Ad-hoc Virtual

TAG Meeting 2017

2nd Ad-hoc Meeting of the Technical Advisory Group on Vaccine-preventable Diseases

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Washington, DC, USA

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

TAG Members

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

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

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

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

Dr. Arlene King
Adjunct Professor
Dalla Lana School of Public Health
University of Toronto
Toronto, Ontario, Canada

Dr. José Ignacio Santos
Professor
Experimental Medicine Unit
Faculty of Medicine of the National Autonomous University of Mexico
Mexico City, Mexico

Dr. Jeanette Vega
Director
Chile's National Health Fund
Santiago, Chile

Dr. Cuauhtemoc Ruiz Matus *Ad hoc* Secretary
Unit Chief, Comprehensive Family Immunization, PAHO/WHO
Washington, DC, United States

Introduction

The Technical Advisory Group on Vaccine-preventable Diseases (TAG) held an ad-hoc virtual meeting on 10 March 2017 to discuss the worsening of the supply situation of the inactivated poliovirus vaccine (IPV) on a global level and in the Region, and the yellow fever outbreak in Brazil.

Dr. Cuauhtémoc Ruiz Matus welcomed TAG members and FGL/IM staff, and then invited the TAG Chair, Dr. Peter Figueroa, to open the meeting. Dr. Figueroa expressed his grave concern about the deterioration of the global IPV supply, which was the key reason that this TAG meeting was called; following the May 2016 TAG recommendation. He also shared an update on the epidemiological situation of the polio endemic countries with the participants, as well as the perspective of global post-switch situation, through his role in the SAGE Polio Working Group.

The TAG thanked and recognized the contributions of Dr. Maria Cristina Pedreira, who is retiring at the end of March 2017, after a successful 17-year career working in immunization at PAHO/WHO. During this time, Dr. Pedreira supported immunization efforts in the Dominican Republic, Nicaragua and Colombia. Since December 2013, she has been a Regional Immunization Advisor in Washington DC, with the main responsibility of coordinating IPV introduction and the successful completion of the switch from the trivalent oral polio vaccine (tOPV) to the bivalent oral polio vaccine (bOPV) in the Region.

The TAG also thanked the PAHO secretariat for the organization of this meeting. This was the second successful virtual meeting of the TAG.

How to face the global IPV shortage

Background

In September 2015, the Global Commission for the Certification of Poliomyelitis Eradication declared that indigenous wild poliovirus type 2 had been eradicated worldwide. Considering that no cases of wild type 2 polio (WPV2) have been detected since 1999, and that the continued use of the type 2 component of tOPV in areas of low coverage contributed to the occurrence of paralytic polio due to vaccine derived poliovirus type 2 (VDPV2), the SAGE recommended the phased withdrawal of the oral polio vaccine, starting with serotype 2, through the switch from the trivalent oral polio vaccine (tOPV) to the bivalent vaccine (bOPV).

To ensure that new birth cohorts have protection against the type 2 poliovirus, either wild due to any potential failures in containment or vaccine-derived, the SAGE recommended that all countries that exclusively were using OPV introduce at least one dose of the inactivated poliovirus vaccine (IPV) in their routine vaccination schedule.

These recommendations were endorsed by the TAG and the TAG additionally recommended that countries in the Region of the Americas introduce a sequential vaccination schedule, ideally starting with two doses of IPV, followed by two or three doses of bOPV.

In light of the limited IPV supply, and in order to ensure that all countries in the Region had access to IPV prior to the switch, PAHO agreed with the countries that purchase the vaccine through the Revolving Fund (RF), to only introduce one dose of IPV in their routine schedule until there is sufficient supply to introduce a second dose.

Initial response to the limited IPV supply

In May 2016, the TAG held an ad-hoc virtual meeting to discuss the global IPV shortage and the supply situation in the Region and reviewed the scientific evidence about the safety and immunogenicity of the administration of two fractional doses of IPV (fIPV), 0.1 ml or 1/5 of the complete dose, administered intradermally (ID). With the situation presented at that time, the TAG recommended that countries reduce IPV wastage, prepare to respond to a possible shortage of IPV, strengthen outbreak response, evaluate the capacity for the use of ID fIPV in the routine program and strengthen epidemiological surveillance.

During 2016, in order to avoid IPV stock outs in the Region, the RF and the Immunization Unit maintained contact with the vaccine producers and closely monitored and adjusted the vaccine delivery schedule. These actions enabled the Region to avoid IPV stock outs, to date.

