

XXV TAG Meeting



Twenty-Fifth Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases

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Acronyms

| | |
|--------|--|
| AEFI | Adverse Event Following Immunization |
| AFP | Acute flaccid paralysis |
| BM | Bio-Manguinhos |
| bOPV | Bivalent oral polio vaccine, type 1 and 3 |
| CCS | Containment Certification Scheme |
| CDC | Centers for Disease Control and Prevention in the United States |
| CI | Confidence Interval |
| CRS | Congenital rubella syndrome |
| cVDPV | Circulating vaccine-derived poliovirus |
| cVDPV2 | Type 2 circulating vaccine-derived poliovirus |
| cVDPV3 | Type 3 circulating vaccine-derived poliovirus |
| DAT | Diphtheria anti-toxin |
| DCVMN | Developing Country Vaccine Manufacturers Network |
| dPEF | Designated poliovirus-essential facilities |
| DTP3 | Diphtheria-tetanus-pertussis-containing vaccine, third dose |
| DTP4 | Diphtheria-tetanus-pertussis-containing vaccine, fourth dose |
| DTaP | Diphtheria-tetanus-acellular pertussis vaccine (pediatric formula) |
| EIR | Electronic immunization registry |
| EMTCT | Elimination of mother-to-child transmission |
| EPI | Expanded Program on Immunization |
| ES | Environmental surveillance |
| EVM | Effective Vaccine Management |
| EW | Epidemiological week |
| EYE | Eliminating Yellow fever Epidemics |
| GACVS | Global Advisory Committee on Vaccine Safety |
| GAPIII | WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use |
| GCC | Global Certification Commission |
| GNN | Global NITAG Network |
| GPEI | Global Polio Eradication Initiative |
| GVAP | Global Vaccine Action Plan |
| HBsAg | Hepatitis B surface antigen |
| HBIG | Hepatitis B immunoglobulin |
| HBV | Hepatitis B virus |
| HPV | Human papillomavirus |
| IEC | International Expert Committee for Documenting and Verifying Measles, Rubella and Congenital Rubella Syndrome Elimination in the Americas |
| IgG | Immunoglobulin G |

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|-------|--|
| IPD | Invasive pneumococcal disease |
| IPV | Inactivated poliovirus vaccine |
| iVDPV | Immunodeficiency-related vaccine-derived poliovirus |
| JRF | PAHO-WHO/UNICEF joint reporting form |
| LAC | Latin American and the Caribbean |
| LTA | Long term agreement |
| MeaNS | Measles Nucleotides Surveillance database |
| MI4A | Market for Information for Access to Vaccines initiative |
| mL | Milliliter |
| MMR | Measles-mumps-rubella vaccine |
| MMR2 | Measles-mumps-rubella vaccine, second dose |
| MNI | Maternal and neonatal immunization |
| mOPV2 | Monovalent oral polio vaccine, type 2 |
| MR | Measles and rubella vaccine |
| MR2 | Measles and rubella vaccine, second dose |
| NAC | National Authority for Containment |
| NCC | National Certification Committee |
| NITAG | National Immunization Technical Advisory Group |
| OPV | Oral polio vaccine |
| PAHO | Pan American Health Organization |
| PCR | Polymerase chain reaction |
| PCV | Pneumococcal conjugate vaccine |
| PCV7 | 7-valent pneumococcal conjugate vaccine |
| PCV10 | 10-valent pneumococcal conjugate vaccine |
| PCV13 | 13-valent pneumococcal conjugate vaccine |
| PEF | Poliovirus-essential facilities |
| PHC | Primary health care |
| POSE | Polio outbreak simulation exercises |
| PV2 | Type 2 polioviruses (including type 2 wild, VDPV type 2 and OPV/Sabin type 2) |
| RCC | Regional Certification Commission |
| RF | PAHO Revolving Fund for Vaccine Procurement |
| RIAP | Regional Immunization Action Plan |
| RNA | Ribonucleic acid |
| RTM | Remote temperature monitoring |
| RVC | Regional Monitoring and Re-verification Commission |
| SAGE | WHO Strategic Advisory Group of Experts on immunization |
| SDG | Sustainable Development Goals |
| SIA | Supplementary Immunization Activities |
| TAG | PAHO's Technical Advisory Group on Vaccine-preventable Diseases |
| Tdap | Tetanus toxoid, diphtheria toxoid and acellular pertussis vaccine (adolescent/adult formula) |

| | |
|--------|--|
| tOPV | Trivalent oral polio vaccine, type 1, 2 and 3 |
| UHC | Universal health coverage |
| UNICEF | United Nations Children's Fund |
| VAPP | Vaccine-associated paralytic poliomyelitis |
| VDPV2 | Vaccine-derived poliovirus, type 2 |
| VE | Vaccine effectiveness |
| VPD | Vaccine-preventable diseases |
| VSSM | Vaccination Supplies Stock Management software |
| WHA | World Health Assembly |
| WHO | World Health Organization |
| WPV | Wild poliovirus |
| WPV1 | Wild poliovirus, type 1 |
| WPV2 | Wild poliovirus, type 2 |
| WPV3 | Wild poliovirus, type 3 |
| wVSSM | Web-based Vaccine Supplies Stock Management software |
| YF | Yellow fever |

Introduction

The XXV Meeting of the Pan American Health Organization's Technical Advisory Group (TAG) on Vaccine-preventable Diseases was celebrated from 9-11 July 2019 in Cartagena de Indias, Colombia. The slogan for the meeting was "Let's do our part to protect our communities!" to parallel the slogan for this year's Vaccination Week in the Americas (VWA) campaign. The objectives of this meeting included reviewing the progress on several initiatives focused on controlling and eliminating vaccine-preventable diseases (VPDs) and issuing recommendations on ways to address the many challenges faced by national immunization programs in the Americas.

TAG Chair Peter Figueroa, PAHO/WHO Representative in Colombia Gina Tambini, PAHO Assistant Director Jarbas Barbosa, and Colombia's Minister of Health, Juan Pablo Uribe, started the meeting with remarks on the importance of the meeting to continue the Region's efforts to improve the immunization program's reach and impact at the national and regional levels, as well as to face current challenges. Dr. Tambini mentioned that Cartagena is an appropriate setting for the meeting, both because it is Colombia's capital of Human Rights and because the country has demonstrated its commitment to immunization through one of the most updated and comprehensive vaccination schedules in the Americas. Other topics touched upon during these opening remarks included continuing to address the measles outbreaks in Brazil and Venezuela and closing immunization gaps to reach as many unvaccinated individuals as possible.

As is customary at the end of the meeting, the winner of 2019's PAHO Immunization Award selected by the TAG was announced and this year's winner was Beryl Irons. Please visit <http://bit.ly/PAHO-IMAward> for information on past winners.



Credit: PAHO/WHO.

Update on the Regional Immunization Program

The Expanded Program on Immunization (EPI) of the Region of the Americas was created by PAHO in 1977 and has been a flagship program for the Region due to achieving the eradication, elimination and control of various vaccine-preventable diseases (VPDs) through extensive work done by PAHO's Member States. This has allowed the regional immunization program to be recognized as one of WHO's most important and successful programs in the world.

Globally, vaccination coverage has grown rapidly over the past ten years, and the number of available vaccines has significantly increased over the past 20 years. Challenges remain however, including the fact that three countries continue to have endemic polio transmission; the lack of WHO measles-free regions; and 19 million children that have not completed their vaccination schedules.

Progress in the Region has been significant since the creation of the EPI 42 years ago. Comparing vaccination coverages for each of the WHO regions from 1980 to 2017, we see that progress in the Americas has been very significant, despite the presence of unvaccinated or incompletely vaccinated children. Additionally, the Region of the Americas has been the Region with the earliest and most comprehensive introduction of new vaccines (pneumococcal, rotavirus and human papillomavirus [HPV]), and the first Region to eliminate smallpox, polio, rubella, congenital rubella syndrome (CRS), measles, and neonatal tetanus. Important challenges remain, generated by population displacement, large urban growth, social crises caused by economic or political unrest, natural disasters and the high levels of inequity that exist in the Region.

Immunization activities in the Americas are coordinated and guided in accordance with the Regional Immunization Action Plan (RIAP) 2016-2020 approved by Resolution CD54.R8 in 2015 and developed under the framework of the Global Vaccine Action Plan (GVAP). A progress report of the RIAP was submitted to PAHO's Governing Bodies in 2017 and an update will be presented subsequently in 2019.

The RIAP has four Strategic Lines of Action: 1) Sustain the achievements; 2) Complete the unfinished agenda in order to prevent and control VPDs; 3) Tackle new challenges in the introduction of vaccines and assess their impact; and 4) Strengthen health services for effective vaccine administration.

This Plan consists of 13 objectives (6 strategic and 7 general) and is monitored through 29 indicators. According to information from 2018, 15 of these indicators have adequate progress, six are considered in progress and eight have less than the expected progress.

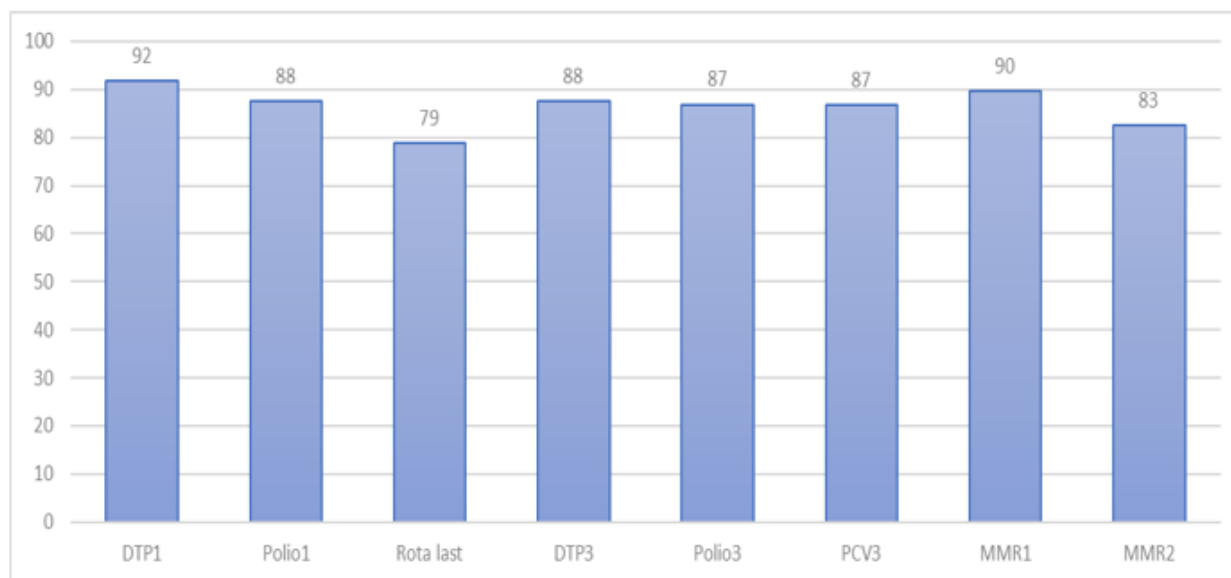
In Strategic Line of Action **1) Sustain the achievements**, some examples of progress are: The Region remains polio-free, as well as free of the endemic transmission of rubella and CRS, and Member States have maintained vaccination as one of their priorities. Unfortunately, the elimination of endemic measles in the Region was not maintained as Venezuela and Brazil re-established endemic measles. The other 33 Member States keep their status as "free of endemic

measles." Additionally, it is necessary to work on making individuals and communities understand the value of vaccines and their right and responsibility to demand immunizations.

Strategic Line of Action 2) **Complete the unfinished agenda** has the following achievements: Haiti eliminated neonatal tetanus; we have begun to address inequity in immunization in the Region, and numerous immunization activities were conducted during Vaccination Week in the Americas (VWA) aiming at improving vaccination coverage at all levels and increasing the visibility of immunization at the regional level. However, maintaining high and homogenous vaccination coverage at all levels remains a challenge:

- 1) Considering coverage with the diphtheria-pertussis-tetanus containing vaccine, third dose (DTP3) as a tracer, the latter was 88% at the regional level (**figure 1**), implying that around 1.5 million children had not been vaccinated at the age at which they should have been vaccinated (with no information available on the number of children that were subsequently vaccinated). This means that, for every 25 children in the Americas, two are left behind and one does not complete the schedule in a timely manner.

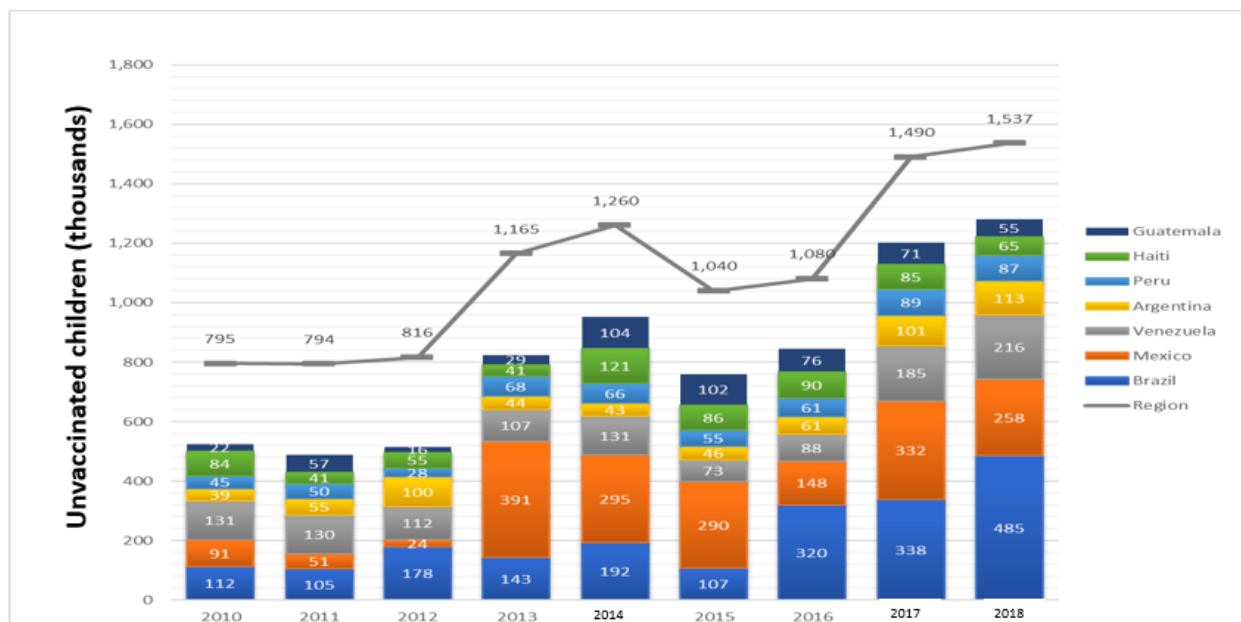
Figure 1. Vaccination Coverage by Biological in the Americas Region, 2018



- 2) The number of children under one year of age who have not received the DTP3 vaccine in a timely manner has increased in recent years (**figure 2**), mainly due to declining coverage in countries with large cohorts of children under one year of age, such as Argentina, Brazil, Mexico, Peru, and Venezuela. Haiti continues to have a significant number of unvaccinated children or children who complete their schedule at a later age than recommended, although their situation improved in 2018.
- 3) Coverage with the DTP3 vaccine analyzed by country income level (according to the World Bank) shows small differences between intermediate and high-income levels, and even though the gap has reduced in recent years, there are still major challenges for low-income countries.

- 4) A major challenge is not only to achieve high coverage at the national level, but to have homogeneous coverage at the subnational and local levels as well. According to 2018 data, 34% of children under one year of age in Latin America and Caribbean (LAC) live in municipalities with DTP3 coverage under 80%, that can also reach a low of 50%.

Figure 2. Populations under One Year of Age Who Have Not Been Vaccinated with the DTP3 Vaccine (in Thousands) in the Americas, 2010-2018



Significant progress has been made in Strategic Line of Action **3) Tackle new challenges in the introduction of vaccines and assess their impact**, such as the fact that 41 out of 52 (79%) countries and territories in the Region have introduced at least one new vaccine (i.e. rotavirus, pneumococcal or HPV vaccines).

There is a need for more operational research to be conducted to guide immunization actions. Another gap is the absence of comprehensive strategies addressing vaccine acceptance and demand, and confidence in the safety of vaccines through advocacy, education, training, and other interventions targeting all audiences. Therefore, it is necessary to take a more holistic approach to the problem of under-vaccination, understanding the social and behavioral determinants of vaccination and involving experts in social sciences, and communication, expanding the traditional skillset of immunization program managers and staff.

With regards to Strategic Line of Action **4) Strengthen health services for effective vaccine administration**, immunization has contributed significantly to achieving the Sustainable Development Goals (SDGs) and through PAHO's Revolving Fund, the availability of vaccines has been guaranteed for most countries and territories in the Americas. Another example of progress in this area is that 33 out of 52 (65%) countries and territories administer the influenza vaccine to pregnant women as a result of integration between immunization and maternal health systems; and 14 countries (27%) have made progress in developing and/or implementing

electronic immunization registries (EIRs). However, more efforts are needed to provide disadvantaged populations with timely access to vaccines, examples of these are indigenous people, migrants and populations affected by natural disasters or social crises.

Considering the four areas of the RIAP, we can see that while the immunization program has been successful thanks to the broad commitment of Member States, there are still major challenges to tackle. Some are beyond the control of immunization program, such as the political de-prioritization of immunization, program management difficulties that sometimes result from health reforms, and insufficient and delayed funding. There are also challenges directly related to the program, such as the need for appropriate strategies to ensure timely access to and availability of vaccines, information systems that allow analyses at all levels for timely decision-making, ongoing training for human resources and employing clear communication strategies at all levels.

