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International Coordination Group on Vaccine Provision for Yellow Fever

Report of the Annual Meeting

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AFRO	WHO Regional Office for Africa
CFR	Confirmed fatality rate
EPI	Expanded Program on Immunization
EYE	End Yellow Fever Epidemics
Gavi	Gavi, the Vaccine Alliance
GTFCC	Global Task Force on Cholera Control
ICG	International Coordinating Group
IFRC	International Federation of Red Cross and Red Crescent Societies
MSF	Médecins sans Frontières
MMR	Measles, mumps and rubella vaccine
PAHO	Pan American Health Organization
PMG	Programme Management Group
SD	Supply Division of UNICEF
UNICEF	United Nations Children's Fund
WHO	World Health Organization
YF	Yellow Fever

Executive summary

The annual meetings of the International Coordinating Group (ICG) on Vaccine provision for epidemic meningitis, cholera and yellow fever (YF) were held back-to-back from 18–20 September 2018 in Geneva. The aims of the annual meeting of the ICG for Yellow Fever, held on 20 September, were for partners and stakeholders to: review the epidemiological situation and epidemic response activities, including ICG requests, in 2017 and 2018; discuss lessons learned and propose recommendations for improvement; discuss the anticipated stockpile size, composition and funding for 2019; and review areas of complementarity between the ICG and End Yellow Fever Epidemics (EYE) Strategy.

After the opening remarks, participants were briefed on the global YF epidemiological situation in 2017 and 2018, with an emphasis on Brazil and Nigeria. UNICEF Supply Division (UNICEF-SD) gave an update on vaccine shipments made over the previous year, and the ICG Secretariat then presented its review of the ICG's performance in terms of meeting its targets for timeliness of vaccine response. Next, representatives of the EYE Strategy shared their views on anticipated vaccine needs for preventive campaigns over the coming years, and on avenues for enhancing coordination between the EYE and ICG secretariats. UNCEF-SD then gave its presentation on stockpile management, current global vaccine reserves, ongoing tendering, vaccine availability and lessons learned. After lunch, Gavi updated participants on the progress towards meeting the objectives of the Gavi Roadmap and its market shaping activities for YF vaccines. Manufacturers then gave their production forecasts for the period 2018–2022 and shared their plans for future investments in production capacity.

From January to September 2018, the ICG received five emergency requests from Nigeria and the Republic of the Congo for YF vaccines, of which three were approved for a total of 4,418,486 doses. Participants agreed that ICG and UNICEF-SD should establish a working group on delivery lead times and to identify and evaluate bottlenecks in the procurement and delivery process, in particular delays related to obtaining approval for importation of vaccines from individual countries. While the EYE and ICG secretariats will continue to enhance their cooperation, it was agreed that the ICG Secretariat, along with UNICEF-SD, should review dose presentation of stockpiled vaccines. The next ICG meeting should include presentations on the implementation of reactive vaccinations campaigns and outcomes such as (independently-assessed) vaccination coverage, wastage factor, adverse events following immunization, and others.

ICG members agreed that the YF stockpile should remain at its current size of 6 million doses. The increase in vaccine supply over recent years was identified as a positive development. According to current projections, global YF vaccine supply is likely to meet demand for emergency, preventive and routine use over the coming years.

Efforts are also underway to implement the recommendations of the external review of the ICG, which was presented to the ICG Secretariat in October 2017. The ICG has established its new Governance and Oversight Committee and is beginning to implement the ICG Accountability Framework, which will be effective from 2019 onwards.

1. Introduction

YF is an acute viral haemorrhagic disease caused by a flavivirus primarily transmitted by mosquito vectors. It is difficult to diagnose, and case identification is often complicated by the co-circulation of malaria and other flaviviruses. Forty countries across Africa and Central and South America are classified as high-risk or with high-risk areas. The virus is primarily spread in two cycles. In the sylvatic cycle, transmission occurs between non-human and primates via *Haemogogus* and *Sabethes* mosquito species. In the urban cycle, *Aedes aegypti* vectors transmit YF directly between humans. A single YF vaccine dose confers long-term immunity in 95% of recipients.

The International Coordinating Group on Vaccine Provision (ICG) was established as an emergency mechanism to respond to outbreaks of epidemic meningitis following outbreaks in the African meningitis belt which resulted in over 200,000 cases and 20,000 deaths. ICG groups and emergency vaccine stockpiles were established for meningitis, YF and cholera in 1997, 2001 and 2013 respectively.

The ICG brings together four founding agencies: The International Federation of Red Cross and Red Crescent Societies (IFRC), Médecins Sans Frontières (MSF), the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO). It also consults with extended partners including technical experts and vaccine suppliers. Gavi, the Vaccine Alliance, is the principal funder of the three vaccine stockpiles.

The ICG's objectives are:

- To provide equitable vaccine allocation through careful and objective assessment of risk, based on epidemiological and operational criteria
- To rapidly deliver vaccines in response to infectious disease outbreaks.
- To coordinate the deployment of limited quantities of vaccines and other essential medicines.
- To minimize wastage of vaccines and other supplies.
- To advocate for readily-available, low-cost vaccines and medicines.
- To work with manufacturers through UNICEF and WHO to guarantee availability of vaccine emergency stock supplies at the global level.
- To follow standard operating procedures and establish financial mechanisms to purchase emergency vaccine supplies and ensure the sustainability of stocks.

