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Vaccines and Vaccinology in Latin America Conference Report

The11th International Symposium on vaccinology for Latin America experts working group

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Abstract

Progress and challenges in the use of vaccines included in the EPI program and the introduction of new vaccines for emerging and re-emerging diseases in a number of Latin American countries were discussed during the 11th International Symposium for Latin America experts (17-19 October 2018, Panama City). Since the establishment of the expanded immunization program in 1977, countries and territories in the Latin America and Caribbean (LAC) region have made significant strides in protecting the populations against vaccine-preventable diseases. In 1994, the region became the first of the WHO regions to eliminate poliomyelitis. In 2015 and 2016, the region declared free of measles, rubella, and congenital rubella syndrome and in 2017 free of neonatal tetanus. Countries in LAC were among the first developing countries to introduce new vaccines such as rotavirus and PCV into their national immunization programs and the PAHO revolving fund has played a central role in improving access to available vaccines at lower prices in the region.

However, due to huge social, economic and political diversity among the countries of the region, optimal vaccination coverage remains a pipe dream. Countries should work together until achieving the desired immunization coverage. Technical cooperation and partnership at regional level would reduce disease burden and vaccination inequality that exist today in Latin America.

Keywords: Conference report; Challenges; Immunization; Latin America; Vaccine

Introduction

Vaccination has made one of the greatest medical achievements in terms of public health, leading to the eradication or extensive reduction of several health-threatening infectious diseases. The example of poliomyelitis is a success history. In 1998, 350,000 cases occurred in 125 countries while today only 4 cases in Pakistan and 19 cases in Afghanistan are reported. Despite impressive achievements in vaccine uptake, vaccination faces new challenges in a world of fast evolving pathogens. Calamities, failure in vaccine preparation, misinformation and the subsequent misperception and fear about safety concerns, anti-vaccine movements and difficulties in vaccine delivery are among the most important challenges. According to the WHO-UNICEF immunization estimates, nearly 1 in 10 infants worldwide did not receive any vaccinations in 2016 [1].

With a population of more than 640,000,000 individuals, Latin America and Caribbean (LAC) region is located in the Western hemisphere and composed of 33 countries. In 1977, the Directing Council of the Pan American Health Organization (PAHO) - constituted by the ministries of health of the countries of the Americas - adopted the resolution of establishing the Expanded Program on Immunization (EPI) in the Americas. Since the establishment the EPI, countries and territories in the LAC region have made significant strides in protecting the populations against vaccine-preventable diseases. However, due to huge social, economic and political diversity among the countries of the region, improvement is still essential to reach optimal vaccine coverage in the region.

Progress and challenges in the use of vaccines included in the EPI program and the introduction of new vaccines for emerging and re-emerging diseases in a number of Latin American countries were discussed during the 11th International Symposium for Latin America experts (17-19 October 2018, Panama City). The meeting

was organized by Fondation Mérieux in collaboration with the Latin American Society of Paediatric Infectious Diseases (SLIPE). A total of 14 countries from the region (Argentina, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, El Salvador, Ecuador, Honduras, Mexico, Panama, Paraguay, Peru, Uruguay) together with experts from Canada, the Unites States, France, United Kingdom, Norway and Switzerland participated.

Vaccination Progress in Latin America and Caribbean

Vaccination is compulsory in a number of LAC countries. The establishment of the EPI has led to an impressive increase in immunization coverage from 50% in the 1970s to over 80% by 1992. In 1994, the region became the first of the WHO regions to eliminate poliomyelitis. In 2015 and 2016, the region declared free of measles, rubella, and congenital rubella syndrome and in 2017 free of neonatal tetanus. As illustrated in Figure 1, LAC has one of the best vaccination coverage (VC). Factors contributing to the successful immunization programs are numerous and include: 1) commitment of countries in considering immunization as a priority and a long-term direct and indirect saving strategy, 2) better understanding of the society about the value of considering immunization as part of a right and responsibility, 3) considering a strong immunization program as an integral part of a well-functioning health system, 4) encouraging sustainable access to funding, 5) quality supply and innovative technologies and promotion of local and regional research, and 6) investigation of new vaccines, and cost-benefit analysis. Furthermore, many countries have good human resources in public, private, and non-governmental organizations (PAHO, SLIPE, or the Commission for the Future of Vaccines in Latin America, COFVAL) and Latin Americans are receptive to vaccines. The PAHO Revolving Fund Vaccine Procurement (RFVP), established in 1987 in 41 countries and territories, played a central role in facilitating pooled vaccine procurement with a reasonable price [2].

