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Editor's note: The thoughtful article by Dr. Andrus and his colleagues in describing the utility of the Pan American Health Organization's (PAHO's) ProVac model[1] reminds us of the startling childhood and adult disease statistics. Whether it is the 440,000 gastroenteritis annual deaths in children younger than age 5 or the 32,000 annual deaths from papillomavirus—with more than 80% in poor and developing countries—these numbers are staggering. Examples such as the experience in Mexico that was described by Santos et al.[2] show the ProVac model can work very well.

The authors suggest that three essential factors need to be addressed if agencies and governments are to attain a sustainable impact: decisions should be nationally based; evidence used to support the decisions must be broad-based; and infrastructure must be in place to support a nationally based process. The ProVac program objectives are rather aggressive, with just a five-year horizon to achieve a series of ambitious goals. At the same time, PAHO is honest: the organization recognizes it has little choice but to move in this direction. PAHO can serve as a model for the rest of the developing world. Lessons learned in the ProVac experience will serve many others well as they attempt a similar, if not more aggressive approach.

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A MODEL FOR ENHANCING EVIDENCE-BASED CAPACITY TO MAKE INFORMED POLICY DECISIONS ON THE INTRODUCTION OF NEW VACCINES IN THE AMERICAS: PAHO'S PROVAC INITIATIVE

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New and underutilized vaccines are becoming available to combat important public health challenges. Each year, rotavirus is estimated to cause approximately 111 million episodes of gastroenteritis, which requires home care, 25 million clinic visits, 2 million hospitalizations, and approximately 440,000 deaths in children younger than 5 years of age worldwide. Children in the poorest countries account for 82% of rotavirus deaths. An estimated 16,000 deaths by rotavirus-induced diarrhea occur annually in Latin America and the Caribbean.[1] Community-based longitudinal studies in Brazil demonstrated an incidence rate of 2.5 episodes of diarrhea per child younger than 5 years of age annually.[2] As rotaviruses occurred in 10% of cases, the mean annual number of rotavirus diarrhea cases per child younger than 5 years was 0.25.

In 2002, the Pan American Health Organization (PAHO) estimated that pneumococcal invasive disease killed 20,200 children every year in the region.[3] Incidence of invasive pneumococcal bacteremia has been documented as high as 212.2 per 100,000 children less than 2 years of age per year in Argentina.[4] These two childhood diseases, for which vaccines are currently available, cause substantial childhood morbidity and mortality in Latin America and the Caribbean.

In addition to new and underutilized vaccines for improving child survival, 32,000 women die each year from cervical cancer caused by human papillomavirus. Significant disparities exist among the subregions of the Americas as age-adjusted mortality rates of 16.0, 15.0, and 12.9 cervical cancer deaths per 100,000 population have been estimated for the Caribbean, Central America, and South America, respectively. These rates are also substantially higher than the 2.3 cervical cancer

deaths per 100,000 population in North America.[5] At a global level, it is estimated that more than 80% of cervical cancer deaths occur in women from resource-poor countries, where little to no cervical screening services are available.[6]

VACCINES LEAD TO HEALTH GAINS

The use of new or underutilized vaccines for these priority diseases presents opportunities to make substantial gains in health, thus bringing many countries closer to achieving the Millennium Development Goals (MDGs) adopted by the General Assembly of the United Nations in 2000. Among several goals adopted, priority goals linked to vaccine interventions include those related to reducing child mortality and improving women's health.[7,8] In particular, the MDG-4 for child mortality reduction specifically stipulates by 2015 a reduction of two-thirds of global deaths in children younger than age 5 compared to levels in 1990. The target then is to reduce child mortality from 95 per 1,000 children younger than age 5 in 1990 to 31 per 1,000 in 2015.

The relative value of these vaccines depends on the burden of disease, vaccine cost, and available resources for introducing the vaccines into National Immunization Programs. As burden of disease and resources available vary among countries and subregions, the decision to introduce these vaccines must be grounded in a greater body of evidence that reflects national conditions.[9,10] In contrast, national policy makers in some countries are making decisions for new vaccine introduction irrespective of the evidence available or necessary. Such actions risk undermining long-term program sustainability.