Recommendations

- Countries should have a strong policy and legal framework to support vaccination as a human right and a social responsibility, with exemptions only for medical reasons, and with a dedicated budget for procurement and program operations, as an integral component of universal health coverage.
- Countries should promote vaccine confidence in immunization services and ensure that there is ready access to vaccination through primary health care services, as well as through a range of other opportunities, such as outreach, evening and weekend services.
- Countries should strengthen VPD surveillance and improve the monitoring of vaccination coverage and the quality and use of data to guide public health action.
- Countries need to achieve timely and complete immunization coverage in infancy and improve coverage for vaccines provided in the second year of life (e.g. DTP4, MR2 or MMR2).

Measles Outbreaks in the Americas

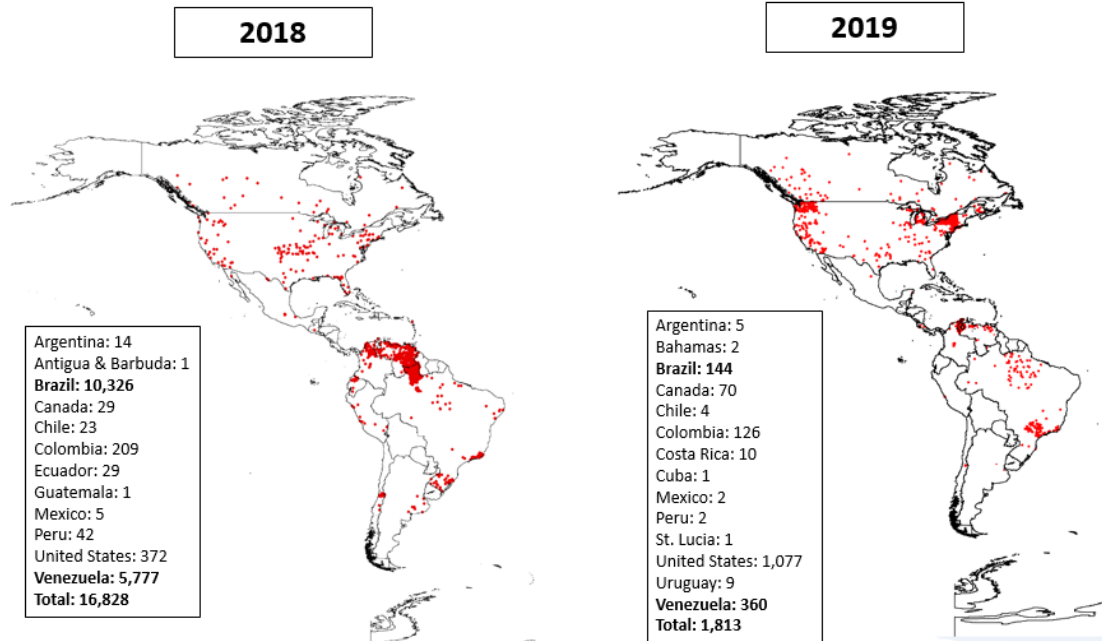
In 2018, there were 16,828 confirmed measles cases reported by 12 countries in the Region of the Americas, with a regional incidence rate of 16.8 per million population. This rate is the highest recorded during the post-elimination period. This unusual increase in cases related to low vaccination coverage in recent years in several countries. In Venezuela and Brazil, low vaccination coverage led to the reestablishment of endemic measles transmission in June 2018 and February 2019, respectively, following 12 months of continuous circulation of the measles virus (genotype D8, lineage MVi/HuluLangat.MYS/26.11) in their territories.

The rapid measles virus spread within and outside Venezuela resulted in importations and import-related cases in eight countries: Argentina (n=9 cases), Brazil (10,304 cases), Canada (n=1 case), Chile (26 cases), Colombia (335 cases), Ecuador (n=19 cases), Peru (24 cases), and the United States of the Americas (USA) (n=4 cases). Except for Colombia and Ecuador, the other six countries also reported imported cases from other regions of the world.

In 2019, there have been 1,813 measles cases in 14 countries, with an incidence rate of 1.8 per million population¹; Brazil, Colombia, USA and Venezuela have had ongoing measles transmission since 2018, while the remaining ten countries have either interrupted transmission following isolated imported cases or are closely following up on secondary cases to ensure the rapid interruption of virus transmission (**figure 3**).

¹ Data as of epidemiological week 25, 2019

Figure 3. Distribution of Confirmed Measles Cases by Sub-national Level in the Americas, 2018-2019



Sources: Surveillance country reports sent to PAHO/WHO's Comprehensive Family Immunization Unit, and Ministry of Popular Power of Venezuela.

During 2018 and 2019, Brazil (56%), Colombia (2%), USA (8%) and Venezuela (33%) reported the highest proportions of measles cases in the Region. The table below summarizes the main characteristics of these outbreaks. The proportions of cases by age group presented refer to two main age groups affected in each country.

Table 1. Characteristics of Measles Outbreaks Reporting the Highest Proportion of Cases in the Americas, 2018-2019*

| | Venezuela** | Brazil | Colombia | United States ^(a) |
|---------------------------------------|--|---|---|--|
| Total of Confirmed Cases | 6,864 | 10,474 | 343 | 1,453 |
| Ages of Cases (%) | <1y (20%); 1-4y (46%) | <1y (17%); 15-29y (46%) | <1y (26%); 1-4y (33%) | 1-4y (32%); 20-39y (16%) |
| Unvaccinated^(b) (%) | 93% | 74% | 91% | 89% |
| Affected states (%) | 23/24 (95%) | 13/27 (48%) | 16/37 (43%) | 2018: 26/50 (52%) 2019: 28/50 (56%) |
| Affected municipalities (%) | 113/335 (34%) | 99/5570 (1,6%) | 34/1122 (3%) | No data |
| Last Onset | 06/04/2019 | 05/25/2019 | 06/15/2019 | 06/19/2019 |
| Genotype | D8 | D8, B3 | D8 | D8, B3, D4 |
| Risk Factors | Difficulty for a rapid response at the state and municipal levels; cumulative low coverage; nosocomial transmission; lack of human and logistic resources; virus spreading in indigenous communities | High migration; difficulty for a rapid response at the state and municipal levels; cumulative low coverage; nosocomial transmission; lack of laboratory kits; virus spreading in indigenous communities | High migration; overload of field outbreak investigation; nosocomial transmission; pockets of susceptible children in some departments; virus spreading in indigenous communities | Under vaccination due to philosophical or religious beliefs; unvaccinated residents traveling internationally |
| Virus Spreading | Quick virus spreading inside and outside of the country | Quick virus spreading to 13/27 states; Amazonas and Roraima concentrated 97% cases. | Virus spread in places with pockets of susceptible individuals in some departments; high vaccine coverage and rapid public health response has limited spread in Colombia. | Virus spread within close-knit communities due to vaccine hesitancy and other community-specific issues; high vaccine coverage and rapid public health response limited the spread |
| Deaths | 79 | 12 | 0 | 0 |

Source: ISIS, MESS, country reports to FPL-IM/PAHO *Data as of epidemiological week 26, 2019. ** Data as of 2017-2019 for Venezuela

- (a) Includes all cases and outbreaks, which is defined as a chain of transmission of 3 or more cases linked in time and space.
- (b) Includes unvaccinated cases, with unknown vaccination history or no data.

Despite the delicate situation of the Venezuelan health system, health authorities managed to organize a national campaign vaccinating 8.6 million children aged 6 months to 15 years old, and 460,844 individuals aged 15 years and older during the second half of 2018. This campaign that reached 97% coverage at the national level was followed by a rapid decline in measles cases. Brazil also carried out a national measles vaccination campaign, vaccinating 10.9/12 million (98%) children 1-4 years of age. In the Amazonas state, vaccination of infants aged 6 months, adolescents and young adults was additionally conducted. In Roraima, vaccination of infants was also carried out. Colombia did not conduct a national vaccination campaign, but the country has managed to successfully interrupt circulation of the virus by responding rapidly to the outbreak, stepping up efforts to find and vaccinate unvaccinated children under 5 years of age and by providing free doses of the measles and rubella vaccine to 88,819 children aged 6-11 months living in municipalities with ongoing measles outbreaks (82% coverage). The country also applied more than 1.1 million doses of the measles-and-rubella-containing vaccine to Venezuelan migrants, targeting children younger than 15 years of age.

In response to the multiple and challenging measles outbreaks in the Americas, PAHO's Comprehensive Family Immunization Unit (IM) intensified its technical cooperation by a)

advocating at the highest political country level for immunization solidarity and strong outbreak response; b) mobilizing \$7.4 million (USD), of which 87% were for Venezuela; c) continuing deployment of regional technical assistance and experienced consultants for outbreak response; d) conducting ten national outbreak response trainings and three sub-regional training workshops; e) strengthening in-country coordination of immunization and surveillance; and f) procuring laboratory reagents and strengthening national molecular epidemiology capacities in eight countries.

Molecular Epidemiology on Measles

Measles is an RNA virus of the *Morbillivirus* genus of the family *Paramyxoviridae*. The single-stranded negative RNA genome consists of 15,894 nucleotides which code for six structural proteins (N, P, L, M, F and H) and two non-structural proteins (C and V). Measles is probably a monotypic virus, as genetic and antigenic variations have been detected in wild-type viruses. Twenty-four measles genotypes have been identified (A, B1, B2, B3, C1, C2, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, E, F, G1, G2, G3, H1 and H2). Genetic analysis of the 450 nucleotides region of the N gene has been used as a tool for molecular epidemiology to track transmission pathways, characterize outbreaks, contribute to interrupting endemic transmission and document importations.

Measles sequence data has been made available in the Measles Nucleotides Surveillance database (MeaNS, available on <http://www.who-measles.org>) supported by WHO. Measles virologic surveillance has been expanded through the laboratories of the global and regional laboratory network. However, in recent years, a reduction in the diversity of circulating genotypes has been observed, creating a challenge to discriminate between closely related viruses within a single genotype. The phylogenetically similar strains observed within a genotype have been designated as “named strains” that represent an epidemiologically significant viral lineage. Named lineages represent at least 50 identical sequences reported within the last two years, and from at least three different countries. Further genetic analyses allowing for a better resolution of the genetic divergences would be useful, especially to document multiple importations of the same genotype and estimates of measles virus mutation rates during long chains of virus transmission.

The Region of the Americas is experiencing a similar situation. During 2017, a total of 159 measles sequences were reported to MeaNS in four countries (Argentina, Canada, USA and Venezuela) and three measles genotypes were identified within multiple importations: B3 (52.8%), D8 (45.9%), and H1 (1.3%). Different B3 and D8 lineages were identified (five and three lineages, respectively).

In 2018, eleven countries reported a total of 460 measles sequences to MeaNS (1 in Antigua and Barbuda, 8 in Argentina, 105 in Brazil, 27 in Canada, 17 in Chile, 79 in Colombia, 16 in Ecuador, 1 in Guatemala, 2 in Mexico, 198 in the USA, and 6 in Venezuela); in 91,5% of the sequences reported, genotype D8 was identified and in 8%, genotype B3; only two sequences (0.5%) were associated with the D4 genotype. One interesting issue was related to the multiple importations

of D8 genotypes and the documentation of different lineages within countries of the Region; in Argentina, two lineages; Canada, four different lineages and in the USA, six different lineages.

For the first time in the history of measles elimination in the Americas, a country in the Region had multiple importations of the same genotype and lineage. Colombia reported a total of 79 measles sequences to MeaNS in 2018; 61 of these were identical (same genotype and lineage); 34/61 were identified in imported cases and 27/61 were identified in cases without history of travel. 18/79 sequences were identified with 1 nucleotide of change; 8/18 had history of recent travel and 10/18 had an unknown source.

This situation raises the concern that sequencing the N-450 gene is probably not enough to differentiate between new importations or chains of transmission. Amplifying the measles genomes of other regions can facilitate the identification of different chains of transmission. More deep sequence analysis is needed to achieve a better understanding of the mutation rate of the virus during the chains of transmission and to facilitate the identification of multiple importations of the same genotype and lineage coming from different sources.

Proposal for a Regional Framework to Monitor and Re-verify Measles and Rubella Elimination

The Regional Monitoring and Re-verification Commission (RVC) for Measles and Rubella Elimination met in June to develop consensus on the elements from the original 2011 Plan of Action for verifying elimination that should be maintained and those that need updating. The Commission agreed to the framework developed during the meeting, with substantial modifications to the original objectives, basic principles and essential criteria. The Commission also concluded that endemic countries applying for re-verification would need to document absence of transmission for more than one year, using rigorous criteria developed by the Commission. Those who did not meet the criteria would not be re-verified as free of measles.

During the TAG meeting in Colombia, TAG members emphasized the importance of using the standard and sensitive suspected measles case definition (fever and rash), as re-verification of elimination will require the review of one year of use of this case definition. TAG also reminded countries that during outbreaks, countries may consider the criteria of clinical and epidemiological links to a confirmed case for case confirmation. However, it is important that countries temporarily altering measles case definitions, such as during arbovirus outbreaks or outbreaks of other fever-and-rash-causing diseases, document their use.

Finally, countries may consider reactivating their national measles committees to monitor the sustainability of elimination, to promote the development and implementation of annual national plans for the sustainability of measles elimination, and to ensure that these reports are submitted to PAHO at the beginning of each year.

Recommendations

- TAG expresses serious concern about ongoing measles outbreaks in the Region and urges the affected countries to take urgent action to interrupt measles transmission and stop further spread of the virus.

- TAG strongly encourages the global community to set a target and develop a program for the global eradication of measles and rubella and calls on countries of the Americas and PAHO, in partnership with other Regions, to advocate for establishing this at the next meeting of the World Health Assembly in 2020.
- TAG endorses the proposed regional framework for the monitoring and re-verification of measles and rubella elimination. The standard, sensitive measles case definition should be used in all countries of the Region. Endemic countries will have to document absence of measles virus transmission for more than one year, to meet re-verification criteria.
- TAG strongly urges Member States to achieve 95% vaccination coverage levels at all administrative levels for the two recommended doses of measles and rubella vaccines and ensure high quality surveillance and rapid response. Follow-up campaigns should be conducted based on risk assessments.

Strengthening Pertussis Surveillance in the Americas

Despite the increase in vaccination coverage for DTP3 worldwide, pertussis (or whooping cough) continues to be an important cause of morbidity and mortality in children under 1 year of age and is a cause for concern in public health. The Region of the Americas is not exempt from this situation. In the last 15 years, several countries have reported the resurgence of pertussis among all population groups; on average, ten countries report outbreaks every year. Higher incidence rates have been reported in children aged less than 1 year old. The number of deaths from pertussis reported in the Region of the Americas in the last five years exceeds the number of deaths recorded by other VPDs (e.g., measles, diphtheria).

Regarding vaccination status during the last five years, regional coverage for DTP3 has not reached the regional goal of $\geq 95\%$. The heterogeneity of coverage at the subnational level presupposes the existence of pockets of unvaccinated population that could be susceptible to whooping cough. In 2018, the Region achieved 88% and 75% coverage with DTP3 and DTP4, respectively. Sixteen of the 52 countries and territories in the Americas reported coverage $\geq 95\%$ for DTP3, while four of the 52 countries and territories reported coverage $\geq 95\%$ for DTP4. In that same year, 4115 (27%) of the 15,170 municipalities in the Region reported coverages $< 80\%$ for DTP3. It is estimated that 52% of the cohort of live births of the countries of the Region live in these municipalities.

The lack of standardization for case definitions used among countries and differences in diagnostic capacities (clinical and laboratory) makes it difficult to analyze the regional situation. For this reason, in 2014, the TAG recommended standardizing pertussis surveillance in the Region of the Americas, for which PAHO/WHO convened a working group. The group's first proposal was submitted to the TAG in 2017. However, because WHO was in the process of finalizing global guidelines for pertussis surveillance, the TAG concluded that it would consider the proposal for the regional standardization and strengthening of pertussis surveillance at its next meeting.

In September 2018, WHO published standardized global guidelines for pertussis surveillance. In February 2019, the PAHO/WHO working group held a meeting to review the regional proposal based on epidemiological surveillance standards defined by WHO. The main results of this review are as follows:

1) Case definitions to standardize pertussis surveillance at the regional level:

| | |
|---|---|
| <i>Suspected case (< 1 year of age)</i> | Any case presenting with a cough of any duration, without other apparent cause, accompanied by at least one or more of the following symptoms: <ul style="list-style-type: none">• paroxysms (fits) of coughing• inspiratory stridor• vomiting after coughing or vomiting without any other apparent cause• apnea or <ul style="list-style-type: none">• Clinical suspicion of pertussis |
|---|---|

| | |
|--|---|
| <i>Suspected case (≥ 1 year of age)</i> | Any case presenting with a cough ≥2 weeks duration, or any duration in an outbreak setting, with no other likely diagnosis, accompanied by at least one or more of the following symptoms: <ul style="list-style-type: none"> • paroxysms (fits) of coughing • inspiratory stridor • vomiting after coughing or vomiting without any other apparent cause or • Clinician suspicion of pertussis |
| <i>Laboratory-confirmed case</i> | Any suspected case with laboratory confirmation through: <ul style="list-style-type: none"> • Isolation of <i>B. pertussis</i> (culture) or • Detection of the genomic sequence of <i>B. pertussis</i> by means of PCR or • Elevation of IgG for pertussis toxin in an individual ≥ 11 years of age, and one year or more after administration of the last dose of vaccine. |
| <i>Case confirmed by epidemiological link</i> | Suspected case that has had close contact with a laboratory-confirmed case (or with a case confirmed by epidemiological link in outbreak situations) in the three weeks prior to the onset of cough |
| <i>Probable case</i> | A suspected case that does not meet the confirmation criteria nor the discarded criterion. |
| <i>Discarded case</i> | Suspected case in which another diagnosis was documented |
| <i>In outbreak situations</i> | The definition of a suspected case be modified to include cough of any duration. In case of an outbreak, samples should be collected only from the first 3-10 cases to confirm the outbreak. |

2) Indicators to assess the quality of pertussis surveillance:

| Indicator | Goal | Numerator/denominator |
|--|--------------|---|
| % cases with adequate investigation* (only applies if the country investigates cases) *Adequate investigation includes: completed investigation form, sample collection, line listing of close contacts. This applies in small outbreaks. If any of the above is not carried out, the investigation is considered inadequate. | At least 80% | # of suspected cases with adequate investigation / # of suspected cases x 100 (for a given period) |
| % cases investigated within 48 hours | At least 80% | # of suspected cases with investigation initiated within 48 hours of notification/# of suspected cases x 100 (for a given period) |
| % cases with at least one laboratory sample collected | At least 80% | # of suspected cases with sample collected /# of suspected cases x 100 (for a given period) |

| Indicator | Goal | Numerator/denominator |
|---|--------------|---|
| Respiratory sample at any age, or blood sample for children ≥ 11 years | | |
| % samples received in the laboratory within two days of collection | At least 80% | # of specimens received in the laboratory within two days of collection/# of specimens collected x 100 (for a given period) |
| % of laboratory results reported in a timely manner Timely manner means: PCR: 2 days; Culture: 7 days | At least 80% | # of laboratory results reported in a timely manner/# of specimens collected x 100 (for a given period) |

Recommendations

- TAG urges Member States to achieve pertussis vaccination coverage levels $\geq 95\%$ in all children < 1 year. Coverage with the DPT4 vaccine should be monitored.
- TAG reiterates its previous recommendation on using whole cell pertussis vaccines for the primary infant vaccination series and on initiating vaccination schedules at 6 weeks of age in outbreak situations.
- TAG endorses PAHO's revised guidelines for pertussis surveillance and urges countries to implement surveillance and improve the diagnostic capacity of the laboratory. This will strengthen the reporting and characterization of pertussis outbreaks in the Region. TAG urges countries to implement special surveillance among hospitalized children under one year of age.