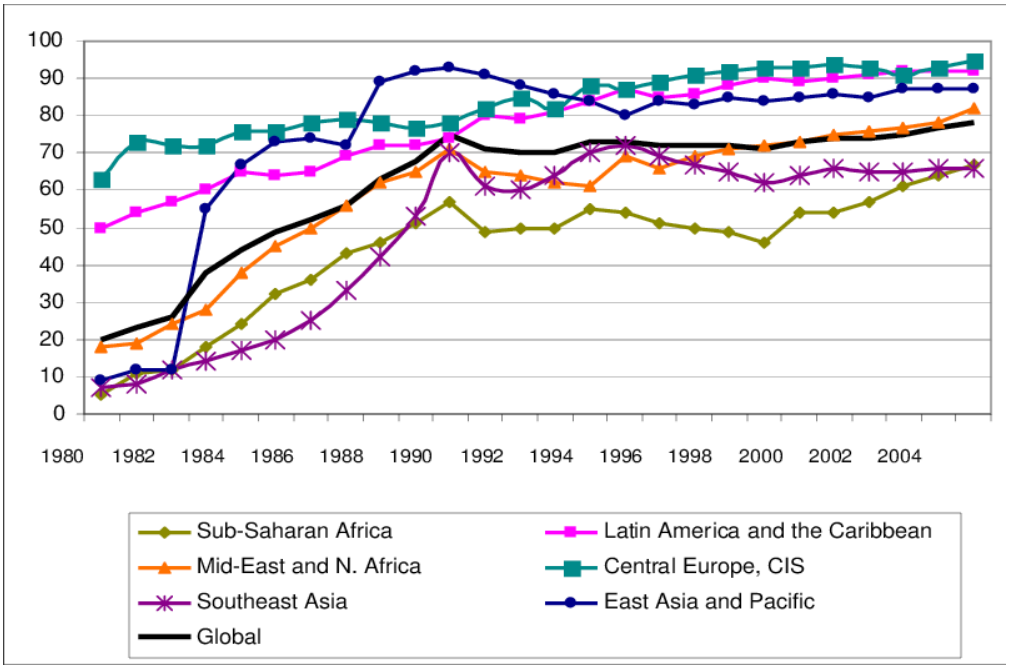

Figure 1: Diphtheria-Tetanus-Pertussis (DTP3) coverage by WHO-region.

Table 1 summarize the immunization program in children less than five years old in participating countries. Available vaccines include Bacillus Calmette-Guerin (BCG), Diphtheria, Pertussis and Tetanus (DTP), *Hemophilus influenzae* B (Hib), Hepatitis B (HBV), Inactivated Polio Vaccine (IPV)/ Bivalent Oral Polio Vaccine (bOPV), Hepatitis A (HAV), Measles, Mumps and Rubella (MMR), Pneumococcal Conjugated Vaccines (PCV), seasonal influenza vaccine, and rotavirus. Varicella vaccine and Human Papillomavirus Vaccine (HPV) are integrated in EPI of many countries while *meningococcus*, yellow fever, dengue and cholera vaccines are available only in some countries. Immunization schedules in LAC region have fostered the development and introduction of life-saving vaccines. Traditionally, the introduction of new vaccines was lower in LAC region but after the year 2000, the gap has been reduced (Figure 2) thanks to the establishment of national legislation [3] and participation of these countries in vaccine trials that allowed the health community to use evidence as the basis for decision-making at local level.

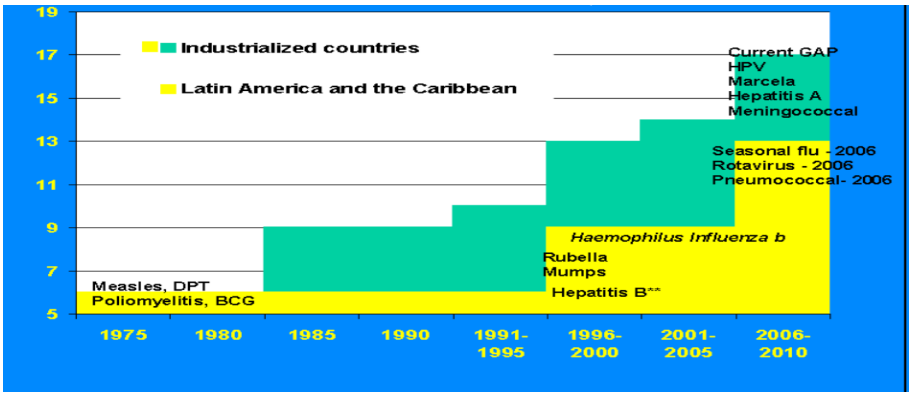

Figure 2: Number of childhood vaccines routinely introduced in industrialized countries and in Latin America and Caribbean, 1975-2010.

