# Ad hoc Virtual

# TAG Meeting 2018

**Third Ad hoc Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases**

**19 March 2018**

**Washington, DC**

**United States of America**

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

## TAG Members

**J. Peter Figueroa** ***TAG Chair***
Professor Public Health
Epidemiology & HIV/AIDS
University of the West Indies
Kingston
Jamaica

**Jon K. Andrus**
Adjunct Professor and Senior Investigator
Center for Global Health, Division of Vaccines and Immunization
University of Colorado
Washington, DC
United States

**Roger Glass**
Director
Fogarty International Center & Associate Director for International Research
NIH/JEFIC-National Institutes of Health
Bethesda, MD
United States

**Akira Homma**
Chairman of Policy and Strategy Council
Bio-Manguinhos Institute
Rio de Janeiro
Brazil

**Arlene King**
Former Chief Medical Officer of Health for Ontario
Adjunct Professor
Dalla Lana School of Public Health
University of Toronto
Ontario
Canada

**Nancy Messonnier**
Director
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Decatur, GA, United States

**José Ignacio Santos**
Professor
Experimental Medicine Unit
Faculty of Medicine of the National Autonomous University of Mexico
Mexico City
Mexico

**Cristiana Toscano**
Professor
Federal University of Goiàs
Goiana, Brazil

**Jeanette Vega***
Director
Chile's National Health Fund
Santiago
Chile

**Cuauhtémoc Ruiz-Matus** *Ad hoc* Secretary
Unit Chief, Comprehensive Family Immunization
PAHO/WHO
Washington, DC
United States

* Not present at ad hoc TAG 2018

## Introduction

PAHO convened an extraordinary meeting of its Technical Advisory Group (TAG) on Vaccine-preventable Diseases to address pressing issues faced by the Region the Americas. The ad hoc meeting was held virtually on 19 March 2018 and covered the yellow fever epidemiological situation in the Americas including the ongoing outbreak in Brazil, the use of fractional yellow fever vaccine doses in response to the outbreak, and the status of diphtheria and measles outbreaks in the Region.

In view of the risk of measles importation and the spread of the measles outbreak in Venezuela to neighboring countries, TAG also discussed a proposal to monitor the sustainability of measles, rubella and congenital rubella syndrome elimination in the Americas and urged countries to prioritize response to measles outbreaks to prevent the reestablishment of endemic measles transmission. An update was also given on the global and regional supplies for both yellow fever and inactivated poliovirus vaccines (IPV).

## Status Update on Yellow Fever Outbreaks in the Americas and Use of Yellow Fever Vaccine Fractional Doses

**Background**

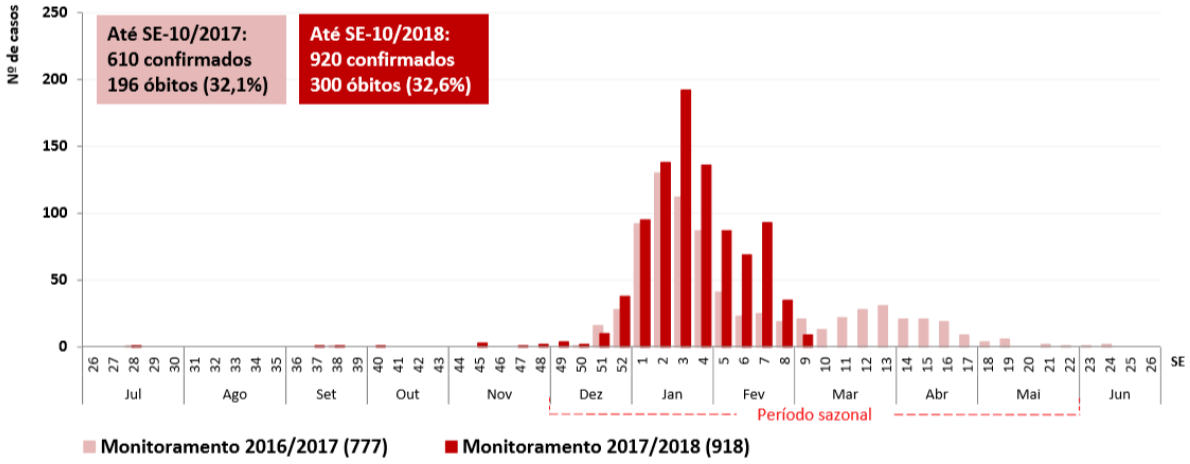
On 12 July 2017, during the XXIV meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases in Panama City, a special session was held as a "Status Update on Yellow Fever in the Americas." An update on the ongoing yellow fever (YF) outbreak and response was presented by representatives of the Brazilian Ministry of Health. This outbreak was deemed the largest in Brazil since the 1940s and expanded to areas of the Atlantic coast that, according to the WHO, were not previously considered to be at risk for YF. TAG endorsed use of the subcutaneous fractional YF vaccine in response to outbreaks occurring in a context of limited vaccine availability, such as the outbreak in Brazil. TAG urged Brazil to continue vaccination activities among residents of and travelers to all affected areas beyond the duration of the outbreak. TAG also called on endemic countries to optimize vaccination delivery, maintain high vaccination coverage among target groups, and strengthen the monitoring of vaccination coverage and of adverse events following immunization (AEFIs). The TAG also urged these countries to strengthen yellow fever epidemiological, virological, vector, and zoonotic surveillance to reassess the risk of yellow fever. Finally, the TAG recognized the efforts of the Global Eliminating Yellow Fever Epidemics (EYE) Strategy in providing visibility to yellow fever in the global public health agenda, and those of PAHO's Revolving Fund for Vaccine Procurement (RF) in ensuring that the vaccine needs for yellow-fever-endemic Member States are met.