Current Landscape of Maternal Immunization in the Americas

Maternal immunization is a promising strategy to reduce infectious-disease-related morbidity and mortality during the first weeks of life. One of the goals of PAHO's Regional Immunization Action Plan (RIAP) is establishing and strengthening maternal and neonatal immunization (MNI) platforms in the context of enhancing health services for effective vaccine administration. The Region has made important achievements such as CRS elimination in 2015 and maternal and neonatal tetanus elimination in 2017.

PAHO's TAG has previously recommended the use of the tetanus-containing vaccine, influenza vaccine and acellular pertussis-containing vaccine (the latter only in the case of outbreaks) among pregnant women. Currently, 32 of the 52 countries and territories of the Americas recommend the tetanus-containing vaccine for women at childbearing age, 34 countries recommend vaccination of pregnant women against influenza and 16 countries recommend the administration of the acellular pertussis-containing vaccine (tetanus toxoid, diphtheria toxoid and acellular pertussis vaccine [Tdap]) in every pregnancy.

Aiming to generate evidence and document lessons about maternal immunization in Latin America, PAHO constituted the Maternal and Neonatal Immunization Group in 2016. A mixed-methods study with the objectives of understanding the state of MNI policies, strategies and practices in the capital cities of five countries (Argentina, Brazil, Honduras, Mexico and Peru) in Latin America, and describing the knowledge and perceptions of pregnant women and health workers regarding MNI has been recently completed. The knowledge gained should enable the Region to advance the use of recommended maternal and neonatal vaccines, and the introduction of future maternal vaccines such as respiratory syncytial virus and group B streptococcus vaccines that will significantly decrease neonatal morbidity and mortality.

Maternal Pertussis Immunization

Pertussis is an endemic and cyclical disease, with peaks occurring at two- to five-year intervals. The main objective of pertussis vaccination strategies is to reduce disease incidence and severe outcomes (defined as hospitalization and deaths) from pertussis infection among infants less than 12 months of age. The reemergence of pertussis has been reported in the Region with a higher incidence rate in this age group, representing one of each three reported cases.

In July 2014, the TAG reviewed the topic and recommended that the response to outbreaks of whooping cough should include: "lowering the age for initiating vaccination to 6 weeks and vaccinating pregnant women only in areas affected by the outbreaks." By then, it was considered that there was not enough evidence for TAG to recommend routine vaccination of pregnant women.

In 2015, a revised position paper on the pertussis vaccine by WHO's SAGE incorporated evidence on the use of additional pertussis vaccination strategies for prevention of early infant mortality. In relation to vaccination during pregnancy, it was recommended that, "Vaccination of pregnant

women is likely to be the most cost-effective additional strategy for preventing disease in infants too young to be vaccinated and appears to be more effective and favorable than cocooning. National programs may consider the vaccination of pregnant women with 1 dose of Tdap (in the 2nd or 3rd trimester and preferably at least 15 days before the end of pregnancy) as a strategy additional to routine primary infant pertussis vaccination in countries or settings with high or increasing infant morbidity/mortality from pertussis (...)"

Ever since, new evidence on Tdap administration during pregnancy regarding safety, immunogenicity, effectiveness, effect on infant immunity, cost-effectiveness and programmatic considerations has become available. Recent reviews from Gkentzi et al, 2017; Brophy et al, 2018; and Campbell et al, 2019 consistently indicate that maternal immunization with the acellular pertussis-containing vaccine, such as Tdap in pregnancy is safe. No significant safety issues have been detected and no increased risk of serious adverse pregnancy, maternal or infant events have been reported in countries currently offering Tdap vaccine for immunization in pregnancy. Regarding immunogenicity, post-immunization increases in antibody levels resulted in more than 90% of women achieving anti-pertussis toxin levels greater than or equal to 10IU/ml one month following immunization and maternal pertussis-containing immunization during pregnancy was found to result in increased infant pertussis antibody concentrations (through efficient transplacental transfer of maternal antibodies).

The effectiveness of maternal pertussis immunization in preventing infant pertussis was first demonstrated in England, by Amirthalingam et al. In 2015, three years after introducing this strategy, vaccine effectiveness (VE) against laboratory-confirmed pertussis for infants aged <3 months was demonstrated to be over 90%. The incidence in this age group remained low despite high activity persisting in those aged one year and older and VE against deaths was estimated at 95% (95% CI, 79%-100%). In the United States, the VE estimate by Skoff et al for Tdap administered during the third trimester was 77.7% (95% CI, 48.3%-90.4%) and 90.5% (95% CI, 65.2% - 97.4%) against hospitalized cases. Other studies conducted in middle-income countries in Latin America (where infant schedules use whole cell pertussis-containing vaccines) also showed that Tdap vaccination during pregnancy is effective. In Argentina, Romanin et al observed a VE estimate of 80.7% [95% CI 52.1%-92.2%] among infants <2 months of age, and Fernandes et al in Brazil estimated a VE of 82.6% [95% CI 60.8-92.3%]) in preventing pertussis among infants <2 months of age. Maternal immunization with Tdap in pregnancy also resulted in a reduction of infant disease severity and hospitalization.

The review from Brophy et al concluded that effects of the maternal acellular pertussis-containing vaccine in pregnancy on decreasing the infant's immunological response after the first doses of the primary vaccine schedule (blunting) have been observed. The clinical significance of these findings is uncertain, and to date there is no evidence of an increased risk of pertussis in infants aged 3-11 months in the United Kingdom and United States. In addition, in the majority of studies, following the receipt of the four DTaP doses with the fourth dose after 15 months of age, statistically significant differences in antibody levels and avidity were not observed between infants whose mothers received the Tdap vaccine in pregnancy and those whose mothers did not receive the Tdap vaccine in pregnancy.

A 2014 systematic review conducted by Rivero-Santana et al in several high income countries examined the cost-effectiveness of different pertussis vaccination strategies and showed that vaccination of pregnant women was the most cost-effective strategy and more effective than cocooning. Most recently, cost-effectiveness studies conducted in low- and middle-income countries have demonstrated similar results.

There is now an increasing body of evidence to support the safety, immunogenicity and effectiveness of maternal pertussis immunization and to support a recommendation for Tdap vaccination in each pregnancy, irrespective of previous Tdap immunization history or the interval between pregnancies (given the rapid waning of maternal antibody observed in studies). The existence of evidence from the Region about the impact and cost-effectiveness of Tdap vaccination during pregnancy also support this recommendation. It is noteworthy that countries considering Tdap vaccination in pregnancy should assess operational and vaccine supply issues as part of their decision-making process. Routine maternal Tdap immunization during pregnancy will provide more robust and complete protection against pertussis among infants compared to immunization in outbreak settings (or during outbreaks) only.

Recommendations

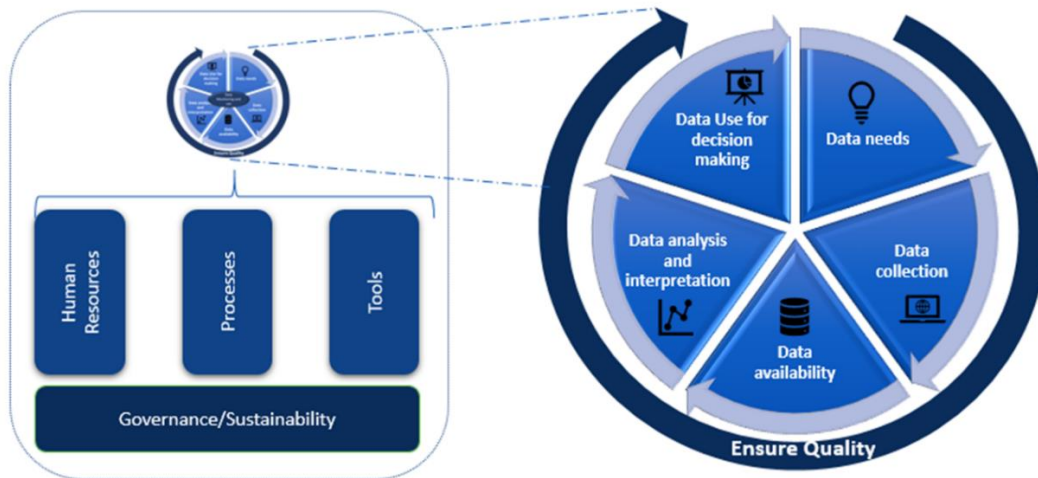
- TAG recognizes the Region's progress in maternal immunization, including pertussis and seasonal influenza vaccination. Countries must continue to monitor vaccine safety among pregnant women.
- TAG recognizes the value of vaccinating pregnant women with Tdap to protect the neonate as an effective complementary strategy to routine primary infant pertussis vaccination, particularly in countries or settings with high infant mortality from pertussis. Thus, TAG endorses the SAGE recommendation for Tdap vaccination in pregnancy, during the second or third trimesters, and at least 15 days prior to delivery. TAG also reinforces the need to sustain high vaccination coverage for DTP3 among infants and DTP4 in the second year of life.
- TAG encourages countries to monitor and report Tdap vaccine coverage among pregnant women as it is important to reach and sustain coverage of more than 50% to ensure effectiveness for this vaccination strategy.
- TAG encourages that countries whom have introduced maternal Tdap vaccination evaluate impact of the vaccine on the long-term protection of children against pertussis, particularly in countries using infant whole cell pertussis-containing vaccines.
- TAG recommends considering the vaccination of health care facility personnel with the Tdap vaccine, prioritizing maternity ward personnel and caregivers for newborns and children under 1 year of age.
- TAG encourages countries to continue documenting maternal immunization practices, associated challenges and best practices to achieve high coverage and the local impact of the strategy.

Immunization Data Quality and Analysis

Since 2002, PAHO's TAG has stressed the importance of countries strengthening data quality to guide public health action, through ongoing and systematic assessments of immunization data, and capacity-building for data analysis. To work towards that goal, TAG recommended in 2009 that countries implement and use electronic immunization registries (EIRs). During subsequent meetings, TAG expanded recommendations to include other important considerations for data quality improvement, including data collection standards, coordination with other actors, system interoperability, data monitoring and evaluation, and the use of innovative mobile health (mHealth) technologies. At the global level, SAGE recommended in 2011 that countries improve the quality and use of national and subnational coverage and surveillance data to enhance country ownership, monitoring, and accountability of immunization service delivery under the Global Vaccine Action Plan (GVAP) (2011-2020). Due to ongoing concerns pertaining to data, SAGE established a working group on the quality and use of global immunization and surveillance data in August 2017. This working group will present a topic-specific report in October 2019.

Based on work that the countries in this Region have done and using PAHO's support, existing data quality and data use frameworks, a process model was developed (**figure 4**) indicating that governance and sustainability are the foundation for data quality and use. The main pillars of data quality and use are human resources, processes and tools. These pillars support the cycle of data needs, data collection, data availability, data analysis and interpretation and finally, data use for decision-making. Each stage of the cycle is crosscut by quality and is moving towards increasing the body of knowledge and evidence of what works to increase data quality and data use, and why actions work.

Figure 4: Process Model for Data Quality and Use



The need for high quality and timely data at the local, national, regional and global levels has grown, and so has the production of information by immunization programs, such as information on new vaccines, monitoring coverage levels in new age groups and at all administrative levels, as well as information on accountability. The Region has faced these challenges by reinforcing the PAHO-WHO/UNICEF joint reporting form (JRF) as the main integrated source of information and stressing the importance of involving countries and other partners in the development of information systems at the earliest possible stages.

In countries of the Americas, data collection is conducted using a variety of paper-based tools such as home-based records, tally sheets, daily and monthly records, and EIRs. In general, the high volume of variables and high quantity of forms that staff need to complete generate an increasingly heavy workload for health workers. The development of norms and procedures and the use of EIRs are among the best practices for data collection in the Region. Ensuring integration under the umbrella of eHealth and interoperability with other systems is important for the use of digital systems.

Data must be available at all levels and to complete the data cycle, there needs to be systematic feedback to the level that is sending or originating the information. WHO and the regional offices have been working towards developing the WHO Immunization Information System (WIISE). WIISE is a collection of applications to collect, manage, analyze and disseminate worldwide immunization and VPD surveillance data reported to WHO. It will streamline processes and workflows and improve the overall governance of immunization data across the WHO system. Countries in the Americas have developed different ways to visualize data on paper (i.e. maps, monitoring charts, bulletins), as well as electronically (i.e. dashboards, web pages etc.).

The last two parts of the cycle, i.e. data analysis, interpretation, and use for decision-making, are interrelated; however, we have found a disconnect between data analysis and use, demonstrating the need to close this gap. The Region has traditionally performed aggregated data analysis, yet the progress of countries in the Americas in implementing and using EIRs has

facilitated more in-depth analyses of the individual cohort data. The use of EIRs has also prompted national teams to define new performance indicators. Moving forward, it is important to take advantage of all the functionalities that the EIR presents, including to analyze geographical information, timeliness, vaccination opportunity, etc. Ultimately, integrated analyses should guide the implementation of immunization strategies and activities that respond to the identified needs.

A recent systematic literature review conducted by PATH and PAHO entitled “Immunization Data: Evidence for Action” found evidence indicating a cyclical relationship between data quality and use. Indeed, data quality improves because of increased data use. Additionally, increased data use generates more demand for higher quality data, which in turn drives actions to improve data quality. As data quality improves, users tend to increase their trust in the data, thus reinforcing data use. We aim to create a culture of high-quality data use, whereby individuals involved in the data cycle create quality data, analyze it and generate informed decisions. Reliable data will be crucial to take the actions that keep our Region free of VPDs.

Recommendations

- TAG encourages countries to continue monitoring immunization and surveillance data quality, and to build a culture of data use for public health action at all administrative levels.
- TAG recommends that PAHO facilitate the documentation of experiences and best practices from countries that have progressed with regards to data quality and use.
- TAG encourages countries to conduct periodic evaluations of data contained in immunization registries, with guidance from PAHO as needed.

Global Update

There has been an increase in wild poliovirus type 1 (WPV1) cases this year. As of epidemiological week (EW) 24 2019, there have been 29 cases of WPV1, compared to 12 cases during the same time in 2018. All cases are from Pakistan (75%) and Afghanistan (25%). Insecurity and access remain critical issues in these countries.

Also, there are multiple type 2 circulating vaccine-derived (cVDPV2) outbreaks occurring on the continent of Africa. The emergence of new strains of cVDPV2 in areas where mOPV2 has been used and tOPV and mOPV2 vials have been found, the recent spread of cVDPV2 into southern Nigeria, including the densely populated Lagos State, and evidence of missed transmission in Nigeria and Somalia, suggest that the situation continues to deteriorate. Insufficient coverage with IPV exacerbates the growing vulnerability on the continent to cVDPV2 transmission. Additionally, cVDPV1 outbreaks in Papua New Guinea and Indonesia and cVDPV3 in Somalia highlight gaps in population immunity due to pockets of persistently low routine immunization coverage in many parts of the world.

Major risks to global polio eradication include: growing risk of cVDPV spread, falling poliovirus type 2 immunity, weak routine immunization, low quality supplementary immunization activities (SIAs), surveillance gaps, lack of access, and population movement. To confront these challenges, the Global Polio Eradication Initiative (GPEI) has recently launched a new plan: The Polio Endgame Strategy 2019-2023. Additionally, they have published updated guidelines on polio surveillance, including polio surveillance among persons with primary immunodeficiency disorder.

Regional Update

This year marks the 25th anniversary since the International Commission for the Certification of Poliomyelitis Eradication in the Americas (ICCPE) declared the Americas free of polio. However, while recognizing and celebrating this milestone, countries of the Americas must remain vigilant. The TAG is concerned that regional coverage for the polio-3 vaccine is declining. The lowest regional polio-3 vaccine coverage since certification in 1994 was reported for the last two years (2017 and 2018). Additionally, pockets of disparity remain a concern. More than a quarter (28%) of all districts in the Region have coverage below 80%. 2018 data shows that 7 out of 10 children live in a district where coverage is below the regional standard (95%).

Currently, 33/52 of countries and territories of the Region use two or more doses of IPV, including Ecuador and Cuba, whom introduced two fractional doses of IPV following TAG's recommendation. However, 19 countries are still using only one dose of IPV. This is of concern because population immunity against type 2 polioviruses continues to decrease, as the cohort of children born after OPV2 withdrawal grows, and the potential risk of importation of cVDPV 2 rises.

Regarding surveillance, only six countries in 2018 met all three key acute flaccid paralysis (AFP) surveillance indicators (Bolivia, Cuba, Mexico, Nicaragua, Panama, Paraguay). However, the quality of AFP surveillance has not been sustained; in just the last 52 weeks, Mexico and Nicaragua have met the three key indicators. Additionally, there is lack of compliance with the standards for final classification of AFP cases.