Country	BCG	HBV	DTP-HepB-Hib	HAV	OPV/IPV	bOPV	PCV	MenCC	DTP	MMR	HiB	Rotavirus	Varicella	Flu	HPV	YF
Brazil	**At birth**	**At birth**	**2, 4, 6 M**		**IPV: 2, 4, 6 M**	**15M 4Y**	**2, 4, 12 M**	**3, 5, 12 M**	**15 M 4 Y**	**12 M**		2, 4 M		6 M		9 M 4 Y
Costa Rica	**At birth**	**At birth 2,6 M**	**2, 4, 6, 15 M**		**Y**		2, 4, 15 M		DTPa 2, 4, 6 M	15 M 7 Y		<8 M	15 M			
Colombia	**At birth**	2, 4, 6 M	2, 4, 6 M	12M	2, 4, 6 M		2, 4, 12 M		2, 4, 6, 18 M	12 M		2, 4 M	12 M	6 M		18 M
El Salvador	**Y**	**Y**	**Y**		**Y**		**Y**		**Y**							
Ecuador	**Y**	**Y**	**Y**		**Y**		**Y**		**Y**	**Y**		**Y**	**Y**	**Y**		**Y**
Paraguay	**Y**	**Y**	**Y**		**Y**		**Y**		**Y**	**Y**		**Y**	**Y**	**Y**		**Y**
Panama	**At birth**	**At birth**	**Hexavalent 2, 4, 6 M Tetravalent DTP+Hib 18 M**	**12/18 M**	**18 M, 4Y**		**2, 4 M**		**4 Y**	**12, 18 M**		**2, 4 M**	**15 M, 4Y**	**6 to 11 M**		**15 M**
Paraguay	**Y**	**Y**	**Y**		**Y**		**Y**		**Y**	**Y**		**Y**	**Y**	**Y**		**Y**
Peru																
Panama	**At birth**	**At birth**	Hexavalent 2, 4, 6 M Tetravalent DTP+Hib 18 M	12/18 M	18 M, 4Y		2, 4 M		4 Y	12, 18 M		2, 4 M	15 M, 4Y	6 to 11 M		15 M
Uruguay																

BCG: Bacillus Calmette-Guérin; HBV: Hepatitis B Vaccine; DTP: Diphtheria; Pertussis and Tetanus; Hib: Hemophilus Influenza B; HAV: Hepatitis A Vaccine; IPV: Inactivated Polio Vaccine (IPV); BOPV: Bivalent Oral Polio Vaccine (BOPV); PCV: Pneumococcal Conjugated Vaccines; MENCC: Meningococcal Conjugated C; MMR: Measles, Mumps and Rubella; FLU: Seasonal Influenza Vaccine and Rotavirus. YF: Yellow Fever and HPV: Human Papillomavirus Vaccine

Table 1: Vaccination schedule in children 0-4 years old in participating countries.

Haemophilus influenzae type b (Hib) is a bacterium commonly found in the nasopharynx of non-immune children, leading to invasive diseases such as meningitis. Before the introduction of the vaccine, the overall incidence of Hib meningitis in infants

below 4 years old was 60 per 100,000 in LAC [4]. Following the vaccine introduction, significant reduction in the incidence of Hib-confirmed meningitis was reported in several LAC countries [5]. Pneumococcal diseases caused by *Streptococcus pneumoniae* are important causes of morbidity and mortality in children <5 years of age in LAC [6]. A recent metanalysis provided incidence rates of culture-confirmed pneumococcal pneumonia ranging from 10.2 to 43.0/100,000 in children [7] in the region. The LAC region has been among the first developing countries to introduce PCV in their immunization schedule since 2009 [8]. As of May 2016, 29 LAC countries and territories were using PCV-10 or PCV-13. Some countries also provided a single catch-up dose to children aged 12-23 months at the time of vaccine introduction [9]. The introduction of the vaccine has led to substantial reduction in the number of invasive pneumococcal diseases [10].

