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PneumoADIP: An Example of Translational Research to Accelerate Pneumococcal Vaccination in Developing Countries

Orin S. Levine[1], Thomas Cherian[2], Raj Shah[3], and Amie Batson[4]

[1]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, [2]Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland, [3]Bill and Melinda Gates Foundation, Seattle, WA, and [4]Human Development Network, World Bank, Washington, DC 20433, USA

ABSTRACT

Historically, the introduction of new vaccines in developing countries has been delayed due to lack of a coordinated effort to address both demand and supply issues. The introduction of vaccines in developing countries has been plagued by a vicious cycle of uncertain demand leading to limited supply, which keeps prices relatively high and, in turn, further increases the uncertainty of demand. The Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) is an innovative approach designed to overcome this vicious cycle and to help assure an affordable, sustainable supply of new pneumococcal vaccines for developing countries. Translational research will play an important role in achieving the goals of PneumoADIP by establishing the burden of pneumococcal disease and the value of pneumococcal vaccines at global and country levels. If successful, PneumoADIP will reduce the uncertainty of demand, allow appropriate planning of supply, and achieve adequate and affordable availability of product for the introduction of pneumococcal vaccines. This model may provide a useful example and valuable lessons for how a successful public-private partnership can improve global health.

***Key words*:** Pneumococcal vaccines; Translational research; Developing countries

INTRODUCTION

Few pathogens rival *Streptococcus pneumoniae* as a cause of childhood illness and death. According to the estimates of the World Health Organization, pneumococcal infections kill more than one million children aged less than five years every year—more than any other vaccine-preventable infection, including measles (1). Unlike HIV and malaria, effective vaccines for the prevention of pneumococcal infections are currently available (2).

Pneumococcal conjugate vaccines, like *Haemophilus influenzae* type b (Hib) conjugates, are safe and highly efficacious for preventing serious infections, such as sepsis, pneumonia, and meningitis (3-5). The vaccines also prevent ear infections and pharyngeal colonization and reduce transmission from vaccinated infants to unvaccinated contacts (6-9). A vaccine containing seven important pneumococcal serotypes has been routinely used for vaccinating infants in the United States since 2000. Its routine use has led to herd immunity, i.e. a decreased incidence of disease among unimmunized persons (10,11). A vaccine containing two additional serotypes of importance in developing countries (in total, nine serotypes) was recently shown to be highly efficacious for preventing pneumonia and invasive infections in African children, including those infected with HIV (5). Based on these results, pneumococcal conjugate vaccines appear to be promising tools for improving child health globally. Further research is still needed to assess their effectiveness in other geo-

Correspondence and reprint requests should be addressed to:
Dr. Orin S. Levine
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St., Rm E8132
Baltimore, MD 21205
USA
Email: olevine@jhsph.edu

graphic regions, such as Asia, where differences in the local serotype distribution may modify the impact the existing 9- or 11-valent vaccines can have, and more local data will be needed to support national decisions to introduce the vaccines.

Given its enormous global burden of disease, it would seem obvious that, once developed, highly-effective vaccines would be demanded by, and supplied to, developing countries. Unfortunately, the experience with Hib conjugate and hepatitis B vaccines shows that the uptake of these life-saving vaccines has been the slowest in the developing world where, ironically, they are needed the most (12-14).

To accelerate the availability of pneumococcal conjugate vaccines in developing countries, the Global Alliance for Vaccines and Immunizations (GAVI) has launched a project management team called the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP). Based at Johns Hopkins Bloomberg School of Public Health, this team was awarded US$ 30 million to coordinate a targeted, multipartner workplan to help GAVI achieve its objectives for pneumococcal vaccination.

LEARNING FROM THE PAST: LESSONS FROM HIB AND HEPATITIS B VACCINES

Hepatitis B and Hib vaccines are safe and effective, can be administered through routine immunization systems, and address important global health problems. These vaccines are routinely used for vaccinating infants in nearly all industrialized countries. However, even as much as 14 years after the introduction of Hib vaccines in industrialized countries, less than 10% of infants in the 75 poorest countries of the world were routinely receiving these vaccines (Fig. 1).

