

# Accelerating Policy, Deployment and Access to New and Underutilized Vaccines in Developing Countries

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Over recent decades, the experience of national immunization programs demonstrates that immunization is one of the “best buys” in public health.<sup>1</sup> Rapid deployment and use of the traditional vaccines against childhood killer diseases have been the most important contributors to reductions in child mortality and increased life expectancy in developing countries. In the Americas, polio was eradicated from the region over fifteen years ago, indigenous measles transmission was eliminated in November 2002 and neonatal tetanus has been eliminated in all but one of the countries of the region.<sup>2</sup> In 2003, the Pan American Health Organization’s (PAHO) Directing Council, composed of all the ministers of health of the countries of the Americas, unanimously adopted a resolution to eliminate rubella and congenital rubella syndrome (CRS) from the Americas by 2010, becoming

the first region in the world to take on this challenge.<sup>3</sup>

Immunization will continue to be essential in reducing child mortality in developing countries and, thus, will prove critical to meeting the Millennium Development Goals (MDGs).<sup>4</sup> Immunization is directly associated with the achievement of child mortality reductions (MDG 4) and maternal health (MDG 5). It also contributes to a decrease in cancer (such as cervical cancer), a major disease of global and regional importance (MDG 6). The human papillomavirus vaccine has the potential to impact this last MDG.

Beyond simply achieving the MDGs, further gains in the reduction of child mortality can be achieved through more effective and wider use of immunization strategies.<sup>5</sup> The World Health Organization’s (WHO) Global Immunization Vision and Strategy (GIVS) recognizes that

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some countries will need to introduce new vaccines against rotavirus and pneumococcal disease in order to achieve the MDGs. Immunization can also contribute to addressing long-standing system-wide barriers (such as cross-training of staff, strengthening of data-management systems) that underlie other causes of failure to reduce maternal, neonatal and perinatal mortality. The strategies to eliminate rubella encompass tactics to reduce the system-wide barriers, particularly when attempting to improve women's health.<sup>6</sup> Reaching adults with seasonal influenza, rubella and human papilloma vaccines will be important strategies for programs to include in their transition from child to family immunization.<sup>7</sup>

This article proposes a framework for making evidenced-based decisions on the introduction of new and underutilized vaccines. It also highlights the experience of rubella and CRS elimination in the Americas as an innovative strategy to ensure rapid uptake of a vaccine to provide timely protection and more rapid prevention of disease, after the decision to introduce the vaccine has been reached. An evidence-based decision to introduce a potentially life-saving vaccine is not enough; it must be coupled with a strategy to ensure rapid deployment and protection.

### **Framework for the Introduction of New and Underutilized Vaccines**

It typically takes two decades, if not more, for new vaccines to be introduced into developing countries. The availability of technologies to wealthier countries rais-

es questions of equity and access among poorer countries. A number of factors are responsible for this long delay, including: insufficient political commitment, cost of new vaccines and insufficient vaccine supply.<sup>8</sup> Shortening this process should greatly contribute to reducing inequities.

One key strategy for shortening the process of vaccine introduction in developing countries is to engage the national leaders responsible for primary health care services, both preventive and curative, and present them with evidence on the burden of disease and the potential impact of new vaccine introduction. Experience indicates that these leaders have great influence on public health policy in their countries, particularly if disease burden estimates indicate substantial morbidity and mortality. However, a systematic, comprehensive approach that addresses the many factors that can influence vaccine introduction policy decisions should be used. The evaluation of every factor in the framework should be rigorous and as complete as possible. One such framework might include the following factors:

- Disease burden data.
- Surveillance systems to monitor and measure disease burden and impact of vaccine introduction.
- Characteristics of the new vaccine and its impact on the feasibility of its introduction into existing immunization systems (e.g. cold chain systems, stock management, staff training and waste disposal).
- Community perception of risk.
- Economic analyses of introduc-

tion to determine cost-effectiveness.