With an estimated 8000 deaths in children less than five years old annually, rotavirus disease was considered as the leading cause of morbidity and mortality related to diarrhoea among children under age of five in LAC. Currently, two WHO-prequalified, orally administered rotavirus vaccines (Rotarix and RotaTeq) are available. In 2006, the region was among the first in incorporating universal rotavirus vaccination, with a median vaccine coverage rate of 89% in the 11 Latin America countries that introduced the vaccine before 2010 [11]. The estimated effectiveness of rotavirus vaccines in the region was 53% against rotavirus infections,73% against rotavirus-related hospitalisations and 74% against severe diarrhoea episodes [12]. In addition, the risk of intussusception was not higher than the background risk in LIC [13]. Globally, influenza affects 10-20% of the population and causes 250,000-500,000 deaths [14]. Despite the existence of a vaccine, influenza represents still a public health problem due to the permanence of viruses in the environment, short incubation period (1-4 days) limiting containment options, and low recognition of influenza as a severe disease. An annual rate of 36,080 (95%CI: 28,550-43,610) influenza-like illness per 100 000 persons-years was reported from the region [15]. As of 2014, 38 out of 43 LAC countries/territories offered influenza vaccines free of charge to high-risk groups i.e. children, elderly, adults with underlying chronic diseases, pregnant women and health care workers [16]. Since 2013, influenza vaccine effectiveness is estimated by a network of influenza surveillance centres called REVELAC-i (Red para la Evaluación de Vacunas En Latino América y el Caribe-influenzais) [17]. The adjusted vaccine effectiveness against influenza-related hospitalization among children ≤5 years and adults aged ≥60 years during 2013 were respectively 47% (95%CI: 14-71%) and 48% (95%CI: 34-60%), supporting the current vaccination strategies in place in the LAC region for both target groups [18]. Studies investigating the efficacy of maternal vaccination with inactivated influenza vaccine are not available in LAC region. However, good efficacy in both mothers and infants have been reported [19-21]. Vaccination reduced also influenza-associated hospitalization in mothers and their infants [22], the risk of stillbirth and spontaneous abortion [23], preterm birth and low birth weight [24]. Influenza vaccine in pregnant women is recommended in all LAC since 2018. *Neisseria meningitidis* is one of the main causes of bacterial meningitis with high morbidity and mortality in developed and developing countries [25]. Meningococcal diseases incidence rates are highly variable in LAC region, the highest burden being reported in Brazil, Argentina, Chile, and Uruguay. In 2010, Brazil was the first country of LAC region to introduce the meningococcal conjugated vaccine, followed by Chile in 2012 [26]. In Latin America, the vaccine is recommended for high-risk groups such as immunodeficient individuals, and those with occupational risk and travellers to endemic areas [27].

Cervical cancer is the second most common cancer and the leading cause of cancer mortality in women in LAC region [28]. Panama was the leading LAC country that included routine HPV vaccination program targeting girls aged 10-11 years with a 3-dose vaccine schedule [29]. As of June 2017, the majority of countries in the region have HPV vaccines with a two-dose schedule for girls 9-12 years of age [30]. The vaccine is administered to both genders in Antigua, Argentina, Bermuda, Brazil, and Panama [31].

IImmunization Programs and Success Histories in Participating Countries

Argentina

Immunization program in Argentina is compulsory and free of charge. From 2008 to 2018, 12 new vaccines have been introduced to the EPI. Currently, 20 vaccines free of charge are available for different age categories. Major achievement includes elimination of poliomyelitis (1984), measles (2000), neonatal tetanus (2007) and rubella (2009). From 2017, the country switched to a new poliomyelitis vaccine scheme that includes 2 doses of IPV and one dose of bOPV. No more cases of hepatitis A and related acute liver failure have been identified since 2008 thanks to the introduction of one dose of Hepatitis A vaccine in 2005 for children at 12 months of age. Diphtheria, Tetanus and Acellular Pertussis (DTaP) vaccine and HBV were recommended for pregnant women in 2012 and introduced to the EPI in 2013 and 2014 respectively. Neonatal mortality due to *Bordetella pertussis* has been reduced by 84% following immunization of pregnant women with DTaP. Influenza vaccine is recommended for Health Care Workers (HCWs), pregnant women, elderly, children 6-24 months, and individuals 2-64 years old with underlying comorbidities.

PCV-13 was introduced in 2013 with 2 plus 1 schedule at 2 and 4 months and a booster dose at one year of age. This has led to considerable reduction of cases of pneumonia in the target population i.e. children <4 years old. A parallel decrease in hospitalization for bacterial pneumonia was observed in adults,

supporting the herd immunity produced by the vaccine. HPV was first introduced in the EPI in 2011 for 11-years old girls born from year 2000. In 2014, the country switched to the quadrivalent vaccine and changed to a two doses schedule in 2015. Since 2017, 11-years old boys are also eligible to receive the vaccine. Argentina faces challenges due to the resurgence of measles by imported cases. National follow-up campaign has been set-up to sustain elimination of measles, rubella and congenital rubella syndrome in the population.