Several factors contributed to the slow uptake of these vaccines. One of the most important factors was the lack of a coordinated effort to address both demand and supply issues before launching of the vaccines in developing countries. While the public sector often sponsored surveillance and research demonstrating the burden of disease or effectiveness of vaccine, there was no accompanying communication effort to assure that the data reached policy-makers. Further compounding the problems, efforts to assure financing for the procurement of vaccine—especially in early years when supplies are constrained and product prices tend to be higher as firms recoup development costs—were limited. Manufacturers of vaccines saw little or no evidence of market demand—i.e. clear expressions of interest in procuring the product backed by credible financing—for these vaccines.

This uncertainty of demand resulted in a 'vicious' cycle that reinforced the obstacles to the uptake of vaccine-constrained supplies of vaccine and high (often inaccessible) prices. With uncertain demand for vaccine, industry had little incentive to invest in increasing the manufacturing capacity to serve the developing-country market. Without an adequate capacity, a manufacturer's opportunity cost of providing vaccines to developing countries is defined by loss of market share and revenue in more lucrative markets. As a result, limited supply of vaccine kept prices relatively high, which, in turn, fuelled the uncertainty of demand in developing countries as decision-makers and financiers evaluated the costs of introduction of vaccine based on relatively high prices (Fig. 2).

Equally important, efforts to work on demand and supply issues were generally undertaken only after safety and efficacy of vaccine were established in industrialized countries. For example, no large-scale trials were conducted in developing countries prior to the licensure of the vaccines in industrialized countries, and industrialized countries had used Hib vaccines routinely for nearly 10 years before the only large-scale trial of effectiveness of Hib vaccine in Asia was initiated. Sequencing activities this way reduced the risk that public funding would support products that might not ultimately prove to be sufficiently efficacious or safe. However, this delay ensured that firms would make manufacturing capacity decisions based on serving developed-country markets—virtually ensuring a supply constraint for resource-poor settings in the early introduction years. Large-scale clinical trials take several years to design and conduct, and the vaccine industry—due to technological and regulatory requirements—needs at least 3-5 years to build or expand the production capacity. As a result, a failure to identify market demand for products in resource-poor settings at the time of global product launching can easily result in delays of 7-10 years before vaccines reach children in the greatest need. The price of this sequential effort was a delay in the introduction of vaccine—a delay that can be measured in deaths of children that might have been prevented.

Also, delaying public investment meant industry absorbed all the risks and failures required to successfully develop safe, efficacious vaccines and, thus, reduced public-sector leverage for affordable prices. Expanding the manufacturing capacity once plants have been built and the capacity has been created is very costly in time, effort, and capital resources. Seeking affordable products that could be sold more profitably in developed-country markets is more difficult than accessing planned capacity. Consequently, the public-private discussions generally did not yield any significant progress on price of vaccine or existing manufacturing capacity. Clearly, if the public sector wants to achieve more affordable prices and greater access to vaccine supply, it must be willing to accept some risks that industry undertakes in developing and commercializing new vaccines, and, by definition, accept when these risks translate into failures.

Fig. 1. Coverage of *Haemophilus influenzae* type b vaccine in the 75 lowest-income countries