- Vaccine supply.
- Political commitment and support.
- Partnerships with the political commitment to ensure sustainability of introduction.<sup>8</sup>

Each of these factors is important; in most situations, no one factor can stand alone. The following are examples when several of these factors come into play.

Brazil first introduced the oral polio vaccine in 1961. Nearly eighteen years after the vaccine's introduction, Brazil still struggled with deployment issues. In 1979, Brazil was faced with increasing polio epidemics and was unable to provide >50% oral polio vaccine coverage in infants. To address these problems, Brazil launched a national long-term action plan. Included in the plan was the implementation of yearly mass vaccination campaigns to vaccinate all infants in two rounds during June and August, with each round lasting one day. The plan was largely driven by the epidemiology and disease burden of polio, which was relatively well defined.<sup>9</sup>

The characteristics of vaccines vary by each antigen and represent a complex subset of essential issues, all of which should be considered. These issues include:

- Immunogenicity and efficacy of the vaccine.
- Duration of immunity.
- Interaction with other antigens.
- Safety and adverse event profile.
- Dosage and route of administration.

- Storage and thermostability.

In addition, vaccine-preventable diseases (VPDs) consist of numerous serotypes (such as rotavirus and pneumococcal disease) and thus require close monitoring of serotype prevalence to determine correct vaccine composition. Furthermore, while seasonal influenza vaccine is considered safe and effective, each year new vaccine strains must be harvested due to ongoing genetic mutations of the virus from season to season.<sup>10</sup> Thus, the duration of protection should only be considered for the year of vaccine production. A vaccine made for 2009 should not be considered for use in 2010. This puts a tremendous burden on the public health infrastructure and manufacturing capacity to ensure yearly safe and affordable supplies of new influenza vaccine.

Use of combination vaccines minimizes the number of injections a child must receive and reduces refrigeration requirements and the quantity of vaccine waste material.<sup>11</sup> In order to maintain the potency of the vaccine from the point of production to the point of use in the field, vaccines must often be refrigerated. These "cold chain requirements" must be maintained during transport across international boundaries, as developing countries largely rely on vaccines produced in developed countries. Combination production minimizes the cold chain space required to keep vaccine antigens potent and also minimizes the number of injections needed, thereby reducing the risk of unsafe injection practices. As new antigens become available, it behooves policy makers to introduce them whenever possible as combination products with already avail-

able vaccines. However, clinical trials must demonstrate there is no adverse effect on the safety or efficacy of the other antigens. For example, adding Hemophilis influenza type B (HiB) antigen to the combination vaccine of diphtheria-tetanus-acellular pertussis-hepatitis B may lower the immunogenicity of the pertussis antigen, resulting in an unexpected increase, rather than decrease, in pertussis cases.<sup>12</sup>

WHO estimates that pneumococcal disease causes an estimated 1.6 million deaths per year, approximately 800,000 of which occur in children aged under five years.<sup>13</sup> To date, only one manufacturer produces the current conjugate 7-valent pneumococcus vaccine used in the United States and Canada. The price and limited supply have prevented the introduction of this life-saving vaccine into the national immunization programs of the other countries of the Americas. Fortunately, new manufacturers will be emerging. The formation of partnerships, such as the Pneumococcus Vaccine Accelerated Development and Introduction Program (ADIP), has catalyzed the fast-tracking of pneumococcus vaccine introduction, striving to reduce the existing inequities in terms of the availability of new vaccines and technologies, particularly for children living in impoverished families. As new manufacturers emerge, the PAHO Revolving Fund, which purchases vaccine for PAHO member states of Latin America and the Caribbean, will serve to forge other partnerships that will sustain introduction of this vaccine over time by negotiating affordable prices for all countries, regardless of their income status.<sup>14-17</sup>

Use of the framework suggested above should help ensure that policy decisions are based on the best evidence and the most

comprehensive analysis of the situation possible. Some countries have introduced new vaccines based solely on political commitment, often resulting from pressure from the manufacturers. Such premature decisions made prior to the completion of a more comprehensive technical evaluation can lead to disruptions in cold chain capacity for vaccine storage and ultimately undermine the motivation of health staff.