Countries are not conducting the 60-day follow-up of AFP cases, which is a major concern, particularly in cases where an adequate stool sample was not obtained. In 2018, only 15% of cases received a 60-day (+/- 7 days) follow-up. In addition, there is late final classification of AFP cases. In fact, eight countries have AFP cases reported in 2018 that are pending final classification.

PAHO has updated the analysis of the risk of vaccine-associated paralytic poliomyelitis (VAPP) in LAC, as follow-up of the work done by Andrus et al. (1989-1991) and Landaverde et al. (1992-2011). The results show that from January 2012 to April 2016 (before the switch from tOPV to bOPV), the overall risk was estimated to be 1 case per 10.1 million doses of OPV administered. After the switch, this risk dropped to 1 case per 15.5 million doses of OPV administered. These results showed an important decrease compared to the previous risk estimations made by Andrus and Landaverde.

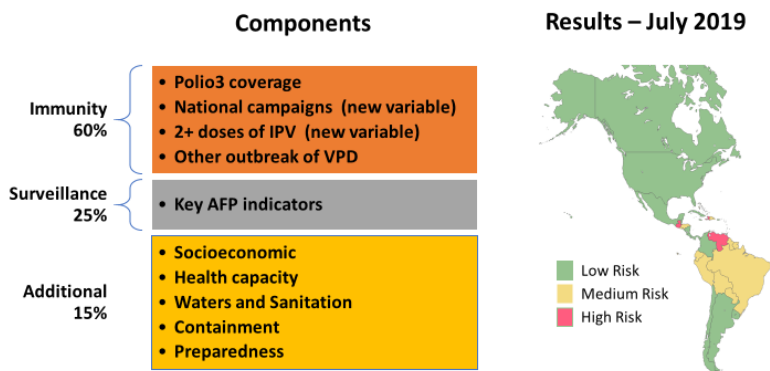
In two countries at high-risk for polio, PAHO with support from the CDC, has implemented environmental surveillance (ES) in Haiti (March 2016-current) and Guatemala (November 2018-current) to supplement AFP surveillance. Two VDPV were isolated in Guatemala (one VDPV1, one VDPV 3) through ES. These are two isolated events, and no evidence of circulating VDPV have been found to date. In the last five years, there have been three iVDPV cases notified in the Region, two from Argentina and one from Colombia. The two in Argentina received antiviral treatment with positive results. Actions have been taken according to the WHO guidelines: collection of stool samples, vaccination of family, vaccination of contacts, active case search, vaccination of the area and control and monitoring of viral excretion.

As part of the global certification process and since 2018, every country has been required to submit an Annual Report on the Documentation of Polio Eradication Status to the Regional Certification Commission (RCC). The evidence in these reports, validated by the NCCs, was used to respond to the request of the Global Certification Commission (GCC) to confirm that the Americas remain free from WPV3. All but six Caribbean countries presented their report (Antigua and Barbuda, Bahamas, Curacao, Guyana, Monserrat and St. Kitts and Nevis).

On 16 May 2019, the RCC certified that the Americas has been free of WPV3 for almost 29 years, with the last endemic case of WPV3 occurring in October 1990 in Mexico. In July 2019, the RCC updated the regional risk assessment for polio. The results show that three countries are at high-risk of having an importation or emergence of polio (Guatemala, Haiti, and Venezuela), 17 countries and territories are at medium-risk, and the remaining 24 are low-risk (**Figure 5**).

In coordination with WHO, PAHO has updated the regional standard operating procedures for responding to a poliovirus event and outbreak. The RCC has requested that all countries have a national outbreak response plan. All countries and territories, except for Antigua and Barbuda, Curacao and Montserrat have submitted at least one version of their national plan. After each submission, PAHO conducts detailed reviews of the plan and provides recommendations to update the plan. As of July 2019, 29 countries have conducted polio outbreak simulation exercises (POSE).

Figure 5. RCC Polio Risk Assessment



Poliovirus Containment Status

Efforts to contain poliovirus type 2 were implemented progressively in 2016 and 2017 and intensified in 2018. WHO has published guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for poliovirus.

The SAGE Polio Working Group met in February 2018 to harmonize recommendations between SAGE and GAPIII on the post-eradication polio immunization schedule and to review other issues regarding the GPEI. Regarding immunizations requirements for countries with poliovirus essential facilities (PEFs), SAGE recommended that countries implement a routine immunization schedule with a minimum of two IPV doses, maintain high population immunity with $\geq 90\%$ IPV2 coverage among infants in the area surrounding the PEFs (100 km), have outbreak plans specifying responses to containment breaches, and conduct outbreak simulation exercises.

At the 71st World Health Assembly in May 2018, WHO Member States unanimously adopted Resolution WHA71.16, urging international commitment to full implementation of GAPIII requirements. With adoption of the resolution, countries are expected to complete inventories of type 2 polioviruses (PV2), destroy unnecessary PV2 materials and advance their inventories of WPV1 and WPV3 materials in accordance with WHO guidance. In addition, countries must reduce the number of facilities designated to retain polioviruses to a minimum, appoint a national authority for containment (NAC) by the end of 2018 and formally engage designated PEFs in containment certification by no later than the end of 2019.

Poliovirus containment includes management of biorisk in laboratories, vaccine production sites, and in other facilities that retain the viruses after eradication; the initial milestone is for

containment of PV2. By August 2018, 29 countries had designated 81 facilities to retain PV2 materials; 22 of them had established a NAC.

Implementation of the GAP III in the Americas

The Region is committed to completing all goals outlined in the Polio Eradication and Endgame Strategic Plan, including the GAP III, which has been adapted for the Region as the Regional-GAP III, endorsed by PAHO's TAG in July 2015. All countries have submitted an average of four reports (range 2-6) on Phase I of GAP III: containment of WPV2/VDPV2 and Sabin2 to the RCC. Between March 2016 and October 2018, the RCC reviewed 99 updated containment reports during RCC meetings. In 2017, the RCC validated 32 switch reports, including the retrieval and destruction of all vials of tOPV.

In an October 2018 meeting, the RCC fully validated 18/23 (22 countries + 1 Caribbean Sub-region) expected reports for infectious and potentially infectious WPV2/VDPV2 materials and 16/23 for infectious Sabin2 materials. By October 2018, five countries in the Region had designated 20 Poliovirus Essential Facilities (dPEFs), Brazil: 1, Canada: 5, Cuba: 1, Mexico: 1, and USA: 12. Eighteen of these will retain WPV2/VDPV2 and Sabin2. In agreement with WHO's Containment Certification Scheme (CCS), the five countries with dPEFs have nominated a NAC. Six dPEFs have submitted the documentation required for the Certificate of Participation (CP) to the NAC for the United States and to the GCC, which is the first step of the global certification process. PAHO and WHO provided a second regional auditors training on April 2019, to support the CCS implementation in the five countries with dPEFs.

Regarding WPV1 and WPV3 materials, 16/23 reports have received RCC validation for inventory of facilities and countries are advancing with the elimination of all unneeded WPV1 and WPV3 materials. The 56th Directing Council, 70th Session of the Regional Committee of WHO for the Americas in Washington, DC, 23-27 September 2018, was informed of Resolution WHA71.16 "Poliomyelitis - containment of polioviruses." A report about the implication and progress in the Region was presented and is available at: <http://bit.ly/2krq9vY>

In January 2019, PAHO Director, Dr. Carissa Etienne, sent letters to the Ministers of Health of all the countries of the Region of Americas to urge their personal engagement and leadership to fully implement Resolution 71.16 to ensure the long-term sustainability of the eradication of poliomyelitis. For countries with dPEFs (Brazil, Canada, Cuba, Mexico and USA), the letter highlights the commitment to apply strict safeguards to keep their countries and the world safe from the risk of facility-associated re-introduction of poliovirus.

The RCC has requested that all countries submit updated containment reports by August 2019, with a complete inventory for type 2 polioviruses, advances for polioviruses types 1 and 3, and destruction of all unneeded poliovirus type 1 and 3 materials. These updated country reports will be reviewed at the 11th RCC meeting planned for October 2019. All dPEFs should have formal engagement with the CCS process no later than 31 December 2019.

Recommendations

- TAG urges countries to fully implement the end game strategy for polio eradication, including maintaining high vaccination coverage, conducting active AFP surveillance, meeting poliovirus containment requirements, conducting risk assessments, developing and implementing mitigation plans and updating outbreak response plans.
- The TAG strongly recommends that the 19² countries that currently use only one dose of IPV, introduce a second IPV dose into their routine immunization schedules.
- In countries where VDPV is detected through environmental surveillance, such as Guatemala, TAG underlines the importance of countries maintaining high vaccination coverage and high-quality surveillance. TAG supports the decision of Guatemala to conduct a nationwide vaccination campaign using bOPV and MMR vaccines. Other high-risk countries in the Region should take appropriate measures to prevent the re-introduction of WPVs or emergence of cVDPVs.
- TAG recommends that PAHO adapt the SAGE Primary Immunodeficiency Guidelines for the Region.

² Belize, Bolivia, British Virgin Islands, Curaçao, Dominica, Dominican Republic, El Salvador, Grenada, Guatemala, Guyana, Haiti, Nicaragua, Paraguay, Saint Kitts and Nevis, Saint Lucia, Suriname, Trinidad and Tobago, Islands of Turks and Caicos, and Venezuela.

Epidemiological Situation of Yellow Fever

Emerging and reemerging diseases pose a continuing threat to global and regional health security. The increasing incidence and geographical spread of arboviral infections, such as the yellow fever (YF) virus, are among the most significant public health concerns in the Americas. In this context, the PAHO Strategic Plan 2014-2019 includes the commitment to support countries in building and upgrading their surveillance and control mechanisms for diseases with a high public health impact.

The YF virus is enzootic in 13 countries of the Americas. In the last several decades, sporadic human cases or limited clusters have been reported following sylvatic exposure, mainly in Bolivia, Brazil, Colombia and Peru. However, a significant increase of human cases has been reported in Brazil since December 2016. Overall, approximately 2,200 confirmed human cases and among them 745 deaths have been reported over two subsequent transmission seasons (May-December 2016-17 and 2017-18). During the 2018-19 monitoring period (until epidemiological week 20, 2019), the number of human cases (82) has decreased by 93.7% compared to the same period in 2018 – 14 deaths have been reported and 48 epizootics confirmed. The human cases followed an epizootic wave that moved progressively from the Amazon basin towards the Atlantic coast of Brazil and reached and bypassed the outskirts of metropolitan areas. No evidence exists that transmission by *Aedes* spp., what is commonly referred to as urban yellow fever, has occurred. Rather, the situation in Brazil during the last three years highlights the risk of exposure via sylvatic vectors that residents of urban and peri-urban areas adjacent to ecological corridors face. Brazil adopted the use of fractional dose yellow fever vaccination in three states (São Paulo, Rio de Janeiro and Bahia) to respond to outbreaks and the risk of urbanization of YF. In 2019, Bolivia has reported 1 confirmed case and Peru has reported 8 human cases (3 confirmed) and 3 deaths.

Yellow Fever Vaccination

The recent YF outbreaks in the Region have highlighted the importance of strong routine YF immunization programs and vaccination campaigns to mitigate the risk of exposure along ecological corridors and prevent large urban YF outbreaks. Countries in the Americas follow PAHO's TAG recommendations to prevent and control YF in the Region, which include:

- Universal introduction of the YF vaccine in national immunization programs for children aged 1 year (and <2 years old) in countries with endemic transmission (co-administration with measles and rubella-containing vaccines, understood as administration of two vaccines at same vaccination visit),
- Preventive vaccination campaigns for at least 95% of populations aged older than 2 years living in enzootic areas during interepidemic periods,
- Vaccination campaigns in response to outbreaks or epizootics (including use of fractional doses in response to outbreaks in case of insufficient vaccine supply), and
- Vaccination of travelers to areas with a risk of YF virus transmission.

- Moreover, endemic countries are encouraged to seize the opportunity of outreach immunization activities to increase vaccination coverage among the routinely targeted groups.

In 2017, TAG endorsed the use of fractional YF vaccine doses in response to outbreaks among individuals >2 years old, in the context of limited YF vaccine availability. In 2018, TAG reiterated its endorsement and indicated that children aged <2 years old, pregnant women and individuals known to be HIV-infected should be vaccinated using a standard 0.5 ml dose, given the lack of data on immunogenicity and reactogenicity in those population groups.

All 13 endemic countries in the Region have included the YF vaccine in their national vaccination schedules with a reported coverage for 2018 in children at one year of age of 63%. According to PAHO's Revolving Fund, only half of the countries' vaccine needs have been met over the past ten years due to global supply issues, resulting in a substantial accumulation of susceptible populations in the Region. Based on that and preparing for the future, a tool has been developed for countries to estimate the susceptible populations in the risk areas, which was presented during a workshop in Peru in November 2018. It is expected that this information will serve as the basis for and drafting a short- and medium-term vaccination forecast plan to inform the WHO Global Strategy to Eliminate Yellow Fever Epidemics (EYE), which is a global framework for accelerated YF control for the period 2017-2026.

Co-administration of measles and rubella-containing vaccines and yellow fever vaccines

PAHO and WHO recommend that live, attenuated vaccines should be co-administered, or administered at least four weeks apart. In most countries, measles and rubella (MR) or measles, mumps and rubella (MMR) and YF vaccines are co-administered to children at 12 months of age. However, some countries, namely Argentina, Colombia, Panama and Peru, have introduced changes in their vaccination schedules, postponing administration of the YF vaccine to the age of 15 or 18 months, based mostly on the number of doses of different vaccines administered at 12-month visit and the potential interference of these two vaccines.

In 2011, a study in Brazil found a significantly decreased immunogenicity against YF, rubella, and mumps viruses when MMR and YF vaccines (full dose) were co-administered compared with administration at different visits separated by four weeks. After these results were published, WHO and PAHO's TAG urged that additional studies be conducted to obtain further evidence on the co-administration of these two vaccines and noted this study as a potential caution regarding the co-administration of these vaccines. In order to answer this research question, the Ministry of Health of Argentina, PAHO, and the Centers for Disease Control and Prevention (CDC) conducted a phase IV, open-label randomized controlled trial to determine if seroconversion rates for measles, mumps, rubella, and YF viruses after co-administration of MMR and YF (full dose) vaccines is non-inferior to seroconversion after sequential administration of the vaccines, separated by four weeks. The study was conducted at four health facilities in the Misiones Province in Argentina from 2015 to 2018 and included children aged 12-13 months.

Seroconversion rates were high for all antigens (95-98%) when the vaccines were co-administered and when they were administered individually. In the intent-to-treat analysis, co-administration was non-inferior to individual administration for all antigens. Looking at the magnitude of antibody titers, there was no significant difference between groups in the distribution of antibody titers for measles, but the titers for rubella, mumps, and YF were significantly lower when the vaccines were co-administered than when they were individually administered. However, the observed titers were substantially greater than the level needed for seroconversion in both the co-administration and individual administration groups. It is unknown whether the small, but significant, difference in titers has any impact on long-term immunity. There was no evidence of safety concerns.

These study results, along with results from two other randomized controlled trials on potential interference between YF and measles-containing vaccines, were presented to the WHO's Strategic Advisory Group of Experts (SAGE) on immunization in October 2018. In addition to the study findings, the potential programmatic implications (missed opportunities for YF vaccination, given that only one dose of YF vaccine is recommended in comparison to two for MR/MMR, which provides a second opportunity for vaccination and a potential decrease in vaccination coverage) of delaying one of these vaccines to a later vaccination visit were discussed. To highlight the potential implications, vaccine coverage figures from four countries in the Americas region that initially co-administered YF and MMR vaccines at the 12-month visit and then moved YF vaccine to the 15 or 18-month visit were shown. In all four countries, vaccination coverage dropped substantially in the year that the vaccination schedule was changed. All countries have shown some recovery in their coverage, but there is still a difference of approximately 15 percentage points in two of the countries, with smaller differences in the other two countries. The conclusion was that delaying vaccination with one of the vaccines to a later visit instead of co-administering them would probably have a far more deleterious effect on population immunity than any potential reduction in the magnitude of the immune response due to co-administration.

Considering the scientific and programmatic implications, SAGE endorsed the following recommendations: WHO maintains its current guidance stating that MR/MMR and YF vaccines should be administered at the same visit or at least four weeks apart, according to the schedule that will maximize coverage for all antigens in the national immunization schedule [*removing all qualifications/precautions about co-administration*]. Additional research is needed to determine if the lower titers or antibody concentrations observed following co-administration of MR/MMR and YF vaccine will impact long-term immunity and cause secondary vaccine failures.

Recommendations

- TAG stresses the importance of achieving yellow fever vaccination coverage levels of 95% in endemic areas through optimal routine immunization and campaigns where indicated.
- In view of the available evidence supporting coadministration of MR/MMR and YF vaccines and the experience of increased drop-outs when YF vaccination is scheduled beyond 12 months of age, TAG recommends that both vaccines be given during the same

visit at 12 months. If administered separately, they should be at least four weeks apart and full coverage with both vaccines should be ensured.