**Yellow fever outbreaks and responses**

Since 2016, several YF epizootics in Brazil have been approaching the Atlantic Coast areas, previously considered non-endemic areas, including the cities of São Paulo and Rio de Janeiro, where approximately 30 million people reside. From July 2017 to 22 March 2018, 1102 human confirmed cases of YF have been identified, of whom 340 have died, in the states of Minas Gerais, Sao Paulo, Rio de Janeiro, Espírito Santo and the Federal District **(figure 1)**. All reported cases were consistent with sylvatic transmission by mosquitoes in the genera of *Haemagogus* spp. YF virus transmission by *Aedes aegypti*, considered urban YF transmission, has not been confirmed in this current outbreak to date.

Of concern, die-offs of non-human primates thought to be secondary to yellow fever infection have occurred in large parks in Brazil with proximity to densely populated cities like São Paulo and Rio de Janeiro. In addition, at least 13 cases of YF have been identified among international travelers related to the current outbreak in Brazil (2 from France, 1 from the Netherlands, 4 from Argentina, 3 from Chile, 1 from Romania, 1 from UK/Germany and 1 from Switzerland). Eleven of the cases had traveled to Ilha Grande, a national park in the state of Rio de Janeiro. None of the travelers had been vaccinated. Additionally, Peru has reported nine confirmed cases during 2018. There is a risk of expansion of YF to other endemic countries in the Region, including the risk of re-urbanization as demonstrated during the 2008 urban outbreak in Paraguay.

**Figure 1. Distribution of Human Yellow Fever Cases from July 2016 to March 2018, Brazil**




Fonte: CGDT/DEVIT/SVS/MS. *Dados preliminares e sujeitos à revisão. A data de ocorrência não estava registrada em duas das notificações do período de monitoramento 2017/2018 (jul/17 a jun/18).

In response to the outbreak, Brazilian health authorities have expanded the YF vaccine recommendations to all residents aged >9 months to the states of Bahia, Espirito Santo, Rio de Janeiro, and São Paulo and have begun large fractional dose campaigns in selected areas of Bahia, Rio de Janeiro, and São Paulo. The WHO also updated vaccine recommendations for travelers to include all areas in Espirito Santo, Rio de Janeiro, and São Paulo and certain coastal areas in Bahia.

On 25 Jan 2018, federal authorities launched YF immunization campaigns using fractional doses in the states of São Paulo and Rio de Janeiro with target populations of 9.3 and 10 million people, respectively. In Bahia, the campaign was launched on 19 February with a target population of 3.3 million. As of 20 March 2018, approximately 6.7 million people have been vaccinated with fractional YF vaccine doses, with preliminary vaccine coverage of 30%. Low coverage may in part be explained by the fact that the government has not declared an official emergency, despite the high case fatality ratio, in addition to low acceptability of the fractional dose vaccination strategy by the general population, health personnel and the media.

The 15.7 million doses of YF vaccine for the campaigns in São Paulo, Rio de Janeiro and Bahia have been distributed by the Brazilian Ministry of Health from doses produced by Bio-Manguinhos. PAHO has collaborated on the purchase of 17 million auto-disable syringes of 0.1cc 27G x 3/8 ml in 2017 and 20 million syringes in 2018. In 2018, the RF in collaboration with the WHO, arranged for approximately 6.4 million of the 20 million syringes from the global stockpile to be made available to Brazil, attending to urgent supply needs for the campaign. The difference of 13.6 million syringes was procured directly through the RF. Given this, there is expected to be sufficient doses and syringes to conduct the current vaccination campaign.

**Use of fractional doses of the yellow fever vaccine**

In view of the global YF vaccine shortage and the occurrence of YF outbreaks in the WHO-AFRO and PAHO regions, in June 2017, the WHO reviewed available data on the use of less than a full dose of the YF vaccine to immunize an individual against YF. Four studies were identified that included three cohorts of mostly adult males. Two cohorts received full and fractional doses (as low as one-thousandth of a dose) of the 17DD vaccine subcutaneously and one received the 17D-204 vaccine either as a full dose

intramuscularly or a fractional dose (one fifth of a dose) intradermally. One of the 17DD cohorts was followed for ten months post-fractional dose vaccination. Based on these data, WHO recommended and the SAGE subsequently approved the use of a fractional YF vaccine dose as part of an emergency response to control an outbreak. In July 2017, PAHO's TAG endorsed this recommendation on the use of a fractional YF vaccine dose in response to outbreaks occurring in situations of limited vaccine supply.

**Table 1. Published Studies on the Immunogenicity of Yellow Fever Fractional Doses[1]**

| Characteristics | Lopes 1988 | Roukens 2008 | Martins 2013 | Campi-Azevedo 2014 |
|---|---|---|---|---|
| Vaccine product | Bio-Manguinhos | Sanofi, Stamaril | Bio-Manguinhos | Bio-Manguinhos |
| Sub-doses tested | 4 dilutions (1:10 – 1:1000) SC | 1/5 of full dose ID | Down to 1/880 of full dose SC | Down to 1/880 of full dose SC |
| Sample size | 259 males | 175 adults | 749 males | 749 males |
| Follow-up | 28 days | 1 year | 10 months | 1 year |
| Readouts | Seroconversion; Geometric Mean Titres (GMT) | Seroconversion; GMT | Seroconversion; GMT | Viremia, cytokines and chemokines |

WHO considered that the available evidence was sufficient to determine that fractional dosing of the YF vaccine to one fifth of the standard dose (0.1 mL instead of 0.5 mL) could be a safe and effective option for mass vaccination campaigns, to control urban outbreaks in situations of acute vaccine shortage. It is worth noting that administration of a fractional dose constitutes an off-label use of the vaccine and that the fractional dose may be administered by the sub-cutaneous or intramuscular routes. Preference should be given to YF vaccine products for which immunogenicity and safety data are available on a fractional dose administered subcutaneously or intramuscularly.