Accelerated disease control and disease elimination strategies can exert a “pull” effect, which serves to catalyze the addition of other new vaccines into routine immunization programs. Measles elimination accelerated the introduction of rubella vaccine. Elimination strategies also address issues of inequity by requiring that vaccination services reach all communities including municipalities with poor coverage, which are usually those with underserved, impoverished and minority populations with the highest disease incidence.<sup>15</sup> Expanding routine coverage to all communities and persons, regardless of income status, religion, gender and ethnicity, is paramount to elimination and eradication efforts.

## **Rubella and CRS Elimination in the Americas**

Rubella is a self-limited febrile illness, which for countries in the pre-vaccine era has been shown to cause widespread outbreaks every five to seven years.<sup>18</sup> Most infections are inconsequential. However, if a woman contracts the infection in the early stages of her pregnancy, the rubella

virus has devastating consequences on the fetus and may result in the loss of the fetus or cause a syndrome known as congenital rubella syndrome (CRS). The syndrome is characterized by a constellation of manifestations, among them stillbirth, mental retardation and other serious birth defects such as deafness, blindness and congenital cardiopathy. A baby contracting this syndrome will suffer a lifetime of significant disability, which is totally preventable with an effective, inexpensive vaccine with proven strategies to eliminate it. PAHO has estimated that, before vaccine introduction into national immunization schedules, more than 20,000 children were born with CRS each year in the region.<sup>19</sup>

As awareness about CRS grew within the English-speaking Caribbean in the early 1990s, various countries conducted costing exercises to determine the economic impact of the syndrome on affected individuals and their families. The direct and indirect economic costs associated with CRS encompass a spectrum of care, from physician and hospital services to special education costs and rehabilitation. For example, the Jamaican Ministry of Health estimated the annual direct costs associated with CRS for one child at \$13,483. In Guyana in 1997, the annual care cost per child with CRS, including indirect costs, was estimated at \$63,990 over the span of a lifetime. As a result of these early costing exercises, efforts became focused on estimating the economic impact of implementing an elimination strategy with rubella-containing vaccines. To that end, the cost-benefit ratio for implementing an elimination campaign against CRS in the Caribbean was estimated to be of 13.3:1.<sup>20</sup> For every dollar invested in eliminating

CRS, the Ministries of Health would save more than \$13 in health costs caring for children with CRS. This became a powerful argument to accelerate strategies to control and eliminate rubella and CRS.

While evidence was being developed to justify elimination strategies using rubella-containing vaccine, countries were already taking action to introduce this antigen into their national immunization programs. In the early 1990s, countries in the Caribbean began introducing the vaccine into their national immunization programs. Chile did so in 1990, Brazil in 1992 and Mexico in 1998. Costa Rica was the exception and had introduced measles-mumps-rubella containing vaccine (MMR) much earlier, in 1986. By 2002, forty-one countries and territories had a rubella-containing vaccine in their national programs, and only Peru, Haiti and the Dominican Republic lacked routine vaccination against rubella. By 2006, only Haiti did not routinely offer a rubella-containing vaccine.

Rubella control efforts were first initiated in the Caribbean by building upon measles elimination activities. In 1988, the Ministries of Health of the Caribbean (consisting of thirteen independent Caribbean states and six United Kingdom territories) resolved to eradicate measles. Vaccination campaigns began in May 1991 using measles-rubella containing vaccine (MR) in eleven participating countries. The use of MR vaccine for measles elimination ultimately set the stage for future efforts to eliminate rubella and CRS.