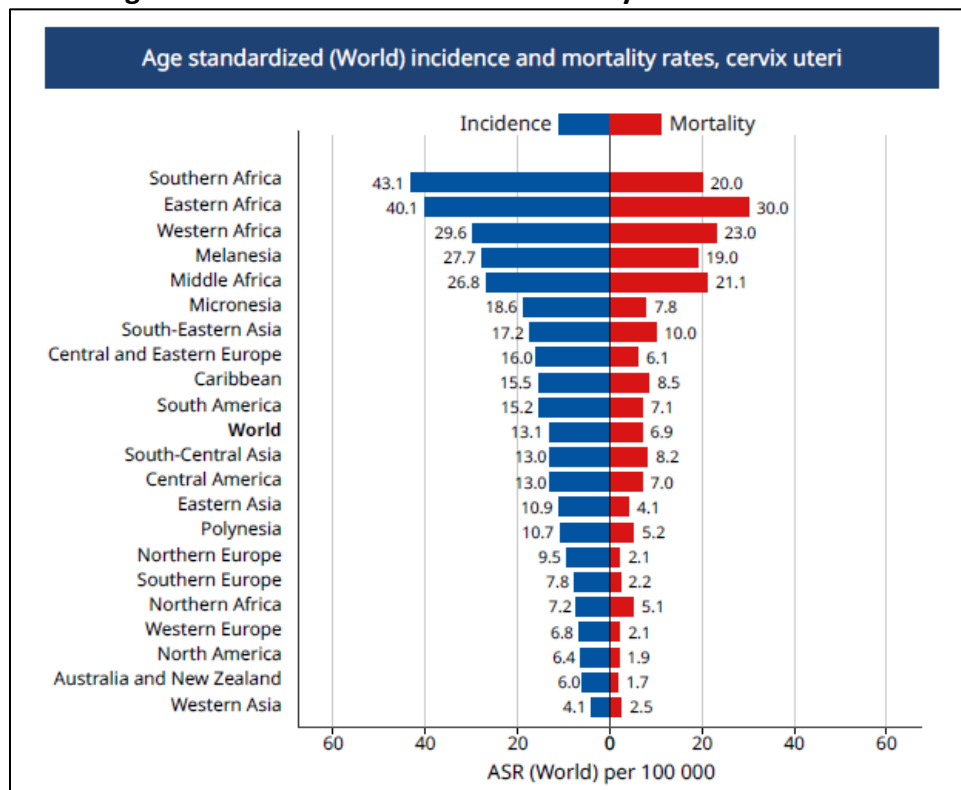
- TAG recommends that further research be conducted in the Region to examine the effect of lower antibody titers against rubella, mumps and YF viruses observed after co-administration on long-term immunity and to rule out the possibility of secondary vaccine failure.

Elimination of Cervical Cancer as a Public Health Problem

Human papillomavirus (HPV) is one of the most common infections of the reproductive tract, responsible for a variety of cancers, such as cervical cancer, and other conditions in both men and women caused by persistent infection with high-risk types of HPV. Cervical cancer can be prevented by vaccination against HPV and by screening and treatment of precancerous lesions.

In the Region of the Americas, cervical cancer is the fourth leading cause of death for women. However, it is the leading cause of cancer death among women in eleven countries in the Region (Belize, Bolivia, Dominican Republic, El Salvador, Guyana, Haiti, Honduras, Nicaragua, Paraguay, Suriname, and Venezuela), and is the second leading cause of cancer death in twelve countries in the Region (Brazil, Dominica, Ecuador, Grenada, Guatemala, Jamaica, Panama, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, and Trinidad and Tobago). An estimated 83,200 women in the Americas are diagnosed with cervical cancer each year, and 35,680 women die from the disease every year. More than half of these women (52%) are under 60 years of age. The global incidence and mortality of cervical cancer is presented in **figure 6**.

Figure 6. Global Incidence and Mortality of Cervical Cancer



Source: The Global Cancer Observatory, May 2019

Cervical cancer screening programs have been established in almost every country in the Region since the early 1970s, and cervical cancer treatment services have been developed in almost every country, although there are significant differences in access. Access to palliative care also

remains a challenge, with only ten countries reporting palliative care services. Significant progress has been noted in disease prevention and control; however, major gaps and challenges remain in reducing incidence and mortality and in preparing the ground for the elimination of cervical cancer as a public health problem.

In 2016, with the aim of strengthening cervical cancer initiatives, the United Nations Joint Global Programme on Cervical Cancer Prevention and Control was established to provide Member States with coordinated technical cooperation through relevant United Nations programmes in order to enhance all initiatives against cervical cancer. In addition, WHO and other United Nations partners are developing a new global cervical cancer elimination strategy to be presented to the World Health Assembly in 2019. These global and regional plans, together with the Prevention and Control Plan 2018-2030 for the Region of the Americas, will contribute to the achievement of the SDGs, in particular, the following targets by 2030: 3.4: “to reduce by one third premature mortality from non-communicable diseases;” 3.7: “to ensure universal access to sexual and reproductive health-care services;” 3.8: “to achieve universal health coverage;” and 5.6: “to ensure universal access to sexual and reproductive health and reproductive rights.” These strategies include HPV vaccination, screening, early treatment, and palliative care.

The Prevention and Control Plan 2018-2030 for the Americas

This plan presents guidance to Member States and the Pan American Sanitary Bureau to strengthen their capacity and establish innovative and effective evidence-based strategies to accelerate the reduction of cervical cancer incidence and related mortality. The plan sets out the following four strategic lines of action:

1. Improve the organization and governance of cervical cancer programs, information systems, and cancer registries;
2. Strengthen primary prevention through information, education, and HPV vaccination;
3. Improve cervical cancer screening and treatment of precancerous lesions through innovative strategies;
4. Improve access to cancer diagnosis, treatment, rehabilitation and palliative care services.

Regarding cervical cancer screening, almost all Member States have stated that these services are available. However, for the program to have an impact, screening coverage must reach at least 70% of the target population. In the Region of the Americas, only seven countries have reported this level of coverage. To have an impact on the burden of disease, significant improvements need to be made in order to reach the 32 million women between 30 and 49 years in the Region who must be screened.

HPV Vaccination as a Strategic Line for the Cervical Cancer Prevention and Control Plan

The first prophylactic HPV vaccine was licensed in mid-2006. Currently, there are three vaccines on the market that can be used to prevent high-risk HPV types: the bivalent vaccine, Cervarix; the quadrivalent vaccine, Gardasil; and the 9-valent vaccine, Gardasil 9. In the Region as of 2018, the PAHO Revolving Fund offers the bivalent and the quadrivalent vaccines.

The introduction of the HPV vaccine into the EPI in the Americas began in 2006, with the United States being the first country to introduce the vaccine. By June 2019, forty countries and territories in the Region of the Americas had introduced the HPV vaccine into their national immunization programs. This indicates that 89.6% of girls in the Region live in countries where the HPV vaccine has already been introduced into the national schedule. The most commonly used vaccine is the quadrivalent (31/40), followed by the bivalent (7/40); only two countries have used the 9-valent vaccine. Eight countries report vaccinating boys and girls (JRF, 2018): Antigua, Argentina, Barbados, Bermuda, Brazil, Canada, Panama and the USA. WHO data from 2018 shows that in the Region of the Americas, 69% of the countries have introduced the HPV vaccine into the EPI, followed by Europe (EURO) with 64%, Western Pacific Region (WPRO) 48%, South-East Asia Region (SEARO) 27%, Africa (AFRO) 17%, and Eastern Mediterranean Region (EMRO) 5%. An analysis of coverage from 2014 to 2016 showed that in the countries under study, 27% (14) had coverage $\geq 80\%$ and 25% (13) had coverage less than 50%. In the Region of the Americas, the coverage among girls during 2018 ranged from 2% to 97%, 17% of the countries (4) had coverage $\geq 80\%$ and 46% (11) had coverage less than 50%, according to 24 country reports in the JRF. Analysis of vaccination coverage has shown that in order to achieve high coverage, several vaccination strategies must be adopted and vaccination in schools must be prioritized and considered part of the "new immunization routine."

In 2017, PAHO's TAG endorsed the SAGE's recommendation, reaffirming the importance of prioritizing high coverage among cohorts of adolescent girls to ensure complete protection against HPV in girls and herd immunity in populations of boys. Countries should prioritize vaccination with two doses in girls aged 9 to 14 years with a six-month interval between doses.

Since licensure in 2006, over 270 million doses of HPV vaccines have been distributed (2016 data). The WHO Global Advisory Committee on Vaccine Safety (GACVS) released its latest review in July 2017, reasserting that the HPV vaccine is extremely safe, that vaccine-associated events are mild and moderate, with spontaneous resolution. Data analyzed by GACVS show that the risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses, and syncope was established as a common anxiety or stress-related reaction to the injection.

In October 2017, PAHO held a workshop in Antigua, Guatemala, with participation from 24 countries in the Region, to share experiences on introducing the HPV vaccine as a follow-up to TAG recommendations from 2017. During this meeting, countries discussed the main lessons learned, such as the difficulty in reaching the vaccine coverage target of 80% of girls. In line with other international findings, school-based vaccination has been shown to improve coverage in the Region of the Americas. Regarding communication, it is important to have an integrated and continuous communication plan, including crisis response, and to develop messages according to each audience. As part of the commitments made at the workshop, PAHO is finalizing guidelines to standardize the calculation of HPV vaccine coverage and estimate the impact of vaccination.

Figure 7. Countries and Territories (n=41) with HPV Vaccine in the Region of the Americas, June 2019



Source: JRF 2018 and country reports.

HPV Vaccine Supply: Constrained Market Conditions for PAHO Revolving Fund

The HPV market is transitioning in 2019. WHO has prequalified three vaccines from two manufacturers: the bivalent (GSK), quadrivalent, and 9-valent (both Merck). However, GSK is planning to exit the market and the 9-valent vaccine will not be available to the Revolving Fund, leaving the quadrivalent vaccine as the sole presentation available during the period 2020-2022. This situation will persist until new suppliers from India and China (Serum Institute of India LTD “SII”, Zerun Biotech and Inovax) are expected to reach WHO prequalification (or local registration). GSK recently indicated to PAHO it may return to the market in 2022.

While HPV vaccine supply is currently enough to meet yearly regional demand (3 million doses), constrained conditions will exist in 2020 beginning with the anticipated transition of national programs from the bivalent vaccine. Special attention to all elements in our regional supply chain for this vaccine will be necessary. Additionally, the Revolving Fund will continue to work to improve the HPV vaccine supply outlook by networking with global partners aligned with the WHO Director General’s call to action on cervical cancer elimination by 2030.

Recommendations

- TAG expresses deep concern over the current challenges facing the supply of HPV vaccine and stresses the importance of meeting countries’ needs in order to reduce the burden of cervical cancer. TAG calls on the global public health community to challenge HPV

vaccine manufacturers to be operationally and ethically responsive to global vaccine supply needs and align with PAHO/WHO's call for action for elimination of cervical cancer.

- In view of the current supply challenge, all countries administering vaccines to girls and boys should prioritize vaccination of girls, achieving HPV coverage >80%. This will induce herd immunity and protect both girls and boys.
- TAG encourages countries to implement school-based HPV vaccination and communication plans to accelerate vaccine uptake and maximize vaccination impact.

In this section, we present an update on the progress of countries and territories of the Americas establishing National Immunization Technical Advisory Groups (NITAGs). Additionally, we present an example illustrating advances made by countries in generating evidence to make decisions on immunization-related topics.

Update on the Status of NITAGs in the Americas

Ministries of health in the Americas have established NITAGs or equivalent independent groups to strengthen decision-making processes and outcomes regarding vaccines and immunization. Comprised of multidisciplinary experts, these advisory bodies provide independent, evidence-based guidance to national health authorities on immunization policy. While the roles and responsibilities of NITAGs in policy formulation vary by country, the committees are considered vital to ensuring a transparent and credible process for decision-making for a range of immunization issues, including the introduction of new vaccines, updates in existing vaccination policies, and monitoring of immunization-related progress and impact.

Both WHO and PAHO have recommended the establishment of independent NITAGs since the early 2000s. Through their endorsement of the regional adaptation of the GVAP, PAHO Member States committed to establishing functional NITAGs in at least 18 countries by 2020. By global standards, the Americas consider NITAGs to be functional if they meet the following indicators:

- Legislative or administrative basis for the advisory group,
- Formal written terms of reference,
- At least five different areas of expertise represented among core members,
- At least one meeting per year,
- Circulation of the agenda and background documents at least one week before meetings,
- Mandatory disclosure of any conflicts of interest.

In 2019, 41/44 (93%) countries/territories in the Americas that shared information with through the PAHO-WHO/UNICEF joint reporting form (JRF) on immunization reported having an active NITAG. A sub-regional TAG called the “Caribbean Immunization Technical Advisory Group” or CiTAG, was created in 2018 and advises 20 English and Dutch-speaking Caribbean countries/territories on immunization. Of the 21 active NITAGs (20 NITAGs and the CiTAG), 18 met the GVAP/RIAP indicator of good functionality, thus meeting the set RIAP target of establishing 18 functional NITAGs by 2020. Of three countries not reporting active NITAGs, one country reported that its NITAG was being created (the Dominican Republic) and another that it was being reactivated (Ecuador). Haiti was the latest country to establish a NITAG and held a formal induction meeting for newly appointed members in August 2019. Two countries with active NITAGs reported not disclosing interests of NITAG members. The other indicator that affected good functionality was the inclusion of at least five main expertise areas in the core membership. While countries have made significant efforts towards establishing clear policies and procedures for the declaration and management of interests, it remains an important

challenge in the Region. Another crucial characteristic of a good NITAG that is not captured by the GVAP/RIAP indicators is the independence of its core members. Several NITAGs in the Region still include members that have direct or indirect supervisory relationships within the immunization program or are employees of ministries of health.

Experience during the last decade has shown that establishing and strengthening NITAGs is critical to improve leadership in making informed decisions about the introduction and financial sustainability of vaccines. Moreover, NITAGs increase the credibility of the government by increasing its capacity for rigorous, transparent evidence-based decision-making. NITAGs can potentially deflect pressure from narrowly focused lobbying groups, including industry, and anti-immunization groups, and allow/obligate members to abstain from decision-making on issues from which they might benefit. NITAGs also help anticipate the needs of immunization programs. For example, the NITAG in Argentina had been monitoring the epidemiological situation of meningococcal disease long before vaccine introduction was considered. In Chile, the NITAG recently examined data from national electronic immunization registries (EIRs) in response to rising concerns about vaccine hesitancy. Finally, in the event of an adverse event following immunization (AEFI) or the questioning of an existing immunization policy, NITAG support is crucial and can neutralize public backlash.

Through PAHO/WHO's technical cooperation on NITAGs in the Region, we have learned that having a solid administrative and legal basis is key to preserving NITAG activity. Moreover, defining clear communication channels between NITAG and the secretariat, as well as a work plan aligned with the needs and priorities of the immunization program, have contributed to a positive evolution of ministry of health/NITAG relations. The use of local data by leveraging existing surveillance and research platforms, and strong support from the secretariat to prepare a solid evidence base have increased ownership of the recommendations. NITAG reporting at a high political level has facilitated acceptance of recommendations by ministries of health. NITAG members' flexibility to attend ad hoc meetings has facilitated addressing pressing requests from health authorities in a timely manner.

There are many opportunities for NITAG growth in the Region, such as the expansion of expertise profiles to include additional specialties such as social sciences, health economics and civil society representation on the committee or as liaison or ex-officio members. Also, NITAGs could benefit from updating their standard operating procedures periodically to increase efficiency and transparency. NITAG secretariats that need additional support for the review and appraisal of immunization evidence may explore leveraging national capacities by collaborating with academic institutions or other government entities that could provide that expertise. Finally, written policies for the management of potential conflicts of interests are essential but should be complemented by good practices in addressing perceived interests. A good practice from the Chilean NITAG consists in declining invitations to events funded by the pharmaceutical industry to avoid perceived conflicts of interest. Members also systematically disclose the position from which they make public statements (i.e. as a NITAG member or individually).

To address the frequent problem of membership terms ending simultaneously, NITAGs could revise the membership renewal procedure so that there is enough time for a successful transition and for experience gained by NITAGs to be preserved over the years. NITAGs could also benefit from increasing visibility among peers and among the general population to strengthen confidence in immunization programs and policies. Finally, NITAGs may benefit from exchanges with other NITAGs to share technical resources, experience, and lessons learned.

In 2016, the Global NITAG Network (GNN) was launched as a global initiative to facilitate exchanges between NITAGs about their experience, processes, evidence reviews, recommendations and policy decisions. By joining the GNN, NITAGs can receive timely updates on useful global and regional resources, publications from other NITAGs, and upcoming GNN support activities. To date, nine NITAGs from the Americas including the CiTAG, have joined the network and six have attended GNN meetings. The next GNN annual meeting will be held in Atlanta, Georgia, USA and NITAG participants will also be invited to the ACIP (the USA NITAG) meeting.

In response to a request from GNN members, the CDC, with PAHO/WHO and NITAG partners, developed a short, user-friendly NITAG assessment tool that examines three areas of performance: functionality, quality of work processes and outputs, and the integration of the committee into the ministry of health policy process. It is currently available in English, Spanish and French for use by NITAGs in external, peer-to-peer or self-evaluations. The tool was successfully piloted in Chile in 2018 with support from the CDC.

The following is an example of countries' advances in generating evidence for decision-making on immunization, as a study conducted by Lucia H. de Oliveira, et al.:

Using Secondary Data to Demonstrate the Impact of PCV on Children Mortality – an Innovative Approach to Generating Evidence for Decision-making

Pneumococcal infections, caused by *Streptococcus pneumoniae*, are one of the most important causes of disease and death among children under 5 years of age throughout the world. Currently, 143 countries globally have introduced pneumococcal conjugate vaccines (PCVs). Therefore, it is critical that their impact on disease morbidity and mortality is measured. In this study, we estimated declines in mortality due to pneumonia in ten countries in Latin America and the Caribbean (LAC) – Argentina, Brazil, Colombia, the Dominican Republic, Ecuador, Guyana, Honduras, Mexico, Nicaragua and Peru. Trends in death due to pneumonia from 2005 to 2015 were analyzed, adjusting for unrelated trends, to estimate declines in pneumonia mortality that occurred in the post-vaccine period. The analysis mostly used the synthetic control method that allows to account for the effects of confounders changing over time, and in settings where it was not possible, seasonal-trend decomposition plus principal component analysis, which first extracts smoothed trends from the control time series and uses them to adjust the outcome.

All analyses and data cleaning were performed in the R software (Vienna, Austria). In total, there were 73,912 deaths due to pneumonia among children aged 2-59 months

during the study period. The reported incidence of death due to pneumonia per 10,000 among children aged 2-59 months in the pre-PCV period ranged from 7.8 in Argentina to 29.6 in Peru. Most countries showed some evidence of a decline in mortality due to pneumonia among children aged 2-59 months following the introduction of PCV and approximately 4500 pneumonia deaths have been averted in this age group since PCV introduction in the ten countries studied. This study has demonstrated that it is possible to evaluate PCV impact in childhood mortality in LAC countries, where routinely collected data from national mortality registries are available. The results confirm the importance of PCVs as a public health intervention, given that these vaccines are showing a great impact on child mortality.