Based on the available clinical data, the minimum dose administered should contain 3000 IU/dose, but no less than 1000 IU/dose (WHO TRS 978 Annex 5). The country should determine the most suitable volume to be used as a fractional dose, considering that the minimum volume of the dose should not be less than 0.1 ml, and taking into consideration the available vaccine product, the potency of the vaccine batch, the supply and availability of suitable injection devices. Vial sizes greater than ten 0.5mL standard doses are not recommended for fractional dosing.

**Table 2. Potency of the Various Available YF Vaccine Products**

| Batch potency* International units (IU) | Product 1 | Product 2 | Product 3** | Product 4 |
|---|---|---|---|---|
| Average | 43651 | 25704 | 18977 | 12874 |
| Maximum | 114815 | 125896 | 177827 | 26284 |
| Minimum | 13490 | 3715 | 4169 | 7578 |
| Average 1/5 | 8709 | 5129 | 4467 | 2569 |
| Minimum 1/5 | 2692 | 741 | 832 | 1516 |

[1] Lopes O et al., J of Biological Standardization 1988; Roukens AH et al, PLoSone 2008; Martins RM et al., Human Vaccines & Immunotherapeutics 2013; Campi-Azevedo AC et al., BMC Infectious Diseases 2014.

*reporting periods varied from 5 to 13 years, depending on the manufacturer
**reported in PFU

Since there are no clinical data available for specific subgroups, this recommendation does not apply to children aged less than two years, pregnant women and individuals known to be HIV-infected. Individuals in these special populations should be vaccinated using a standard dose administered subcutaneously. Fractional doses of the YF vaccine are not intended to replace those used in established routine immunization programs, which must use a full dose administered subcutaneously. Fractional dosing is only intended to serve as a short-term measure to control or prevent a large-scale outbreak. Full doses should be used again in routine immunization programs once enough vaccine is available.

Regarding the duration of immunity conferred by a fractional YF vaccine dose, there is emerging evidence that demonstrates seropositivity eight years following administration of a fractional dose. A cohort of 749 Brazilian adult males who received fractional doses of the 17DD vaccine eight years earlier were re-contacted to obtain longer-term immunogenicity data. Of 318 participants included in this analysis, and who were seropositive at their initial study visits, 271 (85%; 95% CI, 81% to 89%) were seropositive eight years post-vaccination. The seropositive proportion ranged from 80-96% among the six groups who had received a dose of the YF vaccine where the dose administered ranged from a full dose to as little as one-thousandth of a full dose. Geometric mean titers of neutralizing antibodies to YF were similar across all groups, except for the group that received the lowest dose of antigens (i.e., one-thousandth of a full dose), who had significantly higher titers. This study supports use of the fractional YF vaccine in the face of increased demand and insufficient vaccine supply. Re-vaccination does not appear to be necessary for at least eight years. This conclusion will be reviewed when new evidence becomes available.

The reactogenicity of a fractional dose appears comparable to a full dose, based on limited data. The first programmatic experience with fractional yellow fever (fYF) vaccination, in the Democratic Republic of Congo (DRC), suggested no signs of increased risk of serious AEFI. Also, no safety issues were identified based on the administration of 25 and 50 doses from 5 and 10-dose vials, respectively, with multiple punctures of the rubber seal. Vial sizes greater than ten 0.5mL standard doses are not recommended for fractional dosing.

As per Annex 7 of the International Health Regulations, which states that one dose of the YF vaccine confers lifelong protection, international travelers entering or exiting countries requiring the International Certificate of Vaccination or Prophylaxis, with proof of vaccination against YF, as a condition for entering and/or exiting, should receive a full standard dose of the YF vaccine. However, because of the YF vaccine shortage, some countries in the Region have started to vaccinate international travelers using a fractional dose of YF vaccine products for which, at present, immunogenicity and clinical data are not available. Therefore, international travelers who have already received a fractional dose of the YF vaccine should be re-vaccinated with a full standard dose if the International Certificate of Vaccination or Prophylaxis is required as a condition to enter the destination country/countries and/or to exit the country of origin for their journey.

**Current supply situation and forecast for 2018**

The current demand for YF vaccine from countries participating in the RF in 2018 is approximately 13 million doses. To date, PAHO has received commitments from two suppliers for approximately 16 million doses. However, in view of Brazil's campaign and the administrative limitations on exports, the Brazilian manufacturer is facing challenges in meeting its initial commitment of 6 million doses to PAHO.

Given this situation, close collaboration continues with UNICEF should alternative arrangements be required in 2018. The RF is also working with countries considering a third supplier with an alternate presentation in ampules and with the Brazilian manufacturer to resolve these issues.