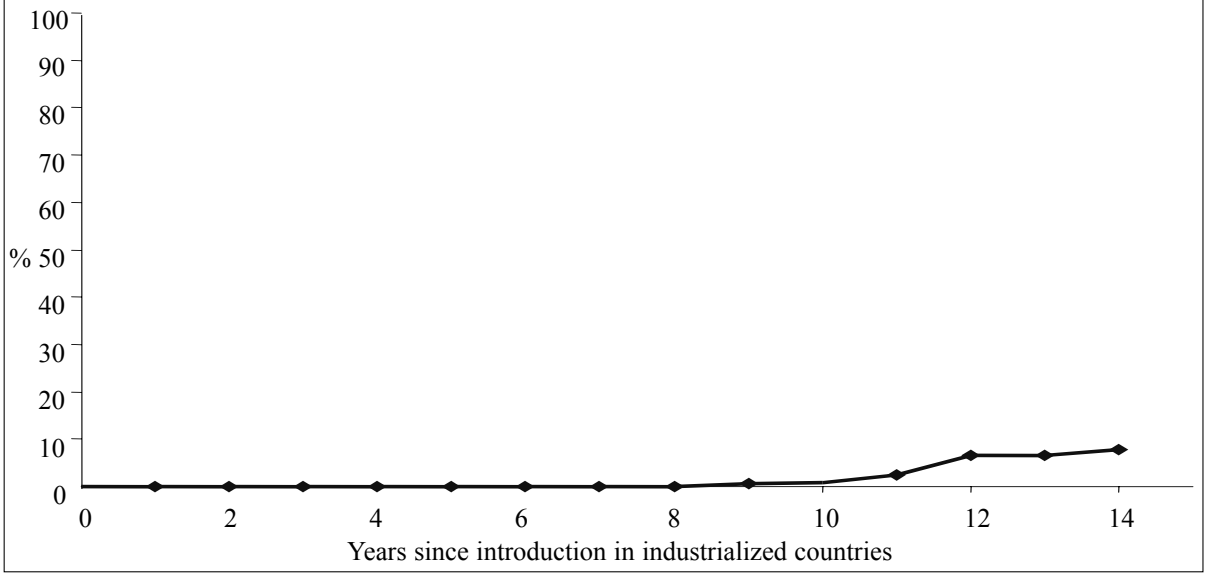
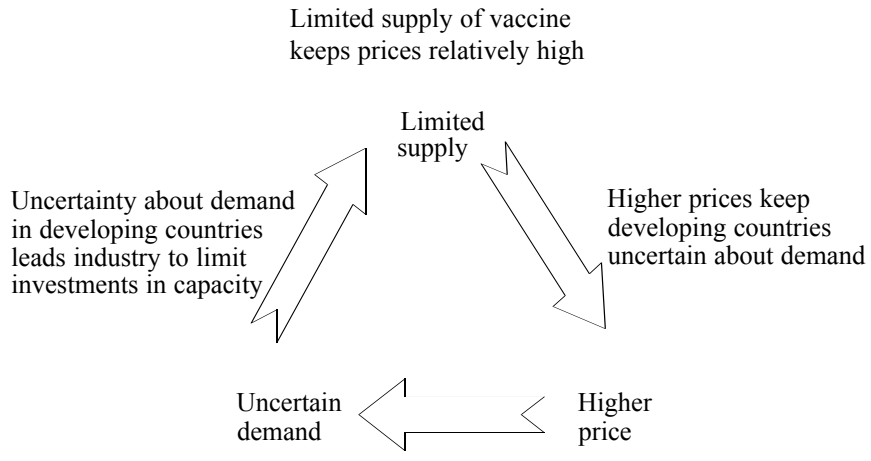


Fig. 2. Introduction of negative cycle of demand, supply, and price that historically created a barrier to affordable, sustainable prices and accelerated vaccine



One of the key strategic objectives of GAVI is to accelerate the use of new, life-saving vaccines in developing countries. The Alliance addresses this objective in various ways and with a number of approaches and tools.

One of the most important of these tools is the Vaccine Fund—a more than one billion dollar fund—that helps support immunization programmes in developing countries (15). Its one role is to help overcome the initial financing obstacles to the introduction of new vaccines by providing initial funding support for procurement. This product-procurement support allows GAVI/Vaccine Fund to pay for products when prices are higher, to motivate firms to enter the supply market, and to ensure stable demand and lower prices in the long term as countries take up larger quantities of vaccine and supply markets mature to meet this expanded product demand. GAVI and its partners have learnt that financing, however, is not the sole obstacle to the introduction of a new vaccine and that a broader approach, including translational research, is needed to assure that the groundwork is laid for the uptake of new vaccines. One example of this broader approach is PneumoADIP.