Current IPV supply situation

The two global IPV producers have faced production problems and consequently have communicated several reductions in the global IPV offers. At this time, it is anticipated that the global IPV supply situation will continue to worsen and will remain low until at least the end of 2018.

The only provider through the RF that offers the vaccine in vials is Bilthoven Biologicals, at a cost of US$1.90 per dose. The other IPV producer, Sanofi, that did not accept the RF conditions, has offered a limited quantity of IPV doses in pre-filled syringes, at a cost of US$5.30 per dose. This offer has helped reduce supply gaps in the Region, but is not sufficient to respond to the total demand.

To date, as a result of the combined efforts among the countries, the RF and the PAHO Immunization Unit, which has included monitoring of IPV stocks in countries, adjustments to the vaccine delivery schedule and permanent discussions with the providers, the countries have received sufficient vaccine

supply to complete their polio vaccination schedule in the target population. However, even whilst maintaining these collaborative efforts, according to information received from countries about their current IPV stocks, it is estimated that as of July 2017, the countries of the Region will begin to face IPV stock-outs.

Scientific evidence on the use of fIPV

The available scientific evidence has shown that two doses of ID fIPV present a higher seroconversion for all serotypes than one full dose of IPV administered intramuscularly (IM). The maternal antibodies interfere with the immunological response, mainly for serotype 2, but there is less interference when the first dose is administered after 2 months of age. Also, the studies showed that the longer the interval between fractional doses, the better the immunological response. Adverse events occur more frequently with ID administration than with IM; however, they are generally mild local reactions such as erythema and induration.

Programmatic and operational considerations for the use of fIPV

In general, the ID administration of vaccines is more difficult than IM; for that reason, it is important that all health workers are adequately trained in order to guarantee safe administration of the vaccine. Additionally, the timely supervision of the introduction of fIPV is critical to ensure the safe and effective implementation of this schedule.

According to the WHO open-vial policy, IPV in multi-dose vials can be used for up to 28 days. For the application of fractional doses, a 0.1 ml 27 G 3/8 syringe should be used – which is the same one that is used for BCG in some countries. There are countries that administer BCG in a 0.05ml syringe, and therefore do not have any stock of 0.1 ml syringes. According to information from the RF, it is likely that the 0.1 ml BCG syringe is not available in the majority of countries.

To introduce a fIPV schedule, updates to the registration systems need to be taken into consideration during the planning, training and supervision processes.

The use of fIPV ID is based on independent scientific evidence and is not specified on the label, which means that it is necessary for countries to follow the procedure of their respective National Regulatory Authority (NRA) to use this vaccine off-label.

TAG Recommendations

After reviewing the projections of production and the delivery schedule for IPV purchased through the RF and considering the potential threat of IPV stock-outs in the Region, as well as the scientific evidence on the immunogenicity of fIPV, the TAG recommends:

- Countries that administer more than 100,000 doses of IPV each year and have the capacity to adequately train health care workers and supervise implementation should immediately begin to prepare to implement a fractional dose IPV schedule. These countries include: Argentina, Bolivia, Brasil, Chile, Colombia, Cuba, Ecuador, El Salvador, Honduras, Nicaragua, Paraguay, Peru, Uruguay and Venezuela.

- The administration of a sequential schedule of two fractional doses followed by two or three doses of bOPV, with the first dose at two months of age and with intervals of 8 weeks between each dose of the basic vaccination schedule during the first year of life.

Vaccination Schedule	Basic			Booster	
	1st	2nd	3rd	4th	5th
	fIPV	fIPV	bOPV	bOPV	bOPV

- Brazil and Uruguay, countries that introduced IPV prior to 2015 and use a schedule of three doses of IPV, should review their vaccination schedules based on the current availability of the vaccine.

- Guatemala, Haiti and the Dominican Republic should carefully consider their capacity to introduce a schedule with two fractional IPV doses, weighing the training and supervision requirements and the need to achieve high coverage, with the risk of facing a stock-out. The TAG assesses that it may be best if these countries do not introduce the fractional dose schedule at this time.

- Countries that use less than 100,000 doses of IPV each year will likely face higher wastage of the vaccine if they are not able to effectively use the quantity of fractional doses in each vial within the timeframe of the open-vial policy. For that reason, these countries should carefully assess their situation because it may not be appropriate for them to introduce a fractional dose schedule.

- The TAG emphasizes the importance of reaching and maintaining vaccination coverage equal to or greater than 95% in each district or municipality.