**Recommendations**

- TAG urges countries facing large YF outbreaks such as the current YF outbreak in Brazil, to activate the mechanisms in place for the rapid mobilization and deployment of all resources needed to control YF outbreaks in a timely manner, in agreement with the Member States' legal frameworks. The highest political commitment is needed at all levels to achieve high vaccination coverage rates in such vaccination campaigns. The lessons learned from Brazil's implementation of the measles-rubella vaccination campaigns should be applied to this YF campaign, including the highest political commitment, resource mobilization, supervision and coordination, accurate microplanning, risk communication and accountability.
- TAG reiterates its endorsement of the use of a fractional YF vaccine dose in response to outbreaks occurring in a context of limited vaccine availability. Children aged less than two years, 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.
- TAG stresses the importance of achieving 95% fractional YF vaccine coverage levels in a short time period for the intervention to be effective at controlling an outbreak. Strategies should be developed to reach high risk groups such as young males in rural or urban areas. Countries should implement a nominal immunization information system to monitor the corresponding coverage levels and vaccine safety.
- Based on available data from an 8-year follow-up study in adult males vaccinated with 17DD vaccine, which demonstrated sustained immunity in individuals who seroconverted after vaccination, TAG considers that a fractional dose could provide protection for at least eight years. Based on current evidence, re-vaccination is not required in an area in which vaccination with a fractional dose has been conducted in response to an outbreak. This recommendation will be revisited when new evidence becomes available.
- Given that data on the immunogenicity and safety of fractional YF vaccine are currently only available for one product that is administered via the same route as the full dose product*;* countries should give preference to this product. Endemic and non-endemic countries that are vaccinating against yellow fever should consider the potency of the vaccine batch, the supply situation and availability of suitable injection devices when deciding on the use of a fractional dose **(table 2)**.
- TAG recommends that endemic and non-endemic countries that use fractional doses of the YF vaccine, conduct further follow-up, product-specific immunogenicity and safety studies to increase the body of evidence on the use of fractional vaccine doses.
- TAG re-emphasizes the need to administer YF vaccine to national and international travelers following a thorough individual risk assessment, which considers both clinical risk and opportunities for exposure to the YF virus. TAG also emphasizes that under the current International Health Regulations, the International Certificate of Vaccination or Prophylaxis, with proof of vaccination against YF, which might be requested as a condition for entering and/or exiting a country, is only valid if the administration of a full standard 0.5 ml YF vaccine dose is documented.
- TAG urges the continued utilization of information from surveillance activities and risk assessments to prioritize vaccination, control measures and the allocation of the limited vaccine supply to countries.

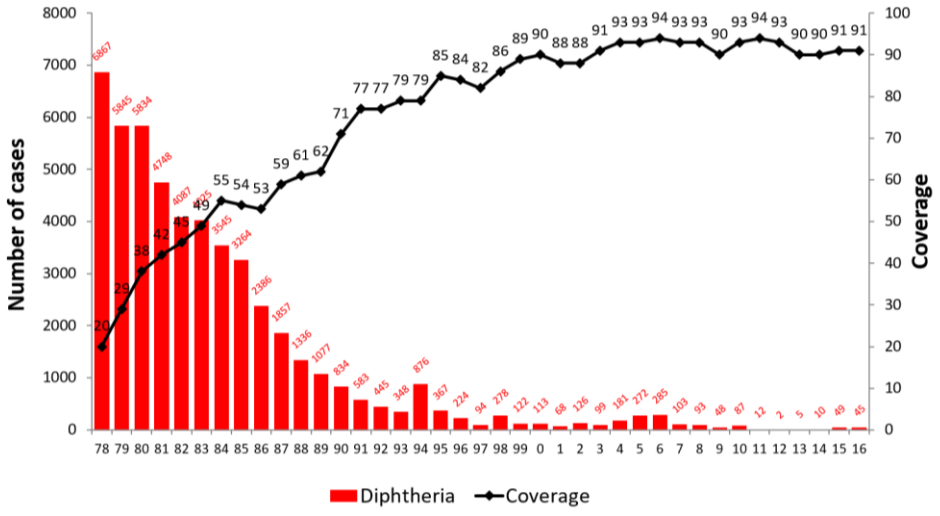
- In the context of the global YF vaccine shortage, TAG urges PAHO's RF to continue all efforts to ensure that the vaccine needs of YF-endemic Member States are met.

## Status Update on the Ongoing Diphtheria Outbreaks in the Americas and Current Outbreak Response

### Epidemiology of diphtheria in the Americas

Since the introduction and widespread use of diphtheria vaccines, diphtheria has been well controlled in the Region of the Americas **(figure 2)**, with a few cases occurring in past decades. Between 1993 and 2004, outbreaks were reported in Colombia, the Dominican Republic, Ecuador, Haiti, and Paraguay. However, the failure to maintain high levels of DPT3 coverage and cold chain breaches has resulted in the reappearance of diphtheria cases, especially in overcrowded and poor areas, and among people with no vaccination history or incomplete vaccination series. Currently, there are ongoing outbreaks in Haiti and Venezuela. Neighboring countries have reported imported cases (Dominican Republic, Brazil, and Colombia). The diphtheria outbreak situation is detailed below.

**Figure 2. Number of Diphtheria Cases and DTP3 Vaccine Coverage, the Americas, 1978-2016**




Fuente: EPI Tables, PAHO-WHO/UNICEF Joint Reporting Form (JRF) , and country reports. 2017

### Haiti

In Haiti, since the beginning of the outbreak in Epidemiological Week (EW) 50 of 2014 and until EW 6 of 2018, 410 probable cases of diphtheria were reported, including 75 deaths (Case Fatality Ratio [CFR]: 18%). Reported CFRs were 22.3% in 2015, 27% in 2016 and 10.7% during 2017 and 2018. Cases were reported from 40 districts in the nine states. Haiti has implemented control measures since the beginning of the outbreak, with support from PAHO/WHO. Health authorities are planning to conduct a vaccination campaign, consisting of three rounds, using DTP and Td vaccines, targeting children from one to <15 years of age residing in the nine affected states. The first round is planned for 11-15 March 2018. Dates for the second and third rounds are yet to be determined. The total target populations for these campaigns include 986,353 children 1-6 years of age and 1,249,429 children aged 7-14 years. There is a budget gap of $US 1.7 million for the proposed second and third rounds of those vaccination campaigns.