The PneumoADIP strategy is a departure from previous public-sector efforts to accelerate the introduction of vaccine in developing countries. The strategy incorporates lessons from the experience with Hib and hepatitis B vaccines and an understanding of the principles of a private-sector product launching. An essential feature of the strategy is the recognition that, to avoid the 15-year time lag, PneumoADIP and its stakeholders must be willing to assume some risks that industry typically assumes in high-income countries. For example, much of the necessary research to establish the potential benefit of pneumococcal conjugate vaccination in developing countries will not provide results at least until mid-2005. Results of these ongoing studies may indicate that further efforts to introduce pneumococcal conjugate vaccines in developing countries are not warranted. However, starting to engage and communicate with national and international decision-makers now, rather than waiting until the research is completed, is a necessary risk to assure that time is not lost in the event that the research supports the use of these vaccines.

Based on analyses undertaken by McKinsey & Co., on behalf of GAVI, World Bank, and Bill and Melinda Gates Foundation, the ADIP strategy was designed to focus on reducing the uncertainty of demand (More details on analyses of McKinsey & Co. are available at http://www.vaccinealliance.org/home/Resources_Documents/Policy_Technical/Accelerating_RD/adip_rfp.php). The ADIP framework, therefore, is designed to (a) establish the value, (b) communicate the value, and (c) deliver the value of vaccine. Establishing the value of vaccine involves developing local evidence of the burden of disease and the efficacy of vaccine, especially from surveillance and trials that are relevant to specific early-adopting countries. This evidence base must be communicated effectively to decision-makers and key opinion leaders to assure that data-driven decisions are made. Delivering the value of vaccine requires that the financing and delivery system and the vaccine itself are available to translate data-driven demand into actual vaccination. Furthermore, these efforts need to occur pre-launch to successfully influence planning of capacity, availability of product, and pricing.

To meet these goals, ADIP is directed by a small team of professionals with experience in research, surveillance, communications, business development, and financing. To facilitate partnership with industry, the team includes professionals with both private-sector and public-sector experiences. In their discussions with McKinsey & Co. and GAVI, representatives of industry indicated that, if the public sector, through a coordinated ADIP effort, can reduce the uncertainty of demand and hence reduce the risks to them, they are prepared to discuss reducing the price of vaccine and making investments in capacity needed to supply the GAVI-eligible countries.

Using the existing data, McKinsey & Co. estimated that a successful ADIP effort could accelerate the use of pneumococcal vaccine in the Vaccine Fund—eligible countries and ultimately prevent nearly 2.2 million child deaths during 2006-2020. Perhaps more importantly, however, as an innovative framework for public-private partnership, a successful PneumoADIP could pave the way for other successful collaborations for improving global health in many areas.

TRANSLATIONAL RESEARCH IS CRITICAL TO SUCCESS

The success of ADIP will depend largely on its ability to identify the key areas of uncertainty, e.g. burden of disease, safety and efficacy of vaccine, cost-effectiveness, and financing, that are impeding the introduction of vaccine and then supporting the translational research needed to address these information gaps. One priority setting approach, employed by PneumoADIP, is to develop a dynamic 'investment case' for the introduction of pneumococcal vaccine that includes modelling

the economic value of vaccination in developing countries over time. This dynamic model allows product demand (defined by uptake), product price (defined by existing capacity, supplier market maturity, and the degree of certain demand), and aggregate benefits of vaccine used to vary across time. This allows for the reality that the vaccine may cost more in early introduction but prices are expected to fall as uptake increases and multiple suppliers enter the market. Sensitivity analyses for the variables and assumptions in the model help identify the extent to which changes in these assumptions impact the economic 'investment case'. Variables or assumptions that have a high degree of uncertainty and which influence greatly the economic value of vaccination become high priorities for PneumoADIP to address.