The measles elimination effort in the Caribbean provided the political and epidemiological blueprint for rubella elimination. The subsequent rubella program in the Caribbean was also aided by the intro-

duction of MMR in the infant immunization schedule. Using measles eradication strategies as a template, similar strategies were proposed and implemented for rubella and CRS elimination. Importantly, the current measles surveillance system for fever and rash was expanded to provide information on rubella, thus resulting in an integrated approach for measles and rubella control. This integration of surveillance activities proved to be critical for the subsequent regional rubella initiative.<sup>3</sup> Central to surveillance was a regional laboratory network with regional reference laboratories and national and sub-national laboratories.

Responding to repeat rubella outbreaks, Chile conducted a MR campaign in 1999 targeting women aged ten to twenty-nine years of age.<sup>21</sup> Costa Rica became the first Latin American country to accelerate rubella control activities by conducting a vaccination campaign using MR that included adult male and females targeting over 1.6 million persons five to thirty-nine years of age.<sup>22</sup> In 2000, a National Plan of Action was developed for an integrated measles and rubella vaccination strategy. By establishing a goal for accelerated rubella and CRS prevention, Costa Rica strengthened measles eradication. Since many of the key components for achieving rubella and CRS goals are critical for measles eradication (e.g. strong surveillance systems for fever rash and vaccination delivery systems), the Costa Rican experience illustrated that adopting a goal of accelerated rubella control and CRS prevention strengthened and helped sustain the measles eradication program.

In 2003, the PAHO Directing Council composed of all the Ministers of Health of

the Americas unanimously adopted a resolution calling for rubella and CRS elimination in the Americas by the year 2010.<sup>3</sup> The regional resolution came on the heels of the successful eradication of polio and indigenous measles in the region and was grounded in the experience of the Caribbean and subsequently other countries in Latin America as described above. Since humans are the only host of the rubella virus and since a very effective and affordable vaccine (>95% efficacy) conferring lifelong immunity exists, elimination was deemed achievable. The strategy to eliminate rubella and congenital rubella syndrome is two-pronged:

- 1) rapidly reduce the pool of susceptible population by conducting a mass rubella vaccination campaign with rubella containing vaccine to interrupt transmission of the endemic virus; and

- 2) employ high-quality surveillance to monitor impact and to document that the goal of elimination has been reached. The elimination of rubella and CRS in the Americas will most likely be seen as the second greatest achievement of public health in the twenty-first century, following the interruption of indigenous measles transmission in 2002.

By the early 2000s, rubella vaccination campaigns had been conducted in Brazil, Ecuador, El Salvador, Colombia, Honduras, Nicaragua and Paraguay. Most campaigns target all adults, both men and women, aged under forty years. The age cut-off for the inclusion of children varied by country and by each national strategy to eliminate measles using MR vaccine. In May of 2006, Bolivia conducted its national campaign. In late 2006, the Ministries of Health of Argentina, Peru

and the Dominican Republic announced plans to conduct mass rubella-containing campaigns.<sup>23-24</sup> Haiti, Guatemala, Mexico, Venezuela and French Guyana plan to implement nation-wide campaigns in 2007.

The implementation of one time, high-quality mass vaccination campaigns in both men and women has proven to be effective in the Americas, and countries that have done so appear to have interrupted transmission of endemic rubella virus. Countries that still have a pool of susceptible persons because they do not vaccinate both men and women (i.e. target only women in their mass rubella vaccination campaigns) are continuing to have a low level of endemic transmission of the rubella virus and are potentially putting other countries of the region at risk. Experience indicates that if the mass vaccination campaigns are done well, including the vaccination of both men and women, only one campaign is needed to eliminate the disease and its debilitating syndrome forever.

To ensure the highest quality campaigns, the following criteria should be fulfilled:

- The age group to be vaccinated should be determined based on the epidemiology of rubella in the country, an assessment of the susceptible population, the year of vaccine introduction, subsequent rubella vaccination campaigns and the need to protect women of childbearing age.
- Quality campaigns require vaccinating both females and males, including susceptible adults, and reaching coverage levels close to 100% of the targeted population.
- The highest political commitment and participation should be ensured.
- Full population participation requires intensive social mobilization and local microplanning.
- Information system should be practical and useful.
- Capacity to detect and rapidly respond to safety concerns and other emerging issues during campaigns is necessary.