**Venezuela**

With its first case reported in July 2016, Venezuela had reached 3170 suspected cases as of March 2018, of which 976 (31%) were confirmed, 317 (10%) by the laboratory and 659 (21%) by an epidemiological link. A total of 142 deaths have been reported (17 in 2016, CFR 53%; 103 in 2017, CFR 13%; and 22 in 2018, CFR 15%). In 2016, cases were reported in five of the 23 states (Anzoátegui, Bolívar, Delta Amacuro, Monagas, and Sucre). In 2017, 22 out of the 23 states and the Capital District of Caracas reported confirmed cases by laboratory or epidemiological link. In 2018, 9 states reported confirmed cases. Cases were reported in all age groups; however, the majority affected the age group of 5-39 years, with the highest incidence rate in those 5-19 years of age. In 2017 and 2018, the national health authorities have conducted vaccination activities among contacts of suspected cases. An immunization campaign (Phase 2) will be conducted during 29 May-30 June 2018. All immunization activities are conducted along with measles vaccination campaigns and other routine immunization vaccines (e.g. bOPV, IPV). PAHO/WHO is supporting the outbreak response, including mobilizing additional human resources to support field activities.

**Brazil**

In 2017, 40 suspected cases of diphtheria were reported in 14 Brazilian states, of which 35 were discarded by laboratory results and 5 confirmed in four states: Acre (1), Minas Gerais (2), Roraima (1 fatal case, imported from Venezuela), and São Paulo (1). Three of the five confirmed cases (2 in Minas Gerais and 1 in São Paulo) had received complete vaccination series. The ages of the confirmed cases ranged between 4 and 66 years (with a median of 19 years); four were male and one was female. Additionally, a suspected case was reported during EW2 of 2018, in the state of Bahia and is currently under investigation.

**Recommendations**

**Outbreaks due to vaccine-preventable diseases**

- TAG urges countries facing outbreaks due to vaccine-preventable diseases to increase the visibility of these outbreaks and to seek high-level political support.
- TAG reminds countries of the importance of developing and implementing contingency plans to rapidly respond to outbreaks, those plans should include activities regarding:
    - Accelerated immunization activities and strengthening of the existing routine immunization programs with special emphasis on identifying high-risk areas.
    - Surveillance strengthening (including reporting that no cases have occurred – zero reporting, investigation of all suspected cases) and laboratory response.
    - Reviewing epidemiological data and immunization program information for outbreak monitoring.
    - Increasing public awareness, emphasizing the critical role of communication and activities to sensitize target populations.
    - Coordination of outbreak responses with all stakeholders including scientific societies, civil society, and other agencies or institutions involved. Countries should improve coordination mechanisms with neighboring countries where cross-border threats arise.
    - Post-outbreak activities including a report with a thorough evaluation of the outbreak.
- TAG recommends that all Member States urgently reach unvaccinated populations, including the most vulnerable populations such as those living in peripheral urban and remote areas, border areas, rural and indigenous communities.

**Outbreaks due to diphtheria**

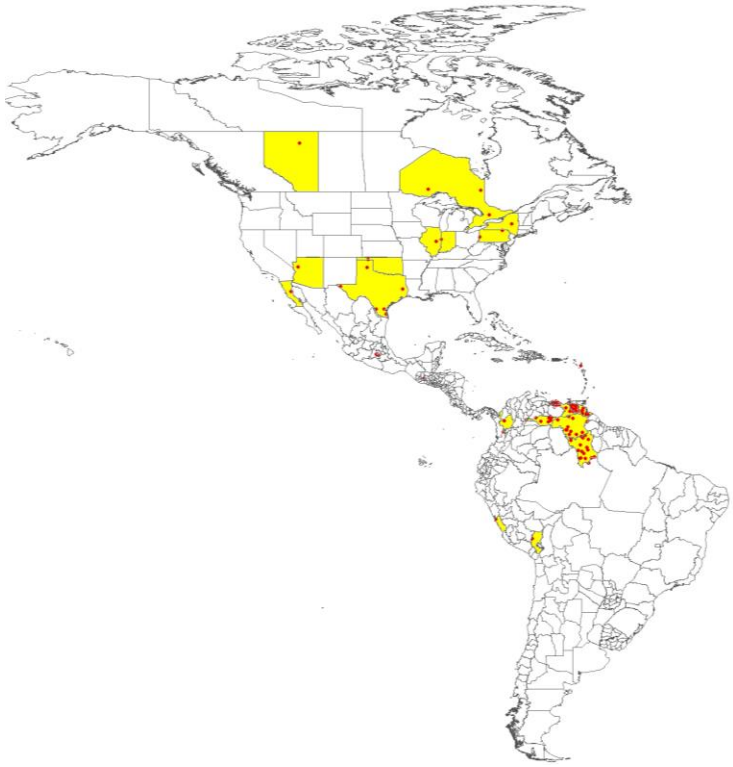
- TAG urges countries with ongoing outbreaks of diphtheria to ensure high-quality vaccination campaigns among targeted populations. Vaccination of health care workers and underserved populations living in densely populated areas is also recommended.
- As per previous TAG recommendations, infants should receive a primary series of 3 doses of the diphtheria-containing vaccine in a combined formulation, such as the pentavalent vaccine – the first dose should be administered as early as 6 weeks of age, principally to ensure rapid protection against pertussis; subsequent doses should be given with an interval of at least 4 weeks between doses; the third dose should be given by 6 months of age, if possible. The available evidence on booster doses suggests that the risk of diphtheria increases with time since the last vaccination, and depends on the total number of doses received. In addition, there is a need to harmonize the vaccination schedules across the diphtheria, tetanus and pertussis vaccinations. Therefore, TAG recommends that immunization programs ensure that 3-booster doses of the diphtheria-containing vaccine are provided during childhood and adolescence. This series will provide protection throughout adolescence and adulthood (up to 39 years of age and potentially longer). The diphtheria booster doses should be given in combination with the tetanus toxoid vaccine, using the same schedule and age-appropriate vaccine formulations – DPT among children 1-7 year(s) old; Td among children over 7 years old; adolescents and adults.
- TAG reiterates the need to closely monitor coverage with Penta3 and booster vaccine doses at the national and subnational levels.