Recommendations

- TAG commends countries and territories for their progress in establishing NITAGs and recognizes their role in strengthening evidence-based decision-making, program sustainability and promoting confidence in immunization.
- TAG stresses that NITAGs must be independent and have written policies for the declaration and management of potential conflicts of interest.
- TAG encourages Member States with established NITAGs to document their lessons learned and calls on PAHO/WHO to facilitate exchanges and peer-to-peer support between NITAGs both within the Region and globally.

Strengthening Cold and Supply Chain Operations and Vaccine Management in the Americas

Cold chain operations in the Americas were built on four pillars: training in program management, research and testing when developing refrigeration equipment for safe vaccine storage, information flow in the EPI program, and cold chain evaluations. However due to recent advancements in technology to manage the cold chain, the use of digital technologies, continuous temperature monitoring devices and software, and the use of newer refrigeration equipment have been added to the fundamental pillars of cold chain operations.

At the beginning of the 2000s, the introduction of several new and expensive vaccines, like rotavirus, and single-dose MMR, PCV, and HPV, as well as increases in the population of each country, gave ministries of health the challenge of rapidly increasing their cold chain storage capacities. This experience in the Region of the Americas provided a model for many countries in other regions to follow in planning increases in their cold chain storage capacities.

To assist ministries of health, PAHO's technical cooperation has focused on three management areas: 1) providing training courses to national immunization staff, 2) providing technical cooperation to build new cold chain facilities and/or new cold rooms, and 3) evaluating cold and supply chain operations. Together, these efforts are strengthening countries' abilities to assure that vaccines are kept potent and that no health service runs out of vaccines and related supplies.

Training

One of the elements necessary to obtain outstanding program performance is having well-trained, informed health workers and managers, who are also updated on new technologies. To this end, PAHO's Comprehensive Family Immunization Unit (IM) has completed the following work:

- 1)** Updated the Cold Chain Module and Modules for the Use, Installation, Maintenance and Troubleshooting of Solar Refrigeration Equipment. A total of 540 persons have been trained with these training materials.
- 2)** Conducted five international training workshops between 2012–2018 in Colombia (2), Dominican Republic, Jamaica and Nicaragua, with more than 700 health staff trained. The workshops covered topics including cold chain, supply chain, vaccine management, temperature mapping and studies to monitor temperature during vaccine distribution throughout the supply chain.
- 3)** Fifteen courses regarding management of the supply chain and distribution of vaccines were carried out between 2010-2018 in Bermuda, Bolivia, Dominican Republic, Haiti (2) Honduras (2), Jamaica, Mexico, Nicaragua, Paraguay (2), Peru, Suriname, and Venezuela. Specifically, the stand-alone version of the Vaccination Supply Stock Management software program (VSSM) and the web-based version of the program (wVSSM) were reviewed. These events trained a total of 448 people.

- 4) It is fundamental to evaluate the performance of cold and supply chain operations to strengthen the management capabilities of health staff and supervisors. IM efforts have carried out eight evaluations on VSSM and wVSSM between 2011-2018 in the Dominican Republic, Haiti, Honduras (2: VSSM and wVSSM), Jamaica, Mexico, Nicaragua and Paraguay.
- 5) A second management tool, Effective Vaccine Management (EVM), was introduced in 2013. Training with this tool was initiated with seven courses, starting in 2013. By 2018, a total of 185 people was trained in EVM courses in five countries: Bolivia, Cuba, Guyana (2), Honduras (2), and Nicaragua.

Technical Cooperation to Build New Cold Chain Facilities and/or Cold Rooms

Member States have scaled up their cold chain operations and vaccine management with technical cooperation provided by PAHO's IM regional office. Over the last 15 years, Member States have quickly built new cold chain facilities or established new cold rooms to accommodate new vaccines for a growing population. With the introduction of PCV, rotavirus and HPV vaccines during the last two decades, Colombia, Honduras, Nicaragua, Paraguay and other countries have built new warehouses to increase vaccine storage at both national, central and sub-regional levels. These efforts have focused on expanding cold chain capacity beyond the national level, which has resulted in a decrease in the costs related to expanding cold chain storage capacities at the national level only. More importantly, having additional vaccine storage space at sub-regional levels has provided program managers with more flexibility in managing supply chain operations and responding to unplanned service level requests for additional vaccine supplies.

Evaluating Cold Chain and Supply Chain Operations

EVM is a management tool that assists managers in determining whether distribution points for supplies and vaccines are optimal to achieve their goals and avoid stock-outs at service levels. EVM evaluations identify needs and weaknesses in management operations, infrastructure gaps and supply operations. The EVM tool collects information on nine criteria to evaluate performance on these operations, aiming to document outstanding performance and conditions needed for effective performance, as well as to highlight those areas that require improvements and/or strengthening interventions to assure that these operations achieve their objectives in supporting immunization services. To date, five countries – Bolivia (2016), Guyana (2014), Haiti (2013-2018), Honduras (2015) and Nicaragua – have completed EVM evaluations. Honduras and Nicaragua achieved the highest EVM scores when compared to other countries in other regions (to date) that have carried out EVM evaluations. These EVM evaluations allowed the countries to purchase new refrigeration equipment, in addition to using new temperature monitoring devices. Moreover, the EVM results recommended the expansion and improvement of storage facilities.

New Tools and Technologies

The introduction of new, expensive vaccines mandated the need to continuously monitor vaccine temperatures to assure that each person is vaccinated with a potent vaccine. Therefore, IM supported the introduction of remote temperature monitoring devices (RTM) for cold rooms and

continuous temperature monitoring devices for facilities using refrigerators/freezers. With the new digital technologies, the IM began training staff from countries in either international (5) or national (8) workshops. Among the many topics covered by these workshops, participants were trained in continuous temperature monitoring devices and RTM, using cell phone technology and e-mail alerts to receive temperature deviations from the monitored equipment. This has facilitated not only better management, but also allowed for rapid response to act in the event of energy or mechanical equipment failures.

As the immunization cold chain and supply chain became more complex, it also became imperative for countries to examine their operations and assure that managers at all levels had “end-to-end visibility” of all their operations. To this end, IM introduced the wVSSM³. VSSM is a vaccine and commodity inventory application, which allows managers to receive information on stock levels for vaccines and other commodities, their location, expiration dates, and other important information to ensure that no immunization services suffer from vaccine or supply stock-outs and helps protect vaccines and syringes from reaching their expiration dates. Moreover, wVSSM allows for a traceability of lot numbers of vaccines and syringes that need to be recalled.

The major challenge that management has faced in effectively using wVSSM is assuring that all health service points have access to the internet. Fourteen countries have installed VSSM, six of which are now using wVSSM (Dominican Republic, Honduras, Jamaica, Mexico, Nicaragua and Paraguay).

PAHO has always advocated for the principle of health equity and in this respect, the countries in the Region have extended their immunization services to more populations, especially those living in remote areas. IM has developed projects and/or assisted countries to introduce solar powered refrigerators. By 2008, IM had provided technical cooperation to almost all countries in the Region in the installation, maintenance and use of solar refrigeration equipment.

An Achilles heel affecting the management operations of the cold and supply chain is the flow of information throughout the system, due to the lack of digital equipment and access to the internet at lower administrative levels. These constraints could make it difficult to achieve the established vaccine coverage goals. Together, EVM and wVSSM can provide the required information to make the best decisions and prepare effective budgets as part of each country’s annual plan of action. It is worth noting that the TAG in Panama (2017) recommended the implementation and use of both EVM and wVSSM tools.

2018 JRF results on cold and supply chain practices indicated that only 15/42 LAC countries and territories are using an electronic/digital tool to manage their vaccine stocks down to the lower administrative levels. Twenty-three/42 countries and territories indicated that they do not

³ In 1997 PAHO introduced inventory software called Commodities and Logistics Management (CLM) in a few countries. The US-CDC and Management Sciences for Health developed CLM for health for managing medical supplies in public health warehouses. VSSM was introduced in 2010, beginning with Nicaragua and Paraguay.

employ technologies at the sub-national level to continuously monitor vaccine storage temperatures. Of the 19 countries that indicated that they use technologies to continuously monitor vaccine storage temperatures, the range of establishments that have such abilities range from 50% and 100%. Regarding the confirmation of countries having a supply chain manager, 27 countries indicated yes, and eleven countries indicated that there is no manager in place. The analysis of these results indicates that countries need to invest in more management skill building and resources to ensure that they have excellent cold and supply chain operations at all levels.

As was stated in the early editions of the EPI Newsletters, today more than ever, governments need to provide the required funds to support their immunization program operations. Managers at all levels need to prepare their annual plans of action and activities (emphasizing new technologies, cold chain equipment, temperature monitoring devices, among others) and their corresponding budgets to guarantee that the required funds are allocated by the budgetary authority. Providing potent vaccines will save money and prevent VPD outbreaks and premature deaths from occurring.

Recommendations

- TAG urges each country to conduct and maintain a cold chain inventory and assessment and, also using this information to plan and make informed equipment purchases.
- TAG recommends that countries implement the use of new, well-accepted and tested technologies to manage cold and supply chain operations, such as prequalified refrigerator equipment, continuous temperature monitoring devices, and inventory control management tools. Countries should purchase WHO prequalified equipment.
- TAG encourages each country to assure that their annual plans of action include investments in, but not limited to: training, supervisory activities, incorporation of new technologies, repair and maintenance of equipment and evaluation activities.

Update on the Global Market, Pressing Supply Challenges and Vaccine Affordability for the Region

PAHO's Revolving Fund (RF) for Vaccine Procurement continues to be a key component of technical cooperation for immunization in the Americas and for the timely access of high-quality vaccines to 41 countries and territories in the Region at the lowest prices. In addition to its contributions to the elimination of VPDs, the RF continues to support the rapid uptake of new and under-utilized vaccines. The RF has been following through with the implementation of TAG recommendations from 2017. Successes have been a shared responsibility across the Region in confronting the challenges of global vaccine markets, implementing appropriate acquisition strategies, refining accurate country vaccine demand plans and aligning with national budgets and financing to minimize the risk of vaccine supply interruptions.

Challenges within the Global Vaccine Market and Supply

Vaccine markets present ongoing challenges for countries participating in the RF. For a significant number of vaccines, there are a limited number of manufacturers, restricting the global supply base, limiting competition and affordable prices. Production timelines are often lengthy and require considerable and careful planning. The RF continues networking with international partners, including the GPEI, the EYE Strategy, the Market for Information for Access to Vaccines (MI4A) initiative at WHO, as well as during UNICEF's annual meeting with suppliers. Similarly, the RF participated in the annual meeting of the Developing Country Vaccine Manufacturers Network (DCVMN) last held in Kunming, China in November 2018.

The Region is concerned with the constrained conditions of the HPV vaccine market. Currently, WHO has three prequalified vaccines from two manufacturers, all of which protect against HPV 16 and HPV 18, the main strains that cause cervical cancer, as shown in **Table 3**.

Table 3. Summary of Demand for HPV Vaccines through the RF, 2019

| Manufacturer | Type | WHO prequalification | Availability to PAHO RF | RF Demand Forecast 2019 (doses) |
|---------------|--------------|----------------------|-------------------------|---------------------------------|
| GSK (Belgium) | Bivalent | 2009 | Through 2019 | 500,000 |
| Merck (USA) | Quadrivalent | 2009 | Indefinite | 2,500,000 |
| | 9-Valent | 2018 | Not available | |

The HPV market is transitioning in 2019. GSK is exiting the market, leaving Merck as the sole supplier from 2020-22 until new manufacturers from India and China (Serum Institute of India LTD "SII," Zerun Biotech, and Inovax) are expected to reach WHO prequalification (or local registration). GSK indicated recently (May 2019) that it may return to the market in 2022.

While the HPV vaccine supply is enough to meet regional demand needs in 2019, constrained conditions will exist in 2020, beginning with the anticipated transition of six national programs from the bivalent vaccine. Given these challenges, special attention to all elements in our regional

supply chain for this vaccine are required. Additionally, the RF has been an active participant in the MI4A initiative at WHO and in the preparation of a market study analyzing the global demand and supply outlook for the HPV vaccine, aligned with the Director General’s call to action on cervical cancer.

The supply of IPV also presents unique challenges for the Region. Supply constraints of prior years’ market conditions for IPV improved in 2019 for the RF to adequately address the regional demand estimated at approximately 8.6 million doses. The current status of IPV demand and supply for 2019 is summarized below in **Table 4**:

Table 4. Summary of Demand for IPV Vaccines through the RF, 2019

| UPDATE DEMAND IPV 2019 (as of 30 June) | | | | | | | |
|--|-------|----------------------|-----------|--------------------------|-------------------------|----------------------|-------------|
| TOTAL ADJUSTED REGIONAL DEMAND (doses) | | | | | | | |
| 8,600,000 | | | | | | | |
| IPV PRESENTATION | | ALLOCATION Dec'18 | % DEMAND | PROCURED (30 June-19) | CONFIRMED Q3-Q4 2019 | TOTAL ESTIMATED 2019 | |
| PFS | 1 ds | 3,000,000 | | | 1,810,000 | 910,000 | 2,720,000 |
| | 5 ds | 2,600,000 | 1,130,000 | | 630,000 | 1,760,000 | 2,960,000 * |
| MULTIDOSE VIAL | 10 ds | 3,000,000 | 550,000 | | 650,000 | 1,200,000 | |
| TOTAL | | 8,600,000 | 100% | 3,490,000 | 2,190,000 | 5,680,000 | |

*This demand may be revised following July 2019 TAG Regional Meeting.

According to the 2018 JRF, seven countries reported that there were interruptions in supply due to one of the following reasons, e.g. budgetary or financial issues, delays in shipments/deliveries, switches to fractional doses, and other countries that use combined vaccines containing IPV and use IPV only as booster and for travelers. These are under review with the concerned countries attending the TAG meeting.

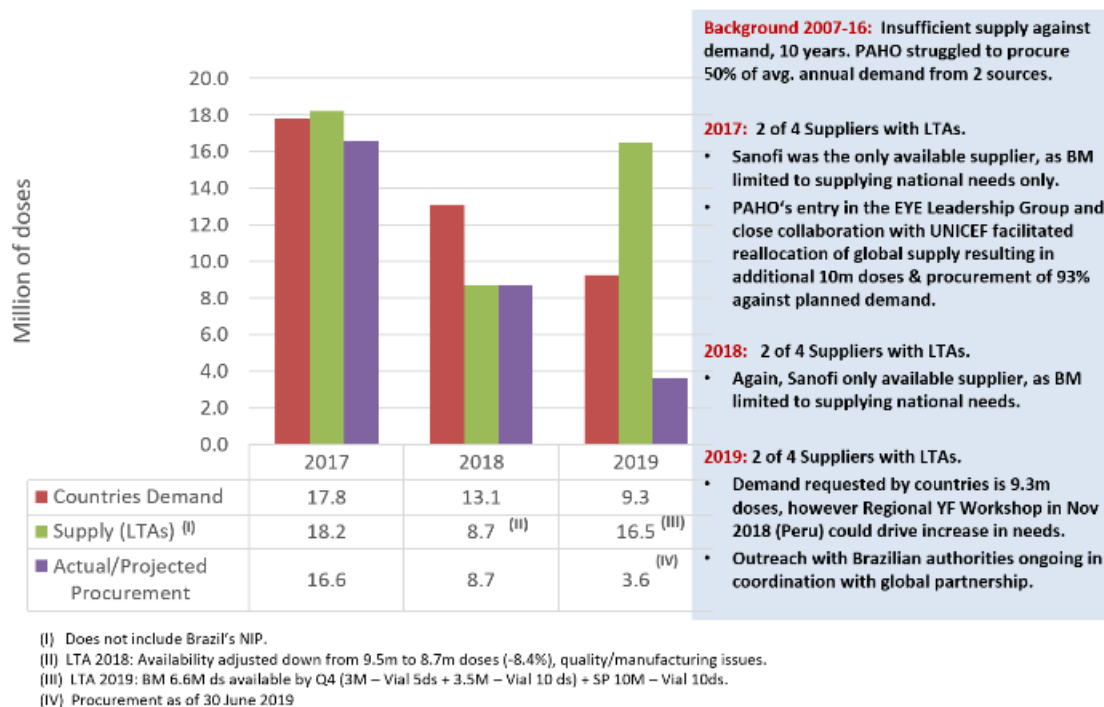
Comments from Member States attending PAHO’s Directing Council in September 2018 directed the RF to maintain its “readiness” in case of any changes in the global IPV supply situation. Accurate demand forecasts together with close monitoring of national inventories (stock reach), will continue to be fundamental tools for the allocation of available vaccine supply, either to cover current needs or additional doses required for the remaining countries considering changing to the 2-dose schedule.

For 2020, the RF expects to have enough supply from the two WHO prequalified manufacturers to meet regional demand. The RF will continue to network with global partners and with manufacturers to assure the supply to Member States as part of continuous efforts to maintain polio eradication in the Region of the Americas.

The yellow fever outbreak in Brazil impacted the availability of YF vaccine supply to endemic countries in the Region, reducing the RF supply plan for 2017 by approximately 60%. Proactively, the RF continues to engage with WHO and UNICEF colleagues as the governing structure for the global EYE Strategy evolves. The RF was named to the Leadership Group together with WHO, UNICEF, and GAVI representatives and is also part of the Supply Sub-committee.

Special attention continues to be given to the 13 YF endemic countries of the Region. In view of the buildup of susceptible populations in these countries, a regional workshop was convened in November 2018 to update countries on the characterization of at-risk populations, and on the definition of strategies and responses to outbreaks.