By June 2006, thirty-seven (84%) of the countries and territories of the Americas (accounting for 75% of the population of the region) had implemented vaccination campaigns, obtaining coverage of over 95%.<sup>7</sup> The seven remaining countries mentioned above are expected to finalize their campaigns by June 2007. The impact of these campaigns and the other strategies to eliminate rubella, such as strengthening routine vaccination, has been impressive. The number of confirmed rubella cases decreased by 96.2% between 1998 and 2005 (from 135,947 in 1998 to 5,209 in 2005).

Prior to accelerated rubella control, less than 20% of rubella cases were confirmed by laboratory or epidemiological link; this figure rose to 96% in 2005. By epidemiological week twenty-six of 2006, 97% of suspect cases had been discarded following laboratory testing.<sup>25</sup> In addition, best public health practices are currently being identified to improve CRS surveillance at the primary care level, to strengthen the capacity to diagnose deficiencies in health services and to ensure expert review of suspect CRS cases. Improvements in CRS surveillance will allow for the moni-

toring of trends and the identification of reservoirs of transmission and will serve as a critical advocacy tool. In 2005, 1,952 suspect CRS cases were reported, and 16 of them were confirmed. By epidemiological week twenty-six of 2006, 342 suspect CRS cases had been reported, and one of them was confirmed. Ultimately, these data confirm the feasibility and value added of coupling rubella-containing vaccine introduction in Latin America and the Caribbean with strategies to rapidly ensure that children and families that need the vaccine will be most likely to benefit. This case study provides an example of using existing systems for new vaccine introduction that will ensure rapid deployment and access. Introduction of rubella vaccine was fast-tracked onto existing systems and disease control strategies that will ultimately lead to its elimination. As stated previously, rapid deployment and use of new vaccines will be critical to achieve the MDGs by 2015. In addition, the implementation of the rubella and CRS elimination program highlights the key steps that program managers must confront when contemplating new or underutilized vaccine uptake, as well as the actual activities critical for successful program implementation. This will be important for new vaccine introductions that have the potential for addressing enormous public health challenges, such as HIV infection.<sup>14</sup> Overall, well-researched and implemented vaccine programs will result in more lives saved, more quickly.

## **Discussion**

In summary, available new and underutilized vaccines will open additional win-

dows of opportunity in developing countries to further reduce the mortality caused by VPDs and help achieve the MDGs by 2015. To that end, rotavirus and pneumococcus vaccines appear to be ideal candidates for child mortality reduction in developing countries. However, to reach the MDGs on time, evidence-based policy decisions, followed by rapid introduction and access to these vaccines, will be essential. Informed policy decisions need to be based on local data, given that these new vaccines are substantially more expensive, and on the epidemiology of VPDs, which may vary geographically. Decisions to introduce new vaccines in developing countries must be supported with clear strategies to guarantee a safe and affordable supply of vaccine. Rapid uptake will require national immunization programs to use innovative strategies for reaching populations that traditionally have not been targeted in childhood immunization programs (young women for human papillomavirus vaccine). Such strategic planning may prevent the slow “trickle-down” process by which new vaccines from developed countries have historically been introduced into developing nations, while ensuring access and equity.

Recent Harvard University research has indicated that the true dimensions of beneficial health impact achieved through childhood immunization have been understated in traditional “best public health buy” concepts of immunization. The cost-effectiveness of immunization using traditional techniques of measurement has been greatly underestimated, suggesting that PAHO Member State investment in immunization continues to represent outstanding value for the money spent.<sup>1</sup>

The proposed framework for new vaccine introduction should be generalizable to countries and regions outside the Americas. Elements of the framework, such as the specific characteristics of the vaccine, logistical issues, surveillance and vaccine supply, exist everywhere and should be considered in all parts of the world. While other elements, such as political commitment and sustainability, vary depending upon what country is being considered, they also remain universally important.