Brazil

The EPI was created in 1973 and currently include 14 vaccines for infants, children and preteens, 8 for teens and adults and 5 for elderly (>60 years). In 2018, the country spent more than US$1,25 billion in immunization program for 300 million doses of vaccines and immunoglobulin to be distributed by the EPI. Recorded national VC is 95% for the majority of vaccines included in the program. However, since 2011, a reduction of 23%, 17% and 23% were recorded for OPV, first and second dose of and measles vaccine respectively. Similarly, outbreaks of yellow fever in 2017-2018 were related to extensive decrease in VC. To seek adherence of the target population, the country set-up strategies such as flexible hours for vaccination centres, active participation of community health agents, vaccination in home, schools and universities. Intra and intersectoral partnerships (media, social networks, scientific societies) and pro-vaccination campaigns have been performed in parallel to counterbalance anti-vaccine movements.

Costa Rica

The National Immunization Program (NIP) was instituted in 1950 with the vaccination against diphtheria, pertussis and tetanus, causing an accelerated reduction in the incidence and mortality associated with these diseases. Following the establishment of Costa Rica's immunization law in 2001, free access to immunization is offered to the whole population and the Ministry of Health and the Costa Rican Department of Social Security should ensure sufficient budgets to purchase vaccines. Success history in the country include elimination of Diphtheria (1975), human rabies (1970), poliomyelitis (1973), and congenital rubella (2001). During the last two decades, the country introduced several other vaccines in its childhood immunization scheme: Hib (1998), influenza (2005), varicella (2007), PCV13 (2009) and IPV and DTaP in 2010. In 2017, the incorporation of rotavirus vaccine and HPV was approved. Vaccination against rotavirus started in February 2019 and HPV begin in June 2019 for 10-year-old girls only. The global coverage for childhood vaccines was ≥90% in 2017. Adult vaccination includes Tetanus-Diphtheria (Td), influenza (2005), PCV13, Pneumo23, influenza, Tetanus-Diphtheria-Acellular Pertussis (Tdap) and cocoon strategy against pertussis (2007).

Columbia

In Columbia, the national community of immunization work with paediatricians and gynaecologists. As of December 2018, coverage rate for pentavalent and MMR vaccines was above 95%. As for other LAC countries, Colombia faced outbreaks of measles. As of March 2018, 4,600 measles cases were reported and 122 cases have been confirmed. Overall, 45 cases were imported, 71 cases were importation associated and 6 cases had an unknown source. The most affected age categories were 1-4 years old children (39%) followed by those under one-year-old (32%). In addition, 8 cases of confirmed diphtheria have also been reported in 2018. The country has achieved important goals including i) development of actions in the poliomyelitis eradication plan, ii) reinforcement of sentinel surveillance of bacterial pneumonias, meningitis, and rotavirus, iii) certification of the elimination of autochthonous measles in the Colombian territory iv) strengthen actions to promote vaccination against HPV, and v) the introduction of four vaccination days per year in the months of January, April, August and October.

The future challenge is to maintain and increase vaccine coverage and complete transition of vaccination to family.

El Salvador

The NIP was implemented in El Salvador in 1976 and epidemiological surveillance of vaccine-preventable diseases started in 1980. Vaccination led to the elimination of several diseases including diphtheria (1987), polio (1988), measles (1996), rubella (2002), congenital rubella syndrome (2007) and neonatal tetanus and Hib (2010). The number of available vaccines as well as the allocated budget showed an increasing trend from 2000 to 2015, but a reduction in the budget in 2016 has led to shortage in supply of yellow fever vaccine, PCV and Hib. The introduction of rotavirus vaccination in October 2006 conducted to significant decrease in the total number of diarrheal and rotavirus cases. During the last five years, PCV13, influenza vaccine (children >5 years old, pregnant, high-risk adult and elderly), IPV, pentavalent (18 months), HBV at birth, tetanus (10 years old and >60 years) and Tdap (pregnancy) were introduced. PCV7 was introduced in 2010 and was substituted by PCV10 in 2011 and by PCV13 in 2018. The introduction of PCV was accompanied with significant decrease in the number of pneumococcal meningitis in children less than 5 years old.

Vaccine coverage is not homogeneous within the country and is in general low in adults and elderly. In 2017, coverage rate for influenza and Tdap vaccine among pregnant women reached 49% and 43% respectively. Influenza vaccine is not accepted by HCPs for whom the vaccine coverage is less than 20%. The main challenges of vaccine program in El Salvador include electronic nominal registries, update of the denominator, enforcement of the vaccine law, incorporation of new or better vaccines (HPV, HAV

and quadrivalent influenza), improvement in VC, surveillance and cost effectiveness analyses. The best solutions to overcome these challenges are advocacy, intervention in health policies, education, alliances and partnership.