Vaccine decision-making

The current decision-making process has historically been driven by regional immunization priorities. Examples include initiatives such as polio, measles, and rubella elimination, and the expansion of childhood routine vaccinations to add Hemophilis influenza type b (Hib) and hepatitis type B (HB) vaccines into national immunization schedules in the Americas. The financial and logistical burden of newer vaccines on already constrained programs will require future decisions to be grounded in more rigorous methodology. Given the urgency to press these new vaccines into use, swift action must be taken to strengthen national decision-making.

Two recent country experiences in 2006 highlight our concern that decisions are being made irrespective of the evidence available. One country introduced varicella-zoster virus vaccine, despite disease burden data and preliminary economic analyses to suggest that pneumococcal and rotavirus infections may be of greater public health significance. Another, much poorer country decided to introduce rotavirus vaccine without addressing the system's capacity for including such a vaccine.

To ensure that future decisions for new vaccine introductions achieve the greatest sustainable impact, three essential factors must be addressed.

Decisions should be nationally based. As previously alluded to, the paradigm must be changed to expand from primarily regional decisions to national-based decisions. These decisions must be supported by national or subregional evidence. While the end products will be distinctly national approaches for new vaccines, regional technical cooperation will continue to play a critical role in supporting the generation of essential evidence and developing sustainable immunization policies.

Evidence used to support decisions must be broad-based. Regional immunization policy decisions have historically relied primarily on the burden of disease and vaccine efficacy; however, the higher cost of new vaccines will require a much broader evidence base ranging from cost-effectiveness and financial sustainability to health systems concerns (see next section).

Infrastructure must be in place to support nationally based processes. In the transition to primarily country-based decisions, national decision-making bodies must have the necessary technical capacity to ensure decisions are reached through rigorous and informed deliberations, drawing on the expertise of national advisory boards. To that end, Ministries of Health of some countries will need substantial organizational support to establish or strengthen these advisory boards.

Maximizing vaccine impact

Achieving the greatest impact with new and underutilized vaccines will require national decisions grounded in local information, representing an expanded body of evidence that is supported by the effective health infrastructure, such as advisory boards of national experts. This article describes some of PAHO's early experiences to strengthen the national capacity to make evidenced-based, informed decisions in the context of the introduction of new and underutilized vaccines, and summarizes a strategy to address the future challenges for sustaining programs when new vaccines introduced are orders of magnitude more expensive than the traditional vaccines.[11,12] The term ProVac is used in this article to capture this concept and serves as the name for the proposed initiative.

FRAMEWORK FOR VACCINE INTRODUCTION DECISION-MAKING

Ideally, when countries make evidence-based, informed decisions, they should be accounting for all the factors listed as follows.[10] Examples are included to illustrate their relevance.

Technical criteria

Disease burden. Pneumococcal disease kills more people than tuberculosis and malaria combined.

Characteristics of the vaccine. Vaccine characteristics include: immunogenicity and efficacy; duration of immunity; type-specific composition in vaccines that have multiple possibilities, such as conjugated pneumococcal vaccine; safety and adverse event profile; dosage and route of administration; and thermostability.

Adverse events and post-marketing surveillance. Most adverse events are mild, but the severe adverse events can be life-threatening and need to be rapidly identified and treated. Otherwise, public confidence in the program will be undermined with obvious future implications on effectiveness of program delivery and acceptance.

Cost-effectiveness and other economic evaluations. If economic analyses demonstrate that an intervention is cost saving, then it is very easy for a policy maker to make a decision, as was the case with rubella elimination. However, few newer public health interventions are truly cost saving. Cost-effectiveness analysis allows for the assessment of incremental costs needed to ensure health gains when compared to other strategies.

Programmatic and operational criteria

Vaccine supply. Maintaining long-term vaccine availability may have inherent impediments, such as technical difficulties in ensuring supply to meet the demand, or a small number of producers again putting supply at risk.

Logistical and operational issues. Single-dose vaccines packaged in large boxes may rapidly consume cold-chain capacity and impede the program's ability to go to scale on delivery, thereby limiting access to its benefits.

Financing strategies. Vaccines that are affordable are much more likely to be sustainable in the national program. More than 26 countries in the region have vaccine laws that require the nation to purchase introduced vaccines and mandate vaccines for the public good. Such laws also help sustain the program.