Another way PneumoADIP identifies key translational research questions is by systematically assessing the perceptions of key decision-makers at national and global levels, including programme managers. In-depth interviews with these policy-makers help assess current perceptions of the disease and the vaccine and identify what additional information will be needed to help them make a decision on the introduction of vaccine. Using this information, PneumoADIP can assure that translational research activities are undertaken to fill gaps in the evidence base that are impeding the ability of decision-makers to determine the value of the introduction of vaccine and that these key individuals participate in the process of collecting that information. By working to support efforts by local leaders, e.g. immunization programme managers and communicable disease surveillance managers, to define the key issues and collect data to resolve them, efforts of PneumoADIP help assure local ownership of data.

One of the key challenges ahead for PneumoADIP is to help developing countries determine the local burden of pneumococcal disease and estimate the potential impact of vaccination for its prevention. Establishing local evidence of the burden of pneumococcal infections will require improving the local capacity to diagnose pneumococcal infections and increasing recognition of the role of *S. pneumoniae* as a cause of pneumonia, even in the absence of a positive blood culture. The gold-standard for diagnosis of serious pneumococcal infection is a positive culture in a normally sterile fluid, like blood or cerebrospinal fluid. While highly specific for pneumococcal infections, these cultures are very insensitive. Thus, culture-based surveillance is useful for monitoring trends in pneumococcal disease but only detects a small fraction of the total burden of pneumococcal infections.

Because most pneumococcal infections go undetected by diagnostic methods, alternative approaches are needed to help countries estimate the total burden of pneumococcal infections based on the fraction of those infections that they can measure. One approach to this method is the 'vaccine probe' study design. In the case of pneumococcal disease, the systematic use of a highly-efficacious vaccine can be used for showing that vaccination is associated with a larger reduction in the incidence of clinically-diagnosed, culture-negative pneumonia than culture-confirmed pneumonia. To effectively demonstrate the burden of pneumococcal infections, studies such as these may be needed in a range of epidemiologic settings.

Pneumococcal conjugate vaccines are formulated to contain a limited number of pneumococcal serotypes. Hence, information on the serotypes causing disease locally and/or regionally will be important for understanding the potential impact of vaccination. Furthermore, data on other consequences of pneumococcal infections, such as prevalence of antimicrobial-resistant infections, and the role of *S. pneumoniae* as a cause of meningitis and/or ear infections may be important for illustrating the significance of pneumococcal infections. Lastly, because pneumococcal vaccines are going to be priced higher than the older vaccines, such as measles and diphtheria-pertussis-tetanus, cost-effectiveness studies are going to be important for demonstrating the economic value of these vaccines.

Further clinical research with pneumococcal conjugate vaccines in developing countries is needed to illustrate to policy-makers the role for these vaccines in improving child health in developing countries. By 2005, three large-scale trials of pneumococcal vaccines will have been undertaken in developing countries—two in Africa and one in the Philippines. While these trials will provide important information about the efficacy of vaccines for the prevention of pneumococcal infections in these areas, their acceptance in substantial areas of the globe—such as South Asia, China, and West Asia—will likely be accelerated by locally-relevant trials. Moreover, studies may be required to evaluate vaccination schedules that will optimize regimens to suit the particular needs of individual countries.

ACCELERATED VACCINE UPTAKE REQUIRES MORE THAN ADDITIONAL RESEARCH

While additional research will play an important role in the efforts of PneumoADIP to accelerate access to and uptake of pneumococcal vaccines, these efforts alone will not be enough. Translation of research into health policy requires that the findings of research and surveillance are communicated effectively to key decision-makers so that these data generate the political will needed to prioritize the introduction and financing of vaccines. Similarly, the PneumoADIP team will need to work on assuring a sustainable supply of vaccines and the financing needed to procure these. To accomplish this, the team will engage countries, donors, and manufacturers of vaccines to develop demand forecasts and potential supply agreements and to explore financing options.

CONCLUSION

PneumoADIP represents an innovative approach to overcoming the barriers that have inhibited the accelerated development and introduction of new vaccines in developing countries. Through a combination of translational research, partnership with the private sector, and efforts to secure financing for the vaccine, the PneumoADIP aims to save hundreds of thousands of children's lives by accelerating the use of new, life-saving pneumococcal vaccines. If successful, this approach may be a useful model for the accelerated introduction of other vaccines and health technologies where they are needed most.

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