Ecuador

The EPI-Ecuador lunched in 1976 was the first in Latin America and included five vaccines (BCG, DPT, AS, tOPV) in <5 years. In 1997, a low that guarantees the permanent supply of vaccines for the EPI has been established. The cooperation agreement with PAHO was signed in 2005, in which it establishes that all vaccines, syringes and cold chain equipment and devices will be acquired through the Revolving Fund. Despite tremendous efforts, the coverage rate for all available vaccines (n=18) in 2017 did not reach 90% except for HPV thanks to coordination with the schools. In 2018, the country faced an outbreak of measles probably originated from imported cases. A vaccination campaign was set-up to limit the outbreak. Major achievement includes 14 years without rubella or congenital rubella, 20 years without autochthonous measles, 24 years without diphtheria and 28 years without poliomyelitis.

The most important challenges are to close vaccination/vaccine gaps, facilitate and implement actions with other institutions to strengthen the immunization strategy and to improve the information and data collection system. These challenges are further complicated by limited resolutive capacity due to the lack of empowerment in vaccination, public-private strategic alliances, lack of training by constant rotation of human talent, deficit of supervision, VC monitoring and lack of computerized nominal registration.

Mexico

Lack of vaccine supply created decrease in vaccine coverage for some vaccines. Since 2018, a law was voted to guarantee the budget for vaccination. The main challenges are lack of staff, insecurity, lack of primary health care structures in peri urban areas, and population mobility. Intensive action to deliver health to the population consist of national health weeks to vaccine the population against diarrhoea, acute respiratory infections, HPV, rubella and measles vaccines. Electronic vaccination card is available since 2015. The country set-up a workshop on Measurement and Monitoring of Administrative Coverage and Methodology for the supervision of "Data Quality" as a strategy to strengthen the validity, integrity and timeliness of vaccination coverage.

Paraguay

Immunization program in Paraguay has led to the elimination of several vaccine-preventable diseases including polio (1985), measles (1998), CRS (2003), rubella (2005), yellow fever (2008), diphtheria (2011). A significant decrease in the incidence of pertussis has also been reported with only 44 cases in 2017. HAV and HPV and Tdap were introduced in 2013. The action plan for 2010-2018 is to reinforce epidemiological surveillance, increase VC (micro planification, analysis of missed opportunities, etc.), strengthen vaccine provision and surveillance of new vaccines introduced within the program to assess its impact, support the capacity of national regulatory authority for the quality control, safety and effectiveness of EPI vaccines, and modernize the cold chain to meet international standards.

Peru

The number of vaccines in immunization program increased from nine in 2000-2004 to 15 currently. The country attained major achievements during the last decade by introducing PCV, rotavirus, influenza vaccine and HPV, the purchase of 52 cold chambers for the whole country and a substantial increase in the immunization budget. Vaccine coverage rate in children is good for the majority of compulsory vaccines except for the second dose of IPV (60% in 2018) and MMR in one-year old children (49% in 2018). The most important challenges are to i) guarantee high and homogenous coverages (≥ 95%) by type of vaccine in each district; ii) guarantee high quality of surveillance and research systems timely in case of a vaccine-preventable disease outbreak iii) implement rapid response to imported cases following standard mechanisms to prevent the reestablishment of endemic transmission; iv) achieve the extension of the vaccination program to other priority age groups, and v) strengthen the education of HCWs without whom vaccination program will not be optimal.

Panama

The NIP includes 23 vaccines, 3 vaccines for special situations, meningococcal vaccine and MMR for the management of outbreaks, and human anti-rabies for exposed individuals. Immunization for risk groups include pregnant women, elderly people with underlying chronic diseases. The first HPV vaccination program in LAC region started in Panama in 2008 for 10-11 years old girls [29].

Uruguay

The control or elimination of vaccine preventable diseases in Uruguay is based on a robust NIP as vaccination is universal, mandatory and free of charge. The population can receive the vaccines in public or private health sector. Coverage for the NIP vaccines was around 94% in 2017. The last case of measles was reported in 1998 and rubella congenital syndrome was eliminated in late 80s. Following the introduction of universal varicella vaccine in 1999, significant decrease in hospitalization, ambulatory visits and intensive care admission was observed. Similarly, after the introduction of universal hepatitis A vaccination in 2009, the number of cases dropped significantly. No more cases have been

reported since 2011. Future objectives are to i) maintain high vaccination coverage of vaccines in children, ii) improve the coverage vaccination of pregnant women (influenza, dpaT) and population with high risk of severe disease for vaccine preventable disease, iii) introduce rotavirus vaccine.