Partnerships. Support of partners during the initial phases of new vaccine introduction has proven important in some countries with poor or borderline economies. Such countries can then gradually assume responsibility for financing over time.

Social criteria

Perception of risk. Although the incidence of some diseases is rare (e.g., meningococcemia), society's perception of the disease consequences is vivid and could influence policy, particularly in a more affluent country.

Political will. High-level political commitment has driven the introduction of some vaccines regardless of the evidence available.

Equity. Many vaccine-preventable diseases disproportionately affect the poor, and immunization is an opportunity to prevent disease in underserved populations. The introduction of some vaccines will contribute to the reduction of health inequities.

CALL TO ACTION

To reach the best overall decision, most experts agree that all the factors previously described need to be critically assessed. However, over the last three years, managers of national immunization programs in the Americas have indicated that they need expanded support with some of these components, particularly cost-effectiveness and economic evaluations of interventions. Furthermore, a recent investigation into the use of economic evaluation studies in the decision-making process in health in Latin America demonstrated that despite increasing interest in introducing economic evaluations as a formal tool, there is little evidence of the conduct and use of these evaluations in most countries.[13]

To that end, with help from partners such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), in July 2004 PAHO conducted a Prevention Effectiveness Workshop to brief national immunization managers and epidemiologists on the aforementioned framework and, more specifically, on methodologies for conducting cost-effectiveness studies and interpretation of their results. In 2006, this meeting was followed up with a ProVac Workshop on Economic Analysis to Support Decision Making on Vaccine Introduction, which was supported by the Bill and Melinda Gates Foundation. All countries participated in a hands-on experience using tools developed by PAHO and its partners for conducting cost-effectiveness analyses of the following

priority vaccines: pneumococcal, rotavirus, human papillomavirus, and influenza.[11]

By September 2006, Ministers of Health in PAHO's annual Directing Council Meeting passed a resolution requesting PAHO to continue to provide technical assistance for evidence-based decisions and the development and use of economic analyses at the country level, but using a regional strategy of coordination to ensure the best use of resources and technical assistance.[14,15] Ministers expressed their fear that the absence of suitable economic analyses represented a weak link in the development of immunization policy. Support was needed from applied epidemiologists and their economic colleagues. While the ProVac initiative is intended to promote and strengthen economic analyses, the initiative will continue to promote critical assessments of all factors in the decision-making framework, as highlighted in the following section on objectives.

PROVAC OBJECTIVES

During a five-year period that will conclude in 2012, this initiative hopes to accomplish the following objectives:

- **Strengthening infrastructure or process.** Countries will have functional advisory boards of national experts for immunization and vaccine introduction.
- **Developing tools for the analyses.** Countries will have methodologically sound and peer-reviewed frameworks and models for estimating disease burden, program costs, and cost-effectiveness available, and the necessary training materials and technical expertise for their use.
- **Strategizing subregional impact.** Subregional strategies should be defined so the minimum burden of research is able to provide comprehensive evidence for all countries. Countries should not feel obligated to do all analyses for all vaccines, but rather select those for which regional or subregional evidence is not sufficient to foster national decisions.
- **Collecting data and conducting analyses.** Countries are collecting the essential national or subregional data to allow for the estimation of disease burden, program costs, and cost-effectiveness analyses using standardized methods.
- **Making evidence-based decisions.** Countries are making decisions considering the different components of the framework for vaccine introduction decision-making.
- **Effectively planning for introduction.** Countries have comprehensive cost plans for new vaccines that incorporate budget impact analysis and financial plans for sustaining funds to support vaccine introduction and its long-term sustainability.
- **Promoting partnerships.** Countries have built durable partnerships with different actors in the national, subregional, and international levels to provide ongoing support to countries long after project determination.

PROVAC COORDINATION AND THE CHALLENGES AHEAD

Recommended measures to be taken to facilitate the conduct and use of local economic evaluations of health-care technologies in Latin America and the Caribbean include capacity building of human resources to perform economic evaluation studies, where networks of researchers in the area have a particular value in facilitating training and the use of expertise from countries. In addition, dissemination and access to existing and ongoing economic evaluations can be improved, making these accessible and available to local decision-makers.