Figure 8. Demand, Supply and Procurement of Yellow Fever Vaccine, PAHO Region, 2017-19



Technical Support to Countries in Demand Planning & Monitoring

Carefully reviewing and analyzing country demand plans continues to be necessary for the RF and there are opportunities to improve their accuracy. As of 2019, only four countries have maintained demand planning accuracy above 80% on more than 80% of the vaccines planned and procured through the RF. To continue strengthening demand planning for countries, several initiatives are under consideration including a training network to improve country knowledge and practices. In close collaboration with PAHO's IM unit, the RF provided regional trainings on vaccine demand planning and in joint country level workshops.

In preparation for the review of 2020 demand plans from countries by end of June 2019, the RF held WebEx orientation sessions with participating countries to review the planning process and use of the updated PAHO 173 form. As of July 2019, 31 of 41 countries and territories (76%) have already submitted their annual plans for 2020.

Budget and Financial Considerations for the RF

Accurate demand plans should be backed up with a reliable budget and financing from national resources. The RF monitors financial situations through aging of invoices received by countries following the receipt of goods in-country. If more than 60 days elapse from the date of the invoice

receipt, the country is considered in arrears and not eligible for continuing to have access to the RF credit line.

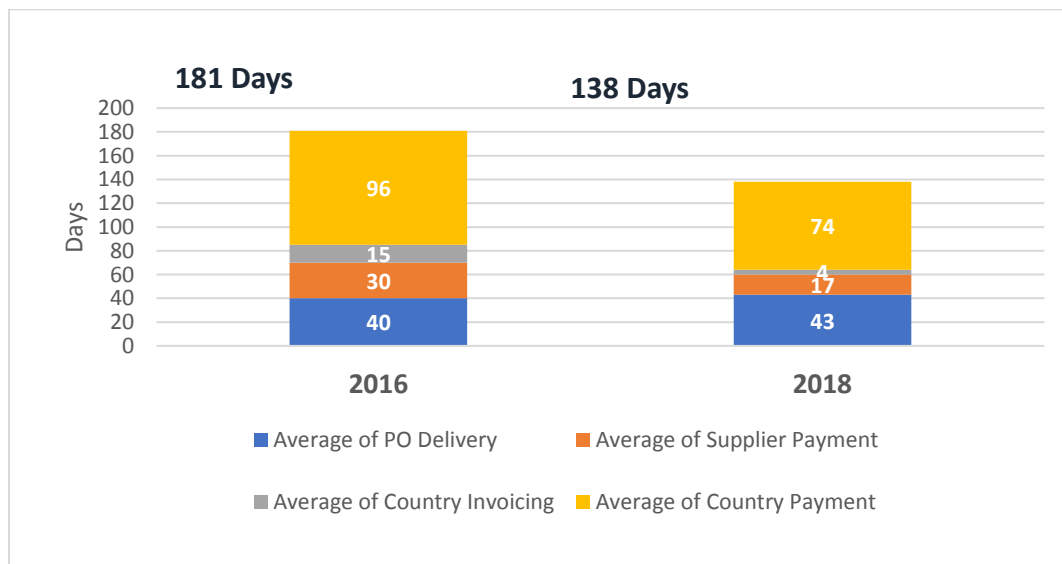
As of 30 June 2019, there were 23 countries in arrears to the RF as shown in **Table 5**. This represents a four-fold increase over the same period last year, June 2018. This is a concern for the RF. The RF remains committed to both monitoring this situation in a monthly manner with PAHO's Department of Procurement and Supply Management (PRO) and PAHO country offices and improving the visibility of payment performance by countries, along with other financial statements for countries.

Table 5. Financial Situation of Countries Participating in RF Credit Line, June 2018/June 2019, Aging (Days)

| Date | NUMBER OF COUNTRIES | | | | |
|---------------|---------------------|-------|-------|--------|------|
| | 1-30 | 31-60 | 61-90 | 91-180 | 181+ |
| End June 2018 | 1 | 0 | 0 | 2 | 3 |
| End June 2019 | 3 | 9 | 12 | 6 | 5 |

The RF also monitors credit line turnover. One of the findings from the RF Assessment in 2017-18 was the underperformance of that turnover. **Figure 9** compares average number of days for Procurement Order (PO) deliveries, Supplier Payments, Country Invoicing and Country Payments for 2016 and 2018.

Figure 9. Revolving Fund Line Turnover, 2016-2018



Upon comparing data from 2016 and 2018, improvements are noted in a total reduction of time from 181 to 138 days resulting from improvements in average times for country invoicing and payment, respectively. Nevertheless, the performance target identified in the RF Assessment is for 1.5 turns per year of the credit line, up from .92 turns measured during the Assessment. More on key points from the RF Assessment follow below.

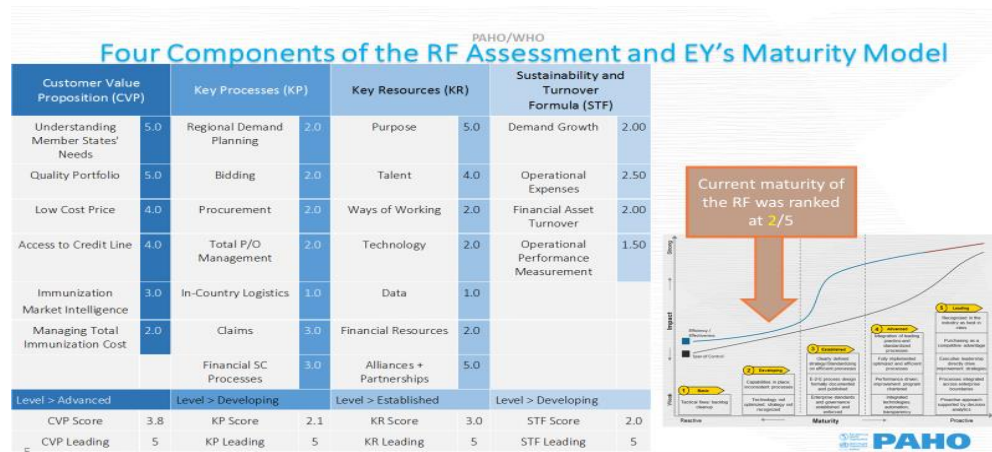
RF Assessment by Ernst and Young (2017-18)

To improve RF performance, an external assessment was conducted in 2017-18 funded by a variety of resources including Member States (procurement fee revenue), PAHO's regular budget, and a WHO grant from the Bill and Melinda Gates Foundation.

The independent Ernst & Young report assessed the RF's current operating model, mapped drivers of change in the operation, and provided short-term and long-term recommendations to preserve the relevance and sustainability of the RF. These were presented by the Ernst & Young team to PAHO's Director and Executive Management team on 18 December 2018. Over the past six months, these recommendations have been reviewed internally by the RF Working Group for a discussion with the Director on 1 July 2019. The following is a summary of key findings. A public version of the report will be made available soon.

The four basic components of the Assessment were the RF's Customer Value Proposition (CVP), Key Processes (KP), Key Resources (KR), and its Sustainability and Turnover Formula (STF). The current state of these components was assessed and benchmarked using a maturity model with a range of scores from 1 to 5, where 1 corresponds to a basic level of maturity and 5 to a leading level, calibrated by best practices in relevant comparable Group Purchasing Organizations (GPO). The results are summarized in **figure 10**.

Figure 10. The Four Components of the Revolving Fund Assessment and Maturity Model



Recommendations

- TAG encourages PAHO to keep updating countries on vaccine markets and to implement proactive responses to specific vaccine issues.
- TAG encourages PAHO to continue supporting global efforts to improve access to affordable vaccines, including regional pooled procurement initiatives beyond PAHO Member States.
- TAG welcomes the report of the RF Assessment and supports the transformational program of work to increase the efficiency and further enhance the support of the RF to countries while maintaining its core principals.
- TAG urges SC countries to make their payments to the RF in a timely manner.

Infections caused by pneumococcal bacteria can be serious, especially in the elderly (aged 65+), and infections caused by many of the pneumococcal serotypes are preventable by vaccines. A conjugate vaccine covering 13 of the over 90 serotypes of streptococcus pneumoniae has been licensed for adults (PCV13) and has shown to be efficacious. However, few countries recommend PCV13 for routine use among older adults because pediatric vaccination programs have reduced the overall circulation of pneumococcal strains included in the 13-valent vaccine, as well as the exposure of older adults to these strains. In LAC, 37/52 (71%) countries and territories have introduced PCV10 or PCV13 into national immunization programs for infants.

Experience from the US and Europe: Invasive Disease among Adults Aged 65+ Years

The United States was the first country to introduce PCV for children, starting with the 7-valent conjugate vaccine (PCV7) in 2000 and changing to PCV13 in 2010. In late 2014, the USA also made a recommendation for PCV13 to be given routinely to all older adults. Data from the U.S. Active Bacterial Core surveillance (ABCs), which tracks invasive disease episodes and collects isolates for serotyping, shows a large reduction in disease caused by vaccine serotypes among adults aged 65 and older after both PCV7 and PCV13 introduction. Disease rates did not change following the introduction of PCV13 for older adults in late 2014. In 2016, few of the remaining cases among either adults or children were caused by vaccine serotypes. While vaccine serotype 3 was the most common serotype among adults, the rates of disease caused by serotype 3 did not change following PCV13 introduction in both children and adults. No increase was seen among older adults in invasive disease caused by nonvaccine serotypes in the years following PCV13 introduction.

Data from surveillance for invasive pneumococcal disease (IPD) conducted in European countries, aggregated through a program called SpIDnet/I-MOVE+, indicates an indirect benefit of childhood PCV programs on disease caused by the serotypes that are included in PCV10 and PCV13 among older adults, like that noted in the USA. In contrast to the situation in the USA, however, a year-on-year increase in non-PCV13 serotype incidence, suggesting serotype replacement disease, was observed among European surveillance sites. This replacement effect was of similar magnitude for disease caused by serotypes included in the 23-valent pneumococcal polysaccharide vaccine, but not in PCV13 and for serotypes not included in any vaccine. SpIDnet/I-MOVE+ results indicate a large indirect effect of childhood PCV programs on IPD caused by the serotypes that are included in both PCV10 and PCV13 among older adults. However, the year-on-year increase in non-PCV13 serotype incidence, suggesting serotype replacement in disease, was observed in all sites.

We conducted a critical appraisal of the published and unpublished literature on pneumococcal disease burden in LAC to assess the data available on the remaining burden of disease in older adults (adults aged ≥ 65 years) that could be prevented if PCV13 were recommended for this age group. A review of four electronic databases and inquiries with experts familiar with pneumococcal burden of disease studies in LAC identified 175 potential data sources.

Among these, 13 relevant data sources, including eight publications and five unpublished documents met the inclusion criteria. Most studies (n=8) were from Brazil, and all except two (from Uruguay) were from countries using PCV10 in their infant immunization programs. Studies of invasive disease (n=3 for adults), pneumonia hospitalizations (n=3) and pneumonia mortality (n=2) showed that disease rates overall were increasing among older adults, a trend that began before PCVs were introduced for children. Analyses comparing changes in rates of pneumonia hospitalizations and mortality after pediatric PCV introduction showed mixed results, with some studies showing a decrease in disease among the elderly and others not detecting any change or an increase in rates. Studies of invasive disease showed that disease caused by serotypes covered by the PCV used in the country's pediatric program dropped after the programs began. Carriage studies (n=3), all of which were from Brazil, showed that limited adults are being exposed to PCV10 serotypes in recent years.

In summary, the studies identified were limited in number and quality by the lack of standard surveillance in LAC, surveillance that monitors rates of disease caused by vaccine serotypes. In addition, the underlying increasing trend of pneumonia and invasive disease rates in the elderly, likely due to population aging and improved access to healthcare, made interpretation difficult for the available studies. The expert group that reviewed the evidence concluded that in countries with robust pediatric PCV programs, the benefits from PCV13 vaccination for all older adults is likely to be limited. Certain groups at very high risk of pneumococcal disease, such as immune-compromised individuals may be more likely to benefit from receiving PCV13 than healthy older adults.

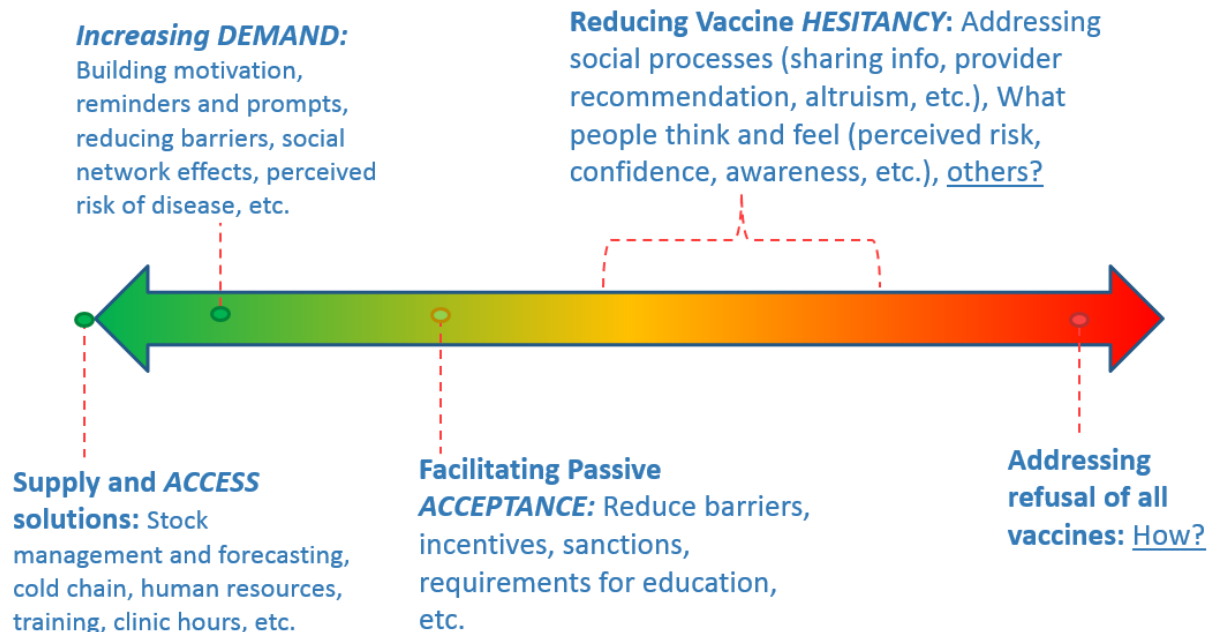
Recommendations

- TAG reiterates its previous recommendation to achieve high PCV vaccination coverage in infants and young children. Evidence indicates that high coverage in this age group indirectly reduces the burden of disease in the elderly and introduction of PCV13 for all older adults is likely to have limited benefit and is not cost-effective.
- Countries should improve the epidemiological surveillance of *Streptococcus pneumoniae* invasive disease in older populations to measure the indirect effects of the vaccination in infants.
- Countries should carry out carriage studies to quantify the remaining burden of vaccine type disease and carriage in children <5 years of age, to determine the extent of vaccine type *pneumococci* circulation in the community, putting older adults at risk of disease.

Access, Acceptance and Demand: Challenges in Vaccination

Despite the Region's achievements in immunization, challenges persist and a decline in vaccination coverage levels has been observed in recent years at national and subnational levels. Various factors pertaining to immunization programs themselves, the health sector or the socio-economic context may have negatively affected vaccine supply and demand, resulting in suboptimal immunization performance (**figure 11**).

Figure 11. Increasing Vaccination Model: Strategies to Address Stages on the Continuum



Past program evaluations and studies conducted in LAC to date have suggested that barriers to vaccination have mainly been associated with vaccine availability and access to immunization services reflecting programmatic and logistical issues. Four studies conducted in Colombia, Dominican Republic, El Salvador, and Guatemala in 2010-11 confirmed that missed opportunities for vaccination of young children under the age of five, were associated with difficult geographic access, inadequate organization of health services, limited availability of vaccines/supplies and of immunization staff. These studies also highlighted the negative impact of healthcare professionals' practices on vaccine schedule completion, such as not requesting the vaccination card during consultations. The current high turnover of immunization staff reported by countries, and the insufficient training and awareness of healthcare workers/providers about VPDs are also affecting both vaccine supply and demand. Finally, misinformation and lack of perception of the risk and seriousness of VPDs in the community may also play a role in decreasing vaccine uptake. Related to this latter issue, WHO has recently included vaccine hesitancy – a delay in acceptance or refusal of vaccines despite availability – in its list of top ten global public health threats.

While LAC have historically benefitted from a generally high confidence in vaccines, as identified in 2016 through a survey conducted in nine countries of the Americas reporting a general

tendency among interviewees to agree that vaccines for children are important, safe, effective and compatible with religious beliefs, recent communication crises in the Region associated with the use of HPV vaccines and yellow fever fractional doses have underlined that vaccine confidence can be fragile and that recuperating it can be a difficult and lengthy process. Similarly, and at the global level, escalating concerns related to vaccine hesitancy and learning from programs that have seen safety or other events contribute to declines in coverage, prompted WHO's SAGE to put forward recommendations in 2017 to all countries, to conduct assessments of vaccine acceptance and demand.

Since 2015, the JRF has collected data on vaccine confidence and hesitancy by asking respondents to list the top three reasons for hesitancy to accept vaccines according to the national schedule in their country. However, this information is insufficient to guide countries' public health actions and published data on the topic are scarce in LAC. Reliable measures to better understand why people are not being vaccinated are needed to ensure that evidence informs the design and evaluation of more tailored and targeted interventions to increase vaccine uptake. Standardized, validated measures to assess reasons for under-vaccination will also facilitate future comparison across and within countries/regions and monitoring of trends.

Once countries have established a diagnosis of reasons for under vaccination, immunization programs may draw on their experience to address immunization system issues through improving vaccine availability, supply, outreach services, and health workers training among other interventions. Nevertheless, some of the current obstacles may require expertise extending beyond the scope and traditional competencies of the immunization program, such as social sciences. Indeed, under-vaccination and non-vaccination linked to healthcare providers and parental knowledge and attitudes may require formative research skills and local interventions. Thus, multi-faceted, innovative approaches are needed to reach the under-vaccinated and unvaccinated, requiring multidisciplinary and intersectoral efforts to strengthen social mobilization, education, and advocacy.