## Update on the Measles Epidemiological Situation in the Americas

In September 2016, the International Expert Committee (IEC) for Documenting and Verifying Measles Elimination for the Americas declared the Region free of endemic measles. The PAHO Region was the first WHO Region to be certified free of measles. While countries in other WHO Regions have made progress towards eliminating measles, some still report endemic transmission and outbreaks (for example Romania, Ukraine and Italy in 2017). The significant global population movement increases the risk of measles importation and poses a threat to the measles-free status of the Americas. Moreover, endemic transmission being defined as a chain of measles virus transmission that is continuous for ≥12 months within the Americas, we report hereafter with concern about the ongoing measles outbreak in Venezuela.

During the first trimester of 2018, a total of 231 confirmed measles cases were reported by the following nine countries: Antigua and Barbuda (1 case), Brazil (29 cases), Canada (4 cases), Colombia (3 cases), Guatemala (1 case), Mexico (4 cases), Peru (2 cases), United States (28 cases), and Venezuela (159 cases) **(figure 3)**.

**Figure 3: Distribution of Confirmed Measles Cases at the Sub-National Level, the Americas, 2018***



**Source:** SysVPD, country reports and Ministry of Health of Venezuela. *Data as of epidemiological week 11 of 2018.

From 1 July 2017 to 24 February in 2018 (EW 26 of 2017 to EW 8 of 2018), Venezuela reported a total of 866 laboratory confirmed measles cases, including two deaths. Children less than 5 years of age were the most affected age group, followed by children 6-15 years of age. The outbreak has primarily affected nine of the 23 Venezuelan states, and 82% of the confirmed cases were identified in the state of Bolivar. Measles virus genotype D8 was identified in specimens collected from the cases, corresponding to a

new imported D8 genotype with no link to the endemic D8 genotype virus that had previously circulated in the Americas.

The outbreak spread to the municipalities of Boa Vista, Cantá and Pacaraima, in the State of Roraima, Brazil, which border the Venezuelan State of Bolivar. As of EW 10 of 2018, a total of 32 cases have been confirmed among unvaccinated Venezuelan citizens residing in Boa Vista (22 cases), Cantá (3 cases) and Pacaraima (7 cases), aged 6 months to 33 years. One hundred and two cases currently remain under investigation among residents of the three municipalities, including one death. In addition, one death was confirmed in a 4-year-old indigenous Venezuelan child in Pacaraima. According to laboratory analysis conducted by the Oswaldo Cruz Foundation (Fiocruz), the measles virus genotype identified is D8, identical to the genotype identified in Venezuela in September 2017.

In Colombia, the National Institute of Health confirmed 3 measles cases among Venezuelan citizens. The first case was a 14-month-old unvaccinated male, originally from the city of Caracas, who was admitted to the hospital and identified as a case in Medellin, Department of Antioquia. The child arrived in Colombia on 2 March and had onset of rash on 8 March. The second case was a 10-month-old male infant from the municipality of Santa Rosa de Cabal, in the Department of Risaralda. The infant had arrived in the country on 13 March and developed a rash on 16 March. The third case was a 10-month-old female, originally from the state of Miranda, who arrived in the department of Norte de Santander. She was hospitalized. Measles virus genotyping results are still pending.

In Peru, the National Institute of Health confirmed 2 measles cases. The first case was a 46-year-old male, resident of the Callao district, with rash onset occurring on 24 February 2018. The probable location of exposure remains under investigation. During the incubation period, the case traveled between Lima, Callao and the district of Vilque Chico (in the Puno region). The second measles case was a 16-year-old male resident of Juliaca, Puno that developed a rash on 28 February 2018. To date, 35 suspected cases have been discarded and eight remain under investigation. Measles virus genotyping results are still pending.

In Mexico, 4 cases of measles were confirmed between EW 1 and 10 of 2018. The first case was a vaccinated 38-year-old female resident of Tijuana, Baja California, who reported rash onset on 11 February of 2018. She had received only one dose of the measles-rubella vaccine. The case had travel history to several European countries and to the United States during her exposure period. Measles virus genotype B3 was identified, confirming likely acquisition in Europe. The three additional measles cases were confirmed in Mexico City, with rash onset occurring between EW 7 and 10. These cases were a 39-year-old woman, her one-year-old son and the infant's 48-year-old caregiver. Measles virus genotyping results are still pending.

Guatemala and Antigua and Barbuda have also reported isolated, confirmed measles cases. The first case identified in Guatemala was a Guatemalan 17-year-old female with travel history to Germany, and the second case identified in Antigua and Barbuda was a 19-year-old English female tourist, who arrived in Antigua from England during her infectious period. Rash onset for the cases occurred on 16 and 22 January 2018, respectively. Measles virus genotype B3 was identified in both cases, confirming likely acquisition in Europe.