The TAG reiterates its recommendations made in May 2016:

1. **Reduce IPV wastage**
   - Ensure strict adherence to the vaccination schedule, using IPV only with children that have turned two months of age after the official introduction date of IPV in the country.
   - Fully implement the WHO open vial policy, which permits the use of open vials of IPV for up to 28 days, provided that the defined criteria are met as outlined in the WHO policy on the use of opened multi-dose vaccine vials.
   - Avoid, whenever possible, the use of IPV in extramural activities, prioritizing vaccination strategies that use fixed or mobile vaccination posts.
   - Closely monitor IPV supply in the country to assure that all services are supplied and all possible service points that could have excessive vaccine wastage are identified, for providing appropriate recommendations.

2. **Prepare to respond to possible IPV shortages**
   - All health workers should be informed about a possible shortage of IPV and prepared to respond to this eventuality.
   - In the absence of IPV for administration as the first dose of vaccination against polio, children should receive bOPV as the first dose in the schedule. In these cases, IPV should be applied at the first contact it is available, as the second, third, or booster dose in the schedule, always respecting the minimum interval of 4 weeks between doses of polio vaccines.
   - Due to the uniqueness of this recommendation, it is necessary to inform all vaccinators about the importance of clearly registering which vaccine was used, in both the national registry and on the child's vaccination card, so that for the next visit it will be clear if the child has already received a dose of IPV or if this dose is still pending.

3. Prepare to respond to polio outbreaks

- All countries should review their polio outbreak response plans, considering the PAHO guidelines, available on the website: www.paho.org/polio.
- Countries should ensure that they can receive the monovalent oral polio virus vaccine type 2 (mOPV2) in a very short time from the global stock pile for outbreak response, which will be sent through UNICEF.
- IPV will not be needed to respond to all type 2 polio outbreaks. However, if it is assessed that IPV use is necessary, the WHO recommends that countries use fractional doses, administered intradermally, to make sure there is sufficient supply to serve all countries in need.
- Countries should evaluate their capacity in terms of skilled human resources to implement a vaccination campaign with fractional doses of IPV administered intradermally. Furthermore, countries should ensure that they can use the IPV vaccine in this way, as recommended by WHO for outbreak response. The recommendation is based on scientific evidence, but is not indicated so on the vaccine inserts, therefore that means that countries must use fractional IPV as off-label use.

4. Strengthen surveillance

- The TAG reiterates that due to the risk of the emergence of cVDPV type 2 in the post-switch period, all countries must maintain sensitive surveillance systems in order to rapidly detect and interrupt any type 2 circulating poliovirus.
- Countries should strive to meet the following quality surveillance indicators for acute flaccid paralysis (AFP):
    - 1 AFP case per 100,000 children less than 15 years old
    - > 80% cases with adequate samples
    - > 80% cases investigated within 48 hours or less

Yellow fever outbreak in Brazil and implications for the Region

Background

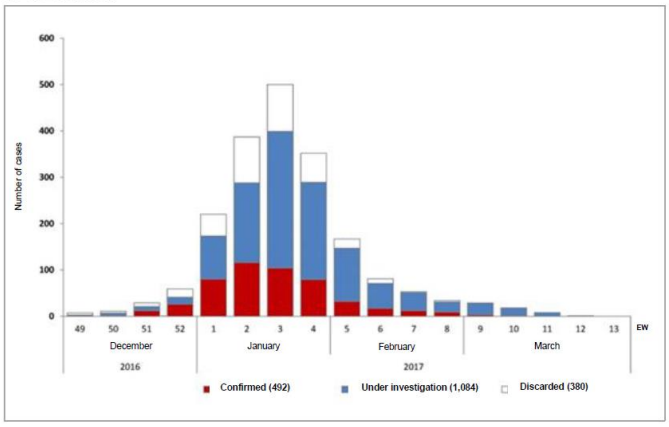
Yellow fever (YF) is an acute viral hemorrhagic disease that is endemic in tropical areas of Africa and 13 countries in Latin America, including Peru, Bolivia, Brazil, Colombia, Argentina, Ecuador, French Guiana, Guyana, Panama, Paraguay, Suriname, Trinidad and Tobago and Venezuela. The primary mode of YF transmission in the Region is sylvatic. However in 2008, cases of YF were reported in the metropolitan area of Asuncion, Paraguay. Prior to this, the last confirmed urban outbreak of YF in the Americas had occurred in Brazil in 1942. These events, in addition to the proliferation of *Aedes aegypti* in the Region, suggest that a high risk of re-urbanization of YF still exists in the Americas.