Vaccination Challenges in Latin America and Caribbean

While some countries in the region have world-class vaccination schemes, other still have them rudimentary. This huge diversity is one of the key parameters leading to inequality in the rate of infant mortality in the PAHO region (Figure 3) Reduction in VC due to political issues has led to the resurgence of diphtheria and measles in Venezuela. Consequently, measles outbreaks have occurred in the neighbouring countries and allowed the reestablishment of measles endemic transmission. OPV is still used in lots of countries even if the first dose should be IPV. Currently, few Latin American countries have vaccination against *meningococcus*. HPV is provided to women in a number of countries but yet needs to be introduced to men. Fluctuation in vaccine supply and poor cooperation of media to inform properly about benefits of vaccines are also factors that impact the vaccine coverage. Having local producers and unification of message among vaccine scientists can most probably help. Immunization coverage is low in many communities within countries in particular for adolescents, adults and pregnant women, leading to the risk of disease re-emergence, importation or new infections.

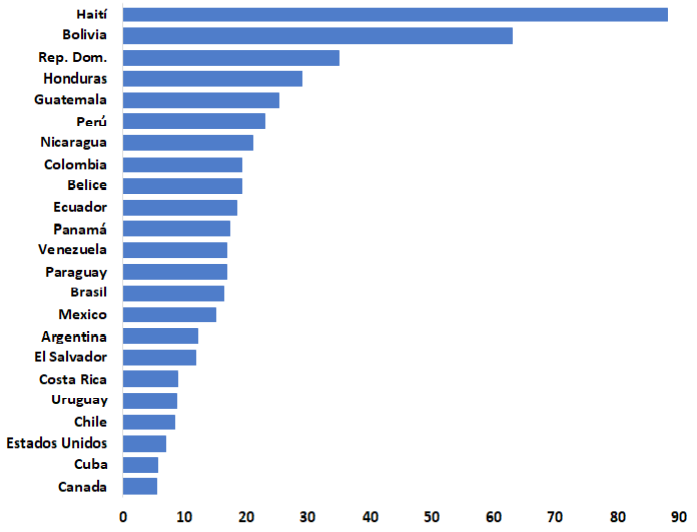

Figure 3: Infant mortality rate per 1000 < 5 years old in PAHO region.

Adult vaccination suffers from gaps and disparities. Strategies to increase VC in adults include improvement of awareness and information campaigns. Personal physicians have been reported as the most trustable person on adults' decision to get immunized [32]. Vaccination questions and concerns should be addressed during a clinic visit most probably by a dedicated team such as nurses. Alternate sites of care such as pharmacies can also enhance convenient access to vaccines. As shown by pertussis, maternal and neonatal tetanus elimination programs, maternal immunization works. Tdap has been introduced in Mexico, Panama, Colombia, Argentina and Brazil during the last decade. Vaccine effectiveness was more than 91% when the vaccine was administrated 8 days before birth [33] and is also effective in the second trimester of pregnancy. Maternal Tdap vaccination reduced pertussis severity [34] and hospitalization in infants. Integration of maternal and infant vaccination strategy can reduce morbidity and mortality in early infancy. Vaccination should be repeated in every pregnancy to achieve high antibody concentration and optimal protection for each new-born. The optimal timing, safety and efficacy surveillance are critical.

The concept of maternal immunization is to boost maternal levels of pathogen-specific IgG antibodies to protect the mother and the infant during a period of increased vulnerability (0-3 months). Maternal IgG can cross the placenta by a selective and active receptor-mediated transport system and confer protection to the foetus [35]. A number of factors such as gestational age at birth, interval vaccination to delivery, maternal IgG level at delivery and infections could alter transplacental antibody transfer [36]. Infant duration of protection is lower in vaccinated versus naturally immune mothers [37]. The key issue on maternal immunization is that recommendation is based on risk-benefit assessment as no vaccines have been licensed specifically for pregnancy. The perceived benefit-risk is a key consideration for the development of novel vaccines for use in pregnancy [38]. Integrating maternal and infant schedule allows protection as soon as possible. If all pregnant women are vaccinated, the EPI program can start later, leading to longer protection.

Conclusions

Vaccines are the most inexpensive means of improving health and lowering morbidity and mortality caused by infectious diseases. Countries in LAC were among the first developing countries to introduce new vaccines such as rotavirus and PCV into their national immunization programs and the PAHO revolving fund has played a central role in improving access to available vaccines at lower prices in the region. PAHO answered also the need of the countries in the region to incorporate local economic evidence into their decision-making process with a focused capacity building initiative called ProVac. The latter aims at strengthening national capacity to make informed, evidence-based decisions regarding vaccine introduction. Current focus of the initiative is on rotavirus vaccine, PCV, HPV and seasonal influenza vaccine. The establishment of the Regional Immunization Action Plan (2015) as the guiding framework for immunization in the LAC region

is another major achievement. The main objective is to adapt the Global Vaccine Action Plan to the regional context, to continue to strengthen the EPI in the region and to ensure universal and equitable access to immunization services.