Measles cases reported in Canada and the United States were either imported or import-associated cases with travel history to other regions of the world; 88% of the confirmed cases were unvaccinated. The age of cases ranged between 6 months and 49 years old. Half of the confirmed cases (53%) reported

travel history to India, Pakistan, United Kingdom and Uganda. The identified measles virus genotypes were D8, D4 and B3.

In response to the aforementioned measles outbreaks, rapid response teams have been implemented and are in the process of implementing the necessary control measures, including strengthening routine immunization and vaccination of susceptible individuals or individuals at high risk (e.g. health care workers, travelers and Venezuelan refugees), active case-finding of suspected measles and rubella cases, contact tracing and follow-ups; cross-border coordination in border municipalities (borders between Brazil and Venezuela; Colombia and Venezuela; Guyana and Venezuela; Peru and Bolivia), and dissemination of national epidemiological alerts and media risk communication messages.

**Recommendations**

- TAG urges countries reporting measles outbreaks to obtain high-level political commitment to ensure the mobilization of the financial and technical resources needed for an adequate response to prevent the reestablishment of endemic disease. This recommendation is particularly important for Venezuela because one year of endemic transmission is rapidly approaching. In addition, neighboring countries are already being affected. A high-quality, nation-wide mass vaccination campaign in Venezuela is urgently needed to stop transmission before the one-year cut-off for preventing re-emergence of endemic transmission (30 June) and to prevent exportations of measles virus to other countries.
- TAG urges countries to maintain measles immunization coverage levels ≥95% in all states and municipalities/districts. TAG also reminds countries of the importance of periodic follow-up vaccination campaigns to close any immunity gaps identified in their populations.
- TAG urges countries/territories to rapidly respond to the importation of measles and rubella cases to prevent the reestablishment of endemic disease transmission.
- TAG reminds countries/territories of the importance of having an emergency measles-rubella vaccine stockpile to enable an adequate response to outbreaks.

## Moving Forward with Monitoring the Sustainability of Measles, Rubella, and Congenital Rubella Syndrome Elimination in The Americas

**Background**

In 2016, the International Expert Committee (IEC) for Documenting and Verifying Measles, Rubella, and Congenital Rubella Syndrome Elimination declared the Region of the Americas free of measles. During the same year, the Americas reported 93 confirmed measles cases, the lowest number recorded during the post-elimination era. During the 29th Pan American Sanitary Conference in September 2017, the Ministers of Health approved a Plan of Action for the Sustainability of Measles, Rubella, and Congenital Rubella Syndrome (CRS) Elimination, for the period 2018-2023, with the purpose of protecting this important public health gain.

**Call to action**

Following up on the discussions of the 2017 TAG meeting in Panama and given the high risk of re-establishment of endemic transmission of measles in Venezuela and subsequently in the Americas, it has become urgent to establish a TAG working group of experts dedicated to:

- Monitoring the sustainability of the elimination of measles, rubella and CRS in the Region through the fulfillment of the objectives and indicators outlined in the regional Plan of Action for sustainability of the elimination;
- Developing a regional framework, with modified technical criteria, if appropriate, to monitor the absence of endemic measles transmission in the Americas, as well as the actions to take in the event of the re-establishment of endemic transmission.

The immediate issues that the group of experts could tackle include:

- The current situation in Venezuela, putting at risk the certification of measles elimination in the Americas.
- Are the current criteria for endemic transmission re-establishment in a country useful for the Region, given the situation in Venezuela and the previous experience in Brazil? If not, how should they be revised or modified?
- Accordingly, if endemic transmission is re-established in only one country, does the entire Region lose its measles, rubella or CRS elimination status?
- If endemic measles, rubella or CRS transmission in a country or in the Region is deemed re-established, what should the criteria and processes for the re-verification of measles, rubella or CRS elimination be?

**Recommendations**

- TAG reiterates its recommendation that countries should prepare and implement the Plan of Action for the Sustainability of Measles and Rubella Elimination, for the period 2018-2023 endorsed by PAHO Member States in September 2017.
- TAG also recommends the establishment of an independent TAG working group of experts to monitor the sustainability of measles, rubella and CRS elimination in the Region of the Americas.

## Update on the Global IPV Supply and Fractional IPV Introduction in the Americas

**Background**

In March 2014, TAG recommended that countries in the Americas introduce the inactivated poliovirus vaccine (IPV), as ideally two IPV doses followed by two or three doses of the bivalent oral polio vaccine (bOPV). By mid-2015, technical issues with scaling up IPV bulk production reduced the availability of IPV doses to implement a two-dose schedule. Countries that purchase the vaccine through the PAHO Revolving Fund (RF) agreed to introduce only one dose of IPV in their routine immunization schedule until there was sufficient global supply to introduce a second dose. Between 2015 and April 2016, 32 out of 51 countries and territories introduced one dose of IPV into their routine schedules. The other 19 countries and territories had previously been using IPV in their routine immunization programs. In 2016, regional coverage for IPV-1 was 92%.

In early 2016, the two global manufacturers that work with the Global Polio Eradication Initiative (GPEI) reported significant reductions in the quantity of IPV that they would be able to provide. In response to the limited supply, the WHO Strategic Advisory Group of Experts (SAGE) on immunization recommended that countries consider a fractional dose schedule of IPV, following scientific evidence that two doses of fractional IPV (fIPV) administered intradermally (1/5 of a full dose, or 0.1ml) provide a better immunological response than one full dose (0.5ml).

In May 2016, TAG held an extraordinary meeting to review the IPV supply situation and the scientific evidence on fIPV effectiveness, as well as the programmatic implications. At that time, TAG recommended that countries reduce IPV wastage, prepare to respond to shortages and evaluate capacities to introduce fIPV.