Vaccination is the most important preventive measure against YF. The vaccine is safe, affordable and provides effective immunity against the disease to 80-100% of those vaccinated within 10 days and an immunity of 99% to those vaccinated within 30 days. A single dose is sufficient to confer sustained immunity and life-long protection, with no need for a booster dose.

The TAG recommendations for YF control are the following: 1) introduction of the yellow fever vaccine in national immunization programs for children 1 year of age in countries with endemic areas; 2) vaccination campaigns during inter-epidemic periods; 3) vaccination campaigns in response to outbreaks or epizootics, and 4) administration of the vaccine to those traveling to areas where there is a risk of transmission of the YF virus, except for those for whom vaccination is contraindicated. Due to a limited global supply of the YF vaccine, the SAGE recommended in 2016 the use of fractional yellow fever (fYF) doses in outbreak responses, with 1/5 of the volume of the normal dose administered subcutaneously.

In December 2016, Brazil started reporting suspected cases of YF, principally in the South East region of the country. No urban YF transmission by *Aedes aegypti* has been confirmed to date. As of March 28, 15 states and the Federal District have reported a total of 2,104 suspected cases, of which 492 laboratory-confirmed cases were confined to only four states: Minas Gerais, Espirito Santo, São Paulo and Rio de Janeiro. Of the total suspected cases, 277 (13%) patients have died. Of the laboratory-confirmed cases, there were 162 deaths, representing a case fatality ratio (CFR) among confirmed cases of 33%.

Distribution of reported case by Epidemiological Week of onset of symptoms. Brazil, as of 23 March



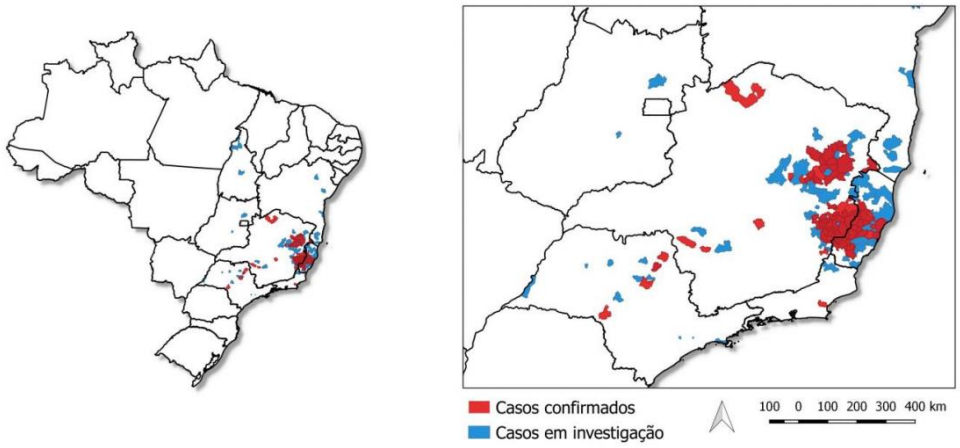
Source: Data published by the Sinan - COES-FA/SVS and reproduced by PAHO/WHO

In Minas Gerais, where over 75% of the confirmed human YF cases are concentrated to date, and Espirito Santo, a state that never had a vaccination recommendation prior to the outbreak, there have been decreases in the number of cases reported over the past six weeks. However, cases continue to be reported in municipalities with low coverage. Cases have also arisen in the states of São Paulo and Rio de Janeiro.

In addition to human disease cases, a total of 1,324 epizootics have been reported to date, of which 389 (31%) were confirmed as related to YF virus, 12 (<1%) discarded, and the remaining under investigation.

Geographic distribution of suspected and confirmed YF human cases

Figura 3 - Distribuição geográfica dos casos humanos confirmados e em investigação de febre amarela à SVS/MS, por município do LPI e classificação.

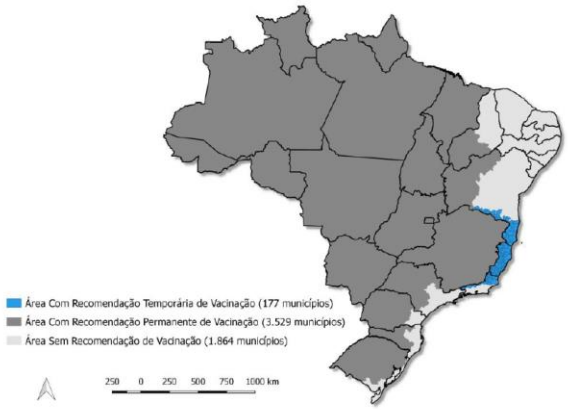


Public health responses and challenges

Brazil recommends a vaccination schedule consisting of two doses of the YF vaccine at 9 months and 4 years of age in all endemic areas. It is recommended that all persons between 5-59 years receive two doses, one at the first contact with health services and a booster dose 10 years later. From 2007 to 2016, the Expanded Program on Immunization (EPI) reported having administered a total of 58.5 million doses of the YF vaccine, reaching 66.5% vaccination coverage in the target population (older than 9 months).