To ensure universal and equitable access to vaccines especially for the most disadvantaged, there is need for new technologies. In particular, the cold chain storage should be modernized. Arktek device is a new technology designed to keep up to 5 litres of vaccines at appropriate temperatures for a minimum of one month in 43°C day time ambient temperatures and no need for electricity. This technology is helping to extend vaccination services in remote health posts. The device has already been used for a vaccination trial in Guinea [39]. Vaccine delivery by drones is also being tested in remote areas and has been shown to be cost-saving [40]. To increase vaccine uptake, supply should also be addressed [41]. Vaccine shortage can happen and reduced dose-schedule can be one option to maintain optimal vaccine coverage. Post-licensure additional RCTs or observational studies assessing the efficacy, effectiveness or immunogenicity of the vaccine may demonstrate that alternative schedules using less doses than recommended by the vaccine manufacturer can provide similar protection. The immunogenicity of a two-dose schedule of HBV combined with HAV was tested in 8-10 years' children and showed that sero-protection was similar to that obtained from three doses [42]. The introduction of one dose of HAV after a country wide outbreak in 2003-2004 in Argentina led to a reduction of 88% in the incidence of HAV infection rates [43]. Similarly, one dose of PCV delivered as one primary and one booster dose could be sufficient against pneumococcal disease [44]. Two doses of quadrivalent HPV vaccine given 6 months apart to 9-13 years old girls produced an immune response noninferior to 3 doses in young women aged 16 through 26 years [45]. Lowering the number of doses could facilitate a greater vaccine acceptance. In addition, the first doses are generally the most important.

At individual level, vaccine uptake can be influenced by vaccine hesitancy and vaccine refusal due to misinformation and the subsequent misperception about safety concerns. Vaccine hesitancy is influenced by many social, cultural, demographic and sociopsychological factors [46]. The top three reasons for hesitancy around the globe were lack of scientific evidence on benefice/risk, religion/culture/gender/socio-economic and knowledge/awareness [47]. However, reasons for hesitancy vary overtime, by vaccine, by age and may be clustered. Dube and collaborators identified 12 approaches to address vaccine hesitancy and to enhance vaccine acceptance [48,49]. At policy-maker level, decision-makers will require economic data as more vaccine become available. Most of the economic evaluation of vaccines focuses on a narrow set of vaccination-mediated health benefits, ignoring the role of vaccination as a driver of wealth [50]. A broader perspective including non-health benefits of vaccines such as productivity, risk reduction, equity/fairness, and fiscal impacts to fully capture the value of vaccines should be considered. Following the recommendation of the Commission on Macroeconomics and Health, the WHO considers a vaccine as highly cost-effective if the amount per Disability Adjusted Life Years averted is less than gross national income per capita. [51]. In Latin America, for every dollar invested in national immunization programs, 15 dollars are saved in the cost of health services and 44 dollars are saved when societal benefits are included. cost-effectiveness studies are unmet need that should be addressed to maintain political commitment in the decision-making process at the highest level in the Latin American countries [26].

In addition to the importance of economic evaluation of vaccines, knowledge on the burden of the disease is also crucial. Indicators for the epidemiological surveillance and burden of vaccine-preventable diseases should be developed together with local and regional research, development and production of vaccines. Countries of LAC should work together in sustainable plans, with medium and long-term measurable goals in research, development and production, to achieve better vaccination programs. Such a work would certainly reduce the burden of disease and inequality that exist today. The 2015 PAHO commitment called for an action for 2016 - 2020 to (i) protect and sustain the achievements, (ii) complete the unfinished agenda, (iii) tackle new challenges and (iv) strengthen health services for the effective delivery of immunization. Participation of opinion leaders (scientific, churches, governmental and non-governmental organization) and the communications media is also an essential allies of immunization programs. The Advisory Committee on Immunization Practices and the Commission for the Future of Vaccines in Latin America work in order to address the challenges facing Latin America [52]. The development of National Immunization Technical Advisory Groups in some LAC had also an important role within national immunisation decision-making and should be strengthened. In summary, in spite of significant advances, the implementation of optimal vaccination coverage remains a pipe dream because many obstacles and challenges remain. The nature of challenges varies and can be medical and scientific (e.g. concerns about safety), structural and demographic (e.g. poor infrastructure), economic and political (e.g. limited resources and high cost) or societal and cultural (e.g. anti-vaccine sentiments). The universal immunization programs can be extensively improved by taking into consideration all the above-mentioned issues and by providing policymakers measures beyond vaccine efficacy and a broader economic evaluation of vaccines.

Going to the best practices includes technical cooperation and partnership at regional level, revolving funds from PAHO, national program reviews every five years and set-up of country

action plan and its implementation every year. Surveillance and rapid coverage monitoring of high-risk municipalities is also crucial.

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