events, and total costs increase by one third.

The results of the modeling clearly indicate that the most powerful economic impact of potential vaccine improvement is related to our ability to decrease the number of inoculations required in a series. The removal of an acellular booster shot from the DTP series decreases overall costs by 20%, from $461 million to $371 million. In the MMR series, removal of the booster dose reduces overall costs by 46%. While vaccine policy has been and should continue to be based on safety and efficacy considerations, the availability of economic information, such as that produced by this model, may assist policymakers in making difficult allocative decisions between competing, worthy research projects.

A model is a simplified representation of reality, and as such, it will never be able to capture every important aspect of complex relationships. We chose to construct a strategic decision model that captures the essence of current practice conditions and avoids the use of complex epidemiological or economic formulas. This makes the model more transparent and useful to decision makers, but it also requires that accurate epidemiological data on disease and vaccination of US

children are available as model *inputs*. The model is designed to inform specific vaccination program investment choices. It is not sophisticated enough to replace epidemiological population models for predicting epidemic impacts, nor is it designed to replace descriptive models for assessing the basic cost-effectiveness of one vaccine compared with another or with other competing health interventions.

Several limitations of the model and of the data on which it is based should be considered when interpreting the model results. The incidence of several of the diseases of interest in the United States is so low that their treatment is no longer part of the standard practice of US physicians. This increases the potential for late diagnosis, poor prognosis, and the underreporting of events, and the available data on these diseases therefore may not adequately capture the risks and cost of these diseases. We have assumed a general level of 50% underreporting of cases in the model. It is quite possible, however, that underreporting is greater than 50%, in which case the model will underestimate both the disease impacts and the disease costs.

Because the model limits the estimation of impact to a population under the age of 5 years, it will not capture morbidity, mortality, or costs specific to disease manifestations in adults. This is especially of concern for a disease such as rubella, in which the health impacts and costs related to arthritic conditions, spontaneous and induced abortions in infected women, and other adult manifestations are omitted.

It should be recognized that the model assumes a "steady state." That is, we assume that the disease and vaccination levels in the scenarios have been in place for a minimum of 4 years prior to the estimate. We also assume that the disease is at a relatively low point in the epidemiological cycle that exists for most of these diseases. It is especially important to remember this assumption when interpreting the results for measles, because the model uses the mean incidence for the years 1984 to 1992, not the high incidence rate observed during the recent outbreak.

The assumptions made in the model undervalue the cost of these diseases to society because they do not include costs to patients, caregiver time, and pain and suffering. The model is also limited in its ability to reflect cost changes that might relate to changes in medical care infrastructure (e.g., the need for isolation units in hospitals or cost changes related to the primary care system). Furthermore, it excludes costs incurred by health departments and the CDC for the management of epidemic outbreaks and case finding.

The development of this model helped identify the factors that must be considered when planning improvements in current vaccine use. The scenario analysis points to the great potential for effecting cost savings in the future if we find the means to improve vaccine efficacy so that the number of required inoculations is reduced. Such an improvement has a large potential payback for the United States and may be expected to benefit other countries as well. □

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Wisconsin Releases Advanced Practice Nurse Public Use Data File

The State of Wisconsin Office of Health Care Information (OHCI) has released the Advanced Practice Nurse (APN) Public Use Data File. The data file contains responses from an Advanced Practice Nurse Profile Survey conducted in the fall of 1994. Included in the survey were all registered nurses licensed in Wisconsin who had identified themselves on OHCI's 1993 Nurse Profile Survey as one, or more, of five types of APN: certified nurse midwife (CNM), certified registered nurse anesthetist (CRNA), nurse practitioner (NP), clinical nurse specialist (CNS), and psychiatric nurse.

The survey collected detailed data on a wide range of practice characteristics. Among the topics covered are type of practice setting and ownership; participation in managed care organizations; number of patients seen weekly; hospital privileges; practice in areas with a shortage of health professionals; malpractice liability insurance coverage and cost; continuing education and plans to pursue bachelor's and master's degrees; reimbursement for services; cross-training and computer access; plans to change number of hours working; and role satisfaction.

Please contact Bob Purvis at (608) 267-0238 for more information.