Evidence for informed decisions on the introduction of new and underutilized vaccines requires core competencies, including applied epidemiologists and economists. Decisions that are grounded in the evidence rely on well-developed advocacy cases and effective, expert policy-making bodies. This needed expertise exists among a diverse array of experts, institutions, and stakeholders.

To that end, the focus of the ProVac Initiative is to align this expertise in a PAHO-led partnership of technical cooperation to National Immunization Programs, vaccine-preventable diseases surveillance groups, and key policy makers within the Ministries of Health. To provide technical support for country teams conducting cost-effectiveness analyses, the ProVac Initiative will use available information technologies to allow for distance-based communication, technical discussion, and sharing of experiences for each of the priority diseases under analysis.

Further, it is envisioned that country teams will include the national immunization manager and others from the Ministry of Health, PAHO staff, and partners from other ministries, universities, and economic institutions. It will be important that country teams have leaders who are responsible for organizing their teams to conduct the cost-effectiveness analyses.

The ProVac Initiative will build a network of Key Centers of Excellence throughout the region, with

known expertise in the area, to support the development of endogenous capacity within subregions to perform economic evaluations for immunization policy. Through technical cooperation and the network of Key Centers of Excellence, the ProVac Initiative will strengthen the capacity at the national and subregional levels to create comprehensive investment cases for new vaccines and make informed decisions based on the comprehensive body of evidence. Recognizing that it is impractical to pursue economic evaluations of all four vaccines in every country of the region, economic analyses in selected countries will be prioritized. Subregional meetings will be used to support this process and to catalyze the sharing of experiences and evidence to benefit neighboring countries.

In some instances, results from economic evaluation studies in different countries may vary and may not be adequate as a function of various local factors. Such factors include differences in demographic characteristics of the study population, disease-specific morbidity and mortality data, availability of services, and programmatic and operational aspects, among others.[16] Either way, evidence-based decision-making regarding the introduction of newly available vaccines, as well as the monitoring of vaccine introduction impact, will require surveillance systems that can provide adequate estimates of disease burden. To that end, sentinel standardized surveillance systems in representative populations in countries or subregions are being implemented.

PAHO and its partners recognize that to benefit the entire region, the ProVac Initiative will continue to require a dedicated management group of professional staff to organize the technical cooperation of the PAHO Immunization Unit, ProVac partners, expert consultants, and the network of Key Centers of Excellence. Through collaboration with leading experts in immunization and health economics from several institutions, the ProVac Initiative will also continue to develop a suite of tools for economic analysis of vaccines against rotavirus, pneumococcus, human papillomavirus, and influenza, and the incremental cost of programs for new vaccines. These models will be rigorous, peer-reviewed, and standardized. To further promote the standardization of methods and results, comprehensive guidelines and frameworks for economic evaluation and priority setting will be developed and made available.

Regional conferences will be held to share experiences and results. The meetings will serve as an opportunity to provide training to regional experts as a component of developing endogenous capacity for economic evaluations for immunization priority setting. Further, the meetings will allow the Immunization Unit, partners, and member countries to refine the ProVac strategy to ensure the greatest sustainable benefit of the initiative. Within each subregion, Key Centers of Excellence will be identified and engaged through letters of commitment.

The components of the framework for decision-making are multiple and varied. The process of policy development and prioritization of decisions will be grounded in consensus development, particularly by the national expert oversight committees. One tool to assist with this process will be the development of white papers by each country that will report on the vision and strategies for vaccine introduction. These papers will be living documents that can be modified as needed and will help balance the components of the framework for decision-making. Although important, economic analysis is only one of several components. The development of these policy papers, as well as the ongoing ProVac consultative process, should help countries determine what components of the decision framework critically require local data and analysis, as opposed to when regional or subregional data could suffice.

It is envisioned that this long-term, comprehensive plan, grounded in the principles outlined previously, will prove useful in serving the countries of Latin America and the Caribbean when addressing the challenges of new vaccine introduction.[12] In five years, PAHO will be able to provide a comprehensive follow-up on continued lessons learned from the ProVac model. In the meantime, countries of other regions of the world face similar challenges in reaching the 2015 MDG targets. However, they cannot afford to wait, and they may gain from the experience accumulated thus far. For most countries, the time for action is now.

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