In response to the outbreak, the Brazilian Ministry of Health temporarily expanded YF vaccination recommendations to 177 new municipalities by March 21, 2017 (Figure below). They revised YF vaccination recommendations.

Geographic distribution of municipalities where the YF vaccine is recommended by type of recommendations, Brazil, March 21, 2017.



Source: *Informe especial febre amarela no Brasil nº 01/2017*, Ministry of Health, Brazil, March 21, 2017.

An emergency meeting of the National Immunization Technical Advisory Group (NITAG) was held on 22 March. After reviewing the available data and subsequent discussions, these were their recommendations:

- Temporary suspension of the booster dose recommendation until further notice;
- Use of fractional doses as part of the immunization strategy to respond to the outbreak, prioritizing urban centers such as Rio de Janeiro, Sao Paulo and Bahia, as needed;
- Suspension of the recommendation to administer MMR and YF vaccines separately during the outbreak and co-administer if necessary to provide protection particularly against YF;

Around 19 million doses of the YF vaccine have been distributed by the Ministry of Health in five Brazilian states. Considering the expansion of the outbreak and the limited availability of the vaccine, Brazil also requested and received 3.5 million doses from the global emergency stockpile of the International Coordinating Group on vaccine provision for yellow fever (ICG). An emergency stockpile consisting of approximately 6 million doses is available to support countries in emergency/outbreak situations in Africa and Latin America. Access to this stockpile responds to strict eligibility criteria, including a thorough analysis of the epidemiological and entomological situation, as well as detailed descriptions of vaccination coverage and foreseen vaccination strategies.

When facing a suspected or confirmed human or primate human case, vaccination actions, ring vaccination and vector control strategies are intensified. Additionally, surveillance of adverse events following immunization (AEFI) is being strengthened at all levels. PAHO/WHO has activated a dedicated Incident Management Structure (IMS) to support Brazil locally and provide support for collaboration with PAHO HQ and WHO.

YF vaccine availability

The global supply of YF vaccines has been limited for years. The PAHO/WHO Revolving Fund provides about 50% of the demand in the Region of the Americas. This situation of vaccine scarcity is worrisome for other endemic countries in the Region, most of whose vaccine demand through the Revolving Fund for 2017 is currently unmet. The Revolving Fund is actively seeking solutions with other manufacturers. It is worth noting that Brazil, being one of the few existing YF vaccine manufacturers globally, has been an important contributor to the ICG emergency YF vaccine stockpile.

TAG Recommendations

- The TAG reiterates its previous recommendations regarding the application of a single dose of YF in endemic areas:
    - One YF vaccine dose is sufficient to provide sustained immunity and life-long protection against the disease, therefore no booster dose is required.
    - Vaccination of at least 95% of the population residing in the area (urban, rural and jungle areas).
    - Countries should ensure that vaccination recommendations for travelers to YF endemic areas are enforced.

- The TAG reemphasizes the importance of YF vaccination through the routine immunization program and of maintaining high coverage levels to prevent cases and outbreaks of the disease. However, in the current outbreak situation of Brazil, YF endemic countries should consider postponing childhood vaccination in non-enzootic areas in order to re-allocate doses for priority areas until the vaccine is more readily available at the regional and global levels.

- The TAG endorses the current WHO recommendation regarding the use of fractional doses in response to outbreaks. PAHO should support countries in the roll out and implementation of fractional doses of YF vaccination as needed, including strengthening of AEFI surveillance following vaccination with fractional doses.

- Given the current outbreak in Brazil and the emergence of cases in areas where cases have not been detected in several years, the TAG urges countries to continue prevention and control efforts as part of a comprehensive plan to:
    - Strengthen epidemiological, virological, vector, epizootic and AEFI surveillance.
    - Reassess the YF risk in endemic countries taking into entomological makeup, account migration patterns, global warming and other human (eco-tourism) trends, among others.
    - Reassess the risk of YF re-urbanization.
    - Monitor and maintain high vaccination coverage among target groups.