In March 2017, TAG met again for another extraordinary meeting and made a strong recommendation that all countries that use more than 100,000 doses of IPV per year begin preparing to switch to a fIPV dose schedule. These 16 countries are: Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Paraguay, Peru, Uruguay and Venezuela. In July 2017, TAG met again for its biannual meeting in the presence of all PAHO Member States, and reiterated these recommendations and had an open discussion with all countries.

Additionally, PAHO's Comprehensive Family Immunization (IM) unit developed materials to support countries with the introduction of an fIPV schedule, including guidelines, advocacy materials and a training video. To date, nine of the 16 countries that use more than 100,000 doses of IPV each year have begun preparations to switch from one full dose of IPV to two fractional doses: Colombia, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua and Paraguay.

Throughout the entire process, the RF and IM have been in close collaboration with WHO/GPEI, WHO/PQ, UNICEF, and have worked with countries to monitor IPV stock levels and allocate shipments with the aim of avoiding stock-outs.

In April 2017, the SAGE announced that the post-certification polio vaccination policy recommendations will be for all countries to have two doses of IPV in their routine immunization schedule for at least 10 years after global OPV withdrawal, using either full or fractional doses. All countries that switch to fIPV will be able to continue using fIPV through the post-certification era. For countries that do not switch to fIPV, they should be prepared to introduce a second full dose of IPV, once there is sufficient global

supply. Countries hosting poliovirus-essential facilities will require the indefinite use of IPV in their routine immunization schedules, in accordance with the Global Action Plan on Containment (GAPIII).

In September 2017, at the 29th Pan American Sanitary Conference and 69th Session of WHO's Regional Committee for the Americas, all Member States passed Resolution CSP29.R16 recognizing the situation of global demand and limited IPV supply, and recognized PAHO's RF as the strategic cooperation mechanism most suitable to provide access to vaccines like IPV. The Member States also called for PAHO to:

- Negotiate extraordinarily for the best possible price for IPV procurement in the Region of the Americas and, if necessary, adjust the terms and conditions of the Revolving Fund for this occasion only, to address the special circumstances currently existing and provide the supply of IPV for the Region of the Americas;
- Maintain coordination with the GPEI throughout this process in alignment with the Polio Eradication and Endgame Strategic Plan 2013-2018;
- Maintain a dialogue with partners and global IPV producers to accelerate and ensure the capacity to produce the necessary doses of IPV for the Region of the Americas; and
- Continue to support the Member States in their preparations for fIPV introduction.

**Current supply situation and forecast for 2018-2019**

The current demand for IPV from countries in 2018 is 11.3 million doses. To date, PAHO has commitments from two suppliers for IPV in five dose vials (IPV-5) pre-filled syringes. The supplier of IPV-5 is again facing challenges in meeting its initial commitment of 7 million doses to PAHO. Close coordination with the GPEI and UNICEF is ongoing to monitor this situation, along with WHO and PAHO. IPV-5 is the preferred presentation for consideration of fractional dosing. For the moment, PAHO is conservatively estimating that 3 million doses will be available from this supplier in 2018. Together with the 2.2 million doses of IPV in pre-filled syringes, this brings the total number of doses available for allocation to countries to 5.2 million, of which approximately 1.8 million doses have been made available to countries in Q1/2018.

As requested by Member States, PAHO conducted extraordinary negotiations in 2017 which resulted in an additional 690,000 doses of IPV in ten dose vials (IPV-10). Negotiations resumed in December 2017 and are ongoing. PAHO expects to sign a new supply agreement for IPV-10 for additional doses in 2018 and 2019.

**Use of IPV in outbreak settings**

In May 2017, WHO updated their guidelines to respond to an event or outbreak of poliovirus. One of the updates included was that IPV is no longer recommended for use in outbreak response settings. For poliovirus type 2 outbreak responses, mOPV2 is the recommended vaccine. For type 1 and 3 outbreak responses, bOPV is the recommended vaccine. The new guidelines are available on PAHO's website, and in December 2017, PAHO provided detailed recommendations for each country to update their outbreak response plans.

**Recommendations**

- All countries should strive to achieve and maintain 95% coverage with IPV in every district and municipality.
- TAG commends the countries that have begun preparation to switch to a fractional schedule of IPV, and encourages them to proceed with implementation of the fIPV schedule.

- TAG commends PAHO for the efforts to improve the IPV supply for the Region. However, recognizing that the ongoing global IPV supply constraints could still affect countries of the Region, TAG recommends that all countries of the Region - without exception - be prepared to respond in the event of a shortage.
    - In case IPV is not available, children should receive bOPV as the first or second dose of the schedule, and receive IPV as a later dose, always respecting the minimum interval of 4 weeks between doses of polio vaccine. It is important that health care workers always clearly record what vaccine was given to each child.
- TAG reaffirms recommendations made previously (May 2016, March and July 2017) regarding reducing IPV wastage, and the importance of reaching and maintaining vaccination coverage ≥95% in each district or municipality.
- The post-certification polio vaccination policy recommends countries have two doses of IPV in their routine immunization schedule for at least ten years after global OPV withdrawal, either full or fractional doses. All countries that switch to fIPV will be able to continue using fIPV through the post-certification era. For countries that do not switch to fIPV, they should be prepared to introduce a second full dose of IPV, once there is sufficient global supply.
- As IPV is no longer recommended for outbreak response, TAG recommends that countries update their national poliovirus outbreak response plans according to the individual recommendations that were provided by PAHO in December 2017.