The successful introduction and accelerated use of a rubella-containing vaccine and the adoption of the regional elimination goal were facilitated by numerous factors that have implications for future vaccines that will enter the market. First, the disease burden was well established in the region, greatly aided by the regional adoption of an integrated measles-rubella surveillance system. This facilitated the political and financial support from national governments that is critical for new vaccine introduction. Furthermore, the availability of data on disease burden assisted with community acceptance and social demand for the vaccine. The actual characteristics of the vaccine, such as rubella in multiantigen combinations available as MR and MMR, facilitated its use by health care workers and its use in the cold chain. Basing rubella control strategies on existing measles strategies ensured programmatic feasibility by not disrupting the existing immunization services or vaccine distribution systems, minimizing any increase in waste management and permitting training of rubella activities to be integrated with those of measles efforts.


In addition, the existence of a strong coordinated regional immunization pro-

gram under PAHO's leadership, coupled with its close working relationship with national Ministries of Health and their national commitments to preventing VPDs, played a critical role in accelerating rubella introduction and control efforts. The regional Revolving Fund ensured that the vaccine supply was guaranteed and available at affordable prices. Fundamental to the regional success with rubella vaccine is the existence of the Revolving Fund mechanism to ensure that new policies reach the actual vaccine providers in health care facilities. New resolutions are adopted by member states at PAHO's yearly meeting of its Directing Council, composed of Ministers of Health of all Member States. These are translated into strategies by PAHO's Technical Advisory Group (TAG) and discussed and debated at regional TAG meetings attended by national EPI directors. In a cascading effect, these new goals, objectives and strategies are discussed at sub-regional meetings and adopted into national policy by National Immunization Commissions. The policy becomes implemented within countries by their national immunization program, often through national and local epidemiology workshops, and solidified by training on all aspects of rubella epidemiology, prevention and vaccine handling at the local level. The Americas is unique in having a system to rapidly disseminate new information, coordinate and standardize immunization activities and ensure that health care workers are adequately trained.

The lessons learned with rubella introduction have implications for new vaccine introduction, as well as its rapid uptake. As countries prepare for the potential introduction of pneumococcal and rotavirus

vaccines, managers should consider ways to take advantage of the existing measles/rubella surveillance system in the Americas, the measles elimination and mortality initiatives in other regions and the polio eradication effort. While countries introduce these vaccines into routine programs, pneumococcal update could potentially be accelerated by integrating with measles and measles/rubella mass campaigns. Likewise, rotavirus vaccine update could be accelerated by integrating with polio campaigns. Although there are operational and technical issues to be taken into account, the advocates and champions of new vaccines should make every effort to learn from the previous vaccine introduction initiatives, including that of Haemophilus Influenza type b (HiB).

An important lesson learned from the accelerated use of rubella in the Americas is the need to implement effective vaccination strategies that reach young and adult populations and to develop sensitive and integrated surveillance supported by laboratory networks. For example, rotavirus champions should explore utilizing the polio laboratory networks not only to collect specimens, based upon standard case definitions, but to process laboratory testing. Finally, with the advent of new vaccines entering the market and the efforts to accelerate the uptake of Hib in other regions, advocates of these vaccines need to coordinate their efforts and not work in isolation. Countries will most likely be faced with choosing between several new vaccines. Disease burden data for VPDs prevented by new vaccines will be critical to make informed decisions as to which new vaccine(s) should be introduced and in what order of priority. The existence

of a sensitive laboratory-based surveillance system is the cornerstone of such decisions, in addition to the other factors in the framework for making evidence-based policy decisions. Ultimately this policy decision should be coupled with a clear and comprehensive strategy for rapid deployment and access in order to prevent needless deaths and other sequelae. To that end, in developing countries the transition of national immunization programs to family immunization programs, providing expanded services to youths and adults, should also contribute to ensuring new vaccines, such as those for HIV and human papillomavirus, are available to those who need them most. 

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