Experience from other Regions, especially the WHO European Region, has shown the importance of moving away from the traditionally supply-oriented immunization programs to applying a more people-centered and comprehensive approach, built on listening to the intended beneficiaries and considering the complexity and the wide range of factors influencing vaccination uptake.

“WHO was established to advance human health—and human behavior is a core determinant of human health and well-being. Now is the time for this fact to be fully accommodated in its structure and programs (Omer and Butler, 2019).” As we enter this exciting era of WHO transformation, it is an important reminder that human behavior is a critical component to be studied and considered when developing public health policy recommendations. It is important to examine reasons for under-vaccination in the Region in a systematic manner and build an evidence base to design effective interventions. Factors such as individual motivation, attitudes and beliefs, but also social, community and cultural factors, legislative, institutional and structural factors should all be considered.

Recommendations

- TAG urges PAHO to develop a regional strategy for vaccine access, acceptance and demand, and support countries in identifying social and behavioral determinants of vaccination and addressing barriers to vaccination.
- Countries should use theory-based approaches to identify local barriers and drivers to vaccination and use these insights to develop tailored, evidence-based interventions to reach vaccination target populations, evaluate their impact and share their findings with other countries.
- Countries should strengthen their preparedness and response to vaccine communication crises which have the potential to erode trust in vaccines and in health authorities delivering them.

Diphtheria in the Americas

Thanks to countries' significant progress in immunization, the Region of the Americas has been free of diphtheria for several decades. However, in recent years, large diphtheria outbreaks have affected Haiti and Venezuela. We describe their epidemiological situation below.

Haiti

Since the beginning of the outbreak in 2014 (EW 51) and through 2019 (EW 16), 271 confirmed cases of diphtheria have been reported based on laboratory confirmation or an epidemiological link to a confirmed case. Cases have been reported from all 10 departments of the country. The cumulative incidence rate for the period from 2014 to 2019 (EW 22) is 2.5 per 100,000 inhabitants. The case-fatality rate among cases confirmed by laboratory or epidemiological link was 50% in 2014, 23% in 2015, 39% in 2016, 8% in 2017, 13% in 2018, and 17% in 2019. In 2019, the highest incidence rate to date has been reported among children 5 to 15 years of age, followed by those 1 to 5-year-old. There is a slight predominance of female cases.

Venezuela

The diphtheria outbreak that began in July 2016 (EW 26) is still ongoing. Since the beginning of the outbreak until EW13 of 2019, 1,711 cases have been confirmed by laboratory, clinically, or by epidemiological link to a case. Cases have been reported in all states. The cumulative incidence rate is 5.9 cases per 100,000 inhabitants. A total of 317 deaths were reported (. In 2019, the highest case-fatality rate occurred in the age group of 5 to 9 years-old (7%), followed by 10 to 15 years-old (4%). Since EW 43 of 2018, the outbreak has been concentrated in people over 18 years of age.

Outbreak Response Activities

In Haiti, outbreak response activities have been focused on communes with reported cases, aimed at children from 1 to 14 years old. To date, vaccination campaigns have been carried out in 44 of the 140 communes of the country. As of May 2019, 1.1 million children aged 1 to 14 have been vaccinated. The reported official coverage is 78%. From May 2-6, 2019, a campaign was carried out in 78% communes of the departments of Ouest and Artibonite. The results of this last campaign are pending publication. Health care workers have not been vaccinated.

In Venezuela, the outbreak response vaccination campaign was initially carried out in nine departments, and progressively expanded throughout the country. As of May 2019, 4.6 million children aged 7 to 15 years have been vaccinated, most of the states have reached $\geq 95\%$ coverage, except for seven states where vaccination activities are ongoing: Anzoátegui, Apure, Bolívar, Cojedes, Falcón, Portuguesa and Trujillo. In addition, the states that have already reached coverage $\geq 95\%$ continue to monitor actions to ensure that no pockets of unvaccinated children remain. Health care workers have been vaccinated.

In addition to the vaccination campaigns, both countries have carried out the following activities: i) updating the national surveillance guidelines, following WHO's new epidemiological surveillance standards; ii) conducting training workshops on case and contact management; iii)

training supervision on the prevention and control of infections associated with health care; and iv) acquisition of diphtheria antitoxin (DAT), which at the beginning of the outbreaks was difficult to achieve, but starting in 2018, has been available through the RF.

Vaccination Schedule and Coverage

The primary vaccination schedule for both countries includes three doses of pentavalent vaccine (DTP + Hep B + H. influenzae). The vaccination schedule in Haiti includes only one booster dose, administered 1 year after the administration of the third dose of the pentavalent vaccine. The Venezuelan vaccination schedule includes three booster doses: at 18 months, 5 years, and 10 years of age.

Vaccination of other age groups in Haiti includes women of childbearing age, as part of the prevention against maternal and neonatal tetanus, and in Venezuela, women of childbearing age, health care workers, and older adults.

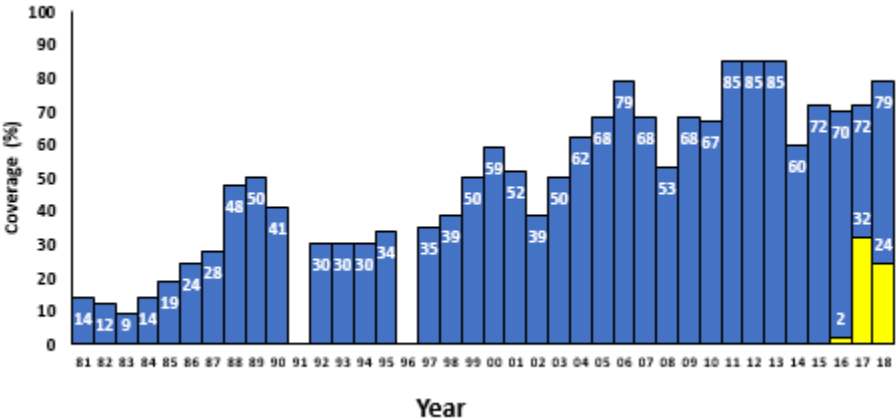
Table 6. Diphtheria Vaccination Schedule, Haiti and Venezuela, 2018

| Country | 1st dose | 2nd dose | 3rd dose | 4th dose | 5th dose | 6th dose |
|-----------|----------|----------|----------|-----------------------|----------|----------|
| Haiti | 6 weeks | 10 weeks | 14 weeks | 1 year after 3rd dose | | |
| Venezuela | 2 months | 4 months | 6 months | 18 months | 5 years | 10 years |

Source: PAHO-WHO/UNICEF 2019 JRF on immunization (2018 data).

In Haiti, vaccination coverage for DTP3 has historically been low. In the case of DTP4 coverage reported in 2018, a deterioration was observed with respect to the previous year (2017: 32%, 2018: 24%). At the municipal level, in 2018 only 33 (24%) of the 140 municipalities in the country achieved coverage of $\geq 95\%$ for DTP3; only 1 in 5 children under 1-year old lives in a municipality with optimal coverage for DTP3.

Figure 12. DTP3 and DTP4 Vaccination Coverage in Haiti, 1981-2018



In Venezuela, the coverage for DTP3 in 2018 was the lowest in the last 10 years (60%), and there was a deterioration in coverage for DTP4 with respect to the previous year (2017: 38%; 2018: 31%). At the municipal level, in 2018 only 68 (20%) of the 335 municipalities in the country achieved coverage $\geq 95\%$ for DTP3. Only 1 in every 11 children under 1 year of age lives in a municipality with optimal coverage for DTP3.

As a result of the low vaccination coverage in both countries over an extended period, there has been a significant accumulation of susceptible populations in all age groups. In the case of Haiti, this situation is aggravated by the non-inclusion of the TAG recommended booster doses in the national vaccination schedule.

Diphtheria Situation in the Remaining Countries of the Region

With respect to the other countries of the Region, there was a high incidence of diphtheria cases (≥ 10 cases per year, in ≥ 3 years of age, 1999-2018) in Brazil and the Dominican Republic. There was a low incidence (< 10 cases per year, in ≥ 3 years of age, 1999-2018) in Bolivia, Canada, Chile, Colombia, the United States and Paraguay. Isolated cases were reported in Argentina, Ecuador, Guatemala and Peru. Only 22 of the 52 countries and territories report having implemented the third booster dose.

Recommendations

- TAG expresses concern over the current outbreaks and reminds countries that all diphtheria events should be reported. Countries with ongoing diphtheria transmission should accelerate immunization activities, identifying high-risk areas, and strengthen the existing routine immunization programs, surveillance and rapid response.
- TAG reiterates its previous recommendation of achieving high vaccination coverage levels with diphtheria-containing vaccines. In addition to the primary DTP series during infancy, countries must ensure that 3-booster doses of the diphtheria-containing vaccine are provided during childhood and adolescence in combination with the tetanus toxoid vaccine, using the same schedule and age-appropriate vaccine formulations (DTP among children 1-7 year(s) old; Td among children over 7 years old, adolescents and adults). All countries should closely monitor coverage with DTP3 and DTP4 at national and subnational levels.
- TAG recommends that all countries in the Region adopt the new WHO standards for the epidemiological surveillance of diphtheria.
- TAG recognizes the efforts made by Haiti and Venezuela to control the diphtheria outbreaks and calls on both countries to strengthen vaccination activities. Haiti should introduce the fifth and sixth booster dose in the national vaccination schedule and vaccinate health care workers.

Hepatitis B Burden

Hepatitis B virus (HBV) infection is a major global health problem causing acute and chronic infections that can lead to liver cirrhosis, hepatocellular carcinoma and death. The risk of chronic infection (defined as being hepatitis B surface antigen positive [HBsAg]) is inversely related to the age at infection. Up to 80-90% of infected infants develop chronic infection; 30-50% of children infected before the age of 6 years; and, <5% of older children, adolescents, and adults with infections acquired after that age. Between 20 and 30% of adults who are chronically infected will develop cirrhosis and/or liver cancer. The vaccine is 95% effective in preventing infection and developing chronic disease and liver cancer due to HBV (it was the first vaccine to prevent cancer). TAG recommendations emphasize the importance of a birth dose of hepatitis B vaccine administered preferably within 24 hours followed by three doses during the first year of life, to reduce perinatal and early childhood transmission.

In the Americas, a model from Center for Disease Analysis (CDA) Foundation in 2016 estimated that 4.0 (2.8-6.5) million people are chronically infected, representing a prevalence among the general population of 0.4% (0.3%-0.6%) and among children under five years of age, less than 0.1%. Another model from the London School of Hygiene and Tropical Medicine (LSHTM) commissioned by WHO, in 2017 estimated that 3.2 (3.1-5.7) million people are chronically infected, representing a prevalence among the general population of 0.5% (0.3-0.7%) and among children under five years of age also less than 0.1%. The differences between these estimates are due to methodological differences in the estimation process. In both cases, most countries in the Region are considered as having low prevalence (<2%); however, there are some areas in the Caribbean and in the Amazon Basin (areas with a high concentration of indigenous populations) with intermediate (2-7%) to high (≥8%) prevalence of HBV infection. It is critical to note that the low incidence among children under 5 years of age at present can be attributed to the widespread use of the hepatitis B vaccine for more than two decades.

Global and Regional Hepatitis B Elimination Frameworks

In May 2016, the World Health Assembly adopted the first Global Health Sector Strategy on Viral Hepatitis, 2016-2021. This strategy has a vision of eliminating viral hepatitis as a public health threat (reducing the prevalence of chronic HBV in children to <0.1%, new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65%) by 2030. Its targets are aligned with those of the SDGs and the elimination of perinatal and early childhood horizontal transmission is considered a milestone on the road to HBV elimination as a public health threat.

In the Americas, in July 2015, TAG recommended that PAHO and countries should evaluate the status of hepatitis B control and the feasibility of elimination. In September 2015, the PAHO Regional Plan on Viral Hepatitis (2016-2019) and the PAHO RIAP (2016-2020) were presented to the Directing Council. Following it, a PAHO Hepatitis Technical Advisory Committee (TAC) and a PAHO Core Group on Hepatitis were established. In 2016, based on progress made by countries and a modelling exercise, the TAG assessed that perinatal and early childhood horizontal transmission elimination of hepatitis B was feasible in the Americas by 2020 by ensuring

vaccination coverage equal to or greater than 95% with the first dose within 24 hours of birth and the third dose of the hepatitis B primary series among children less than one year of age.

Progress towards Elimination and Verification of Hepatitis B Perinatal and Early Childhood Horizontal Transmission

Following TAG recommendations, the Framework for Elimination of Mother-to-Child Transmission (EMTCT Plus) added in 2017 the elimination of HBV infection, as part of the approach for elimination of HIV, syphilis and Chagas. The framework included programmatic objectives related to immunization, HBsAg screening of pregnant women and administration of hepatitis B immunoglobulin (HBIG) in exposed infants and the impact target as $\leq 0.1\%$ HBsAg prevalence in children at five years of age.

All 52 countries and territories in the Region have introduced hepatitis B vaccine (or hepatitis B containing vaccine) in their routine immunization schedules (**figure 13**), with 81% of regional coverage with three doses among children less than one year of age (reported in the 2018 JRF). Progress has also been made on birth dose introduction in the national infant immunization schedules from 18 countries in 2013 to 29 countries in 2019 (which represent more than 90% of the live birth cohort) with a regional coverage with the Hepatitis B birth dose of 72% in 2018. It is also important to strengthen the identification of persons chronically infected with hepatitis B through screening, including routine screening for HBsAg in pregnancy and follow-up interventions for exposed infants. As reported in the EMTCT 2018 progress report, in 2017, 24 out of 31 reporting countries in the Americas indicated having a policy for universal screening of pregnant women for HBV and 22 out of 28 reporting countries indicated that HBIG prophylaxis was made available to exposed newborns. According to WHO, nineteen countries in the Region might have already achieved the impact target for EMTCT and early childhood horizontal transmission in the Region (Argentina, Bahamas, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Saint Kitts and Nevis, Uruguay, United States and Venezuela) and according to the CDA model used by PAHO, thirteen countries (Argentina, Belize, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Guatemala, Nicaragua, Mexico, Peru and United States) might have already achieved the same impact target.

Figure 13. Year of Introduction of Hepatitis B or Hepatitis B-containing Vaccine in the National Schedule



Note: Multiple years correspond to year of introduction in risk/selected areas.

Source: Ropero Alvarez AM, Pérez-Vilar S, Pacis-Tirso C, Contreras M, Omeiri N El, Ruiz-Matus C, et al. Progress in vaccination towards hepatitis B control and elimination in the Region of the Americas. BMC Public Health. 2017;17:325.

In line with the above, methods to assess the progress towards and achievement of the targets by countries are needed. In view of the low prevalence in the general population in the Region, approaches that are being considered:

- a) Desk review of existing country data, including seroprevalence, surveillance and programmatic data.
- b) HBsAg seroprevalence surveys, nationally representative surveys have been recommended by WHO for monitoring progress towards hepatitis B control targets but require large sample sizes in settings of low prevalence. Alternative approaches being considered include more focused surveys targeting high-risk areas or selected population groups. PAHO in coordination with the CDC assessed the feasibility and outcomes of a two-stage protocol in which a risk assessment conducted using existing data was followed by a focused serosurvey in identified high-risk areas. This approach was evaluated and implemented in collaboration with Colombia's ministry of health. This serosurvey was conducted among more than 3,000 children in identified high risk areas and no cases were detected suggesting that Colombia has achieved the impact target. The integration of HBsAg testing into other planned surveys (such as demographic, health, and nutritional) should also be considered. The establishment of systems to track the follow-up of infected women and monitoring outcomes among their infants could also provide relevant data to allow the verification of the elimination of perinatal and early childhood transmission.
- c) Mathematical modelling exercises: Models leveraging existing in-country data and previously published literature may be useful to estimate the cumulative impact (cases and deaths averted) of hepatitis B vaccination programs, to assess the progress of countries towards the achievement of the perinatal and horizontal hepatitis B elimination impact target and to project the potential impact of additional preventive (including immunization) and treatment interventions for chronic HBV infections towards 2030 targets. This process has been recently conducted in Colombia and Cuba by an inter-programmatic team from PAHO in close collaboration with the ministries of health and with the assistance of modelers.

The lessons learned from these experiences, together with those of the verification of elimination of other VPDs and the elimination of MTCT of HIV and congenital syphilis, will guide the development of regional guidelines/guidance to countries and tools for verifying/validating the elimination of perinatal hepatitis B and early childhood horizontal transmission. PAHO will ensure the engagement of relevant stakeholders and partners. This process will benefit from ongoing discussions with other WHO Regional Offices (WPRO) that are advancing on the development of such a process and methodology and will closely relate to WHO's Immunizations and HIV/Hepatitis Units/Departments in Geneva that are also working on the development of global reference standards.

Recommendations

- TAG commends countries with regards to the progress made towards the elimination of mother-to-child and early childhood horizontal hepatitis B transmission and urges

countries to attain high vaccination coverage with hepatitis B birth dose and hepatitis B or hepatitis B-containing vaccines during the first year of life.

- TAG urges PAHO to develop guidance for the verification of mother-to-child and early childhood horizontal hepatitis B elimination in the Americas.

With just a year remaining on the GVAP 2011-2020, the development of the next 10-year strategy began in 2019 – one that sets a new vision for immunization by 2030 in alignment with global health priorities around PHC, UHC and SDGs. This new Immunization Agenda 2030 will be presented to the Ministers of Health at the 73rd World Health Assembly in May 2020 for their endorsement.

Led by WHO with partners, a draft strategy was prepared and shared for public consultation. To ensure the inputs and voices of regions and countries are heard and reflected, various consultations have been organized, including with TAG Members.

An overview presentation was given to TAG members during the TAG meeting, describing the seven strategic priorities and key interventions proposed for the next decade of immunization. This was followed by a full day consultation with countries of the Americas on 12 July.

Recommendations

- TAG supports WHO's countries consultation process for the Immunization Agenda 2030 and encourages countries of the Americas to fully participate in the process and share the regional and national perspectives.