The 2018 annual meeting of the ICG on Vaccine Provision for epidemic meningitis was held on 18 September in Geneva. Participants included representatives of WHO headquarters (HQ), including ICG Secretariat, the WHO Regional Office for Africa (AFRO), the Pan American Health Organization (PAHO), UNICEF, with participants both from HQ and the Supply Division (SD), MSF, the IFRC, Gavi, the Vaccine Alliance and vaccine manufacturers. Representatives from the EYE Strategy, who had just held their annual Strategy Partners' Meeting the previous week in Dakar, Senegal from 11–13 September 2018, also attended.

The 2018 annual meeting follows on from that of the previous year, held on 11–12 May 2017. Action points from that meeting included the need to improve coordination and communication between the EYE governance structures and ICG, to collaborate with countries to assess vaccine needs and relay forecasts to manufacturers, to clarify operational costs and conditions for provision of technical assistance for non-GAVI countries, and to improve reporting on ICG decisions on vaccine requests. It was also agreed to allow WHO colleagues (notably incident managers), to assist in providing information during the ICG decision-making process. Following the completion of the external evaluation of the ICG, it was agreed that the ICG's performance indicators should reflect the respective responsibilities of each ICG partner.

2. Epidemiological update 2018

The last three years have seen unprecedented YF outbreaks and epidemics in geographies without recent cases, highlighting the potential for the rapid amplification of outbreaks in urban settings. In 2016, major urban outbreaks in Angola, with international spread to the DRC, as well as an outbreak in Uganda, resulted in the release of 30,203,470 vaccine doses in response to 13 approved emergency requests to the ICG. These events catalysed the establishment of the EYE Strategy by WHO and partners to tackle the increased risk of YF epidemics in a coordinated manner by 2026.

In 2018, YF epidemics were reported from Nigeria, Ethiopia and the Republic of the Congo.

The increasing underlying risk of YF is driven by accelerating urbanization, climatic change, population growth, encroachment of urban areas on non-human primate habitats and greater mobility of workers—particularly those engaged in activities such as resource extraction. The epidemiological characteristics and drivers of YF risk differ between Africa and the Americas. Not only do transmission cycles, local strains and population immunity differ by region, .these differences call for adaptation of surveillance systems, including non-human primate surveillance, to their local context.

AFRO Region

YF transmission occurs via both urban and sylvatic cycles in Africa. In recent years there has been a shift in the geographical pattern of YF risk in the Region. Despite previous efforts at mass immunization in many countries, vaccination coverage and immunity remain low in many at-risk countries. The majority of countries have sub-optimal routine vaccination coverage, and there exist wide between-country disparities with pockets of low coverage.

Notable outbreaks were reported in Nigeria and the Republic of the Congo over January to September 2018. Significant transmission has been ongoing in **Nigeria** since August 2017 in a wide geographic distribution. The first confirmed case in the current re-emergence was reported on 12 September 2017 in Kwara State and an outbreak was declared two days later. Since then there have been 2,581 total suspected cases, 110 confirmed cases (across 11 states) and 10 deaths among confirmed cases (case fatality rate (CFR): 21.3%). It is probable that these cases represent multiple emergences in different states with a wide geographic distribution; direct epidemiologic linkage between cases is absent. This underscores the high underlying risk of YF in the country and suggests it may have been previously underappreciated. At time of the meeting, the latest confirmed case had been reported in Rivers State on 6 June 2018. Preventive mass vaccination campaigns (as well as five reactive campaigns following ICG requests) were completed in three states in early 2018 and comprehensive campaigns will take place in a further five states (Sokoto, Kebbi, Niger, FCT and Plateau) from November 2018 onwards. Vaccination will also take place in Borno State, although campaigns will be opportunistic in nature due to the security situation. Despite making significant progress in some areas, such as the establishment of a dedicated courier service for epidemiological samples, routine immunization remains low and some regions of the country are difficult to access for emergency or mass preventive campaigns due to conflict or limited transport infrastructure.

A YF outbreak took place in and around Pointe Noire, the second-largest city in the **Republic of the Congo**. The first suspected case was detected on 5 July and had developed jaundice by 9 July. A blood sample was taken the next day, and, by 21 August the case had been confirmed by the regional reference laboratory in Dakar, Senegal. An outbreak was declared as of 22

August, with a total of 192 suspected and 1 confirmed cases reported through the national surveillance system. Of these, 72 suspected cases were reported in Pointe Noire District, primarily in urban areas where population-level immunity is believed to be low and the density of *Aedes aegypti* vectors is high.

In the **DRC**, 454 suspected and 4 confirmed cases were reported from January to August 2018. The most recent confirmed cases, which were over July and August, were in the Bas Ouélé and Tshuapa regions in the north and the Lualaba Region in the south of the country. Investigations are ongoing to determine whether there is indication of outbreak with ongoing spread. Between January and July 2018, suspected YF cases were also reported in **Benin**, **Burkina Faso**, **Central African Republic**, **Chad**, **Côte d'Ivoire**, **Gabon**, **Ghana**, **Guinea**, **Mali**, **Niger**, **Senegal**, **Sierra Leone** and **Togo**.

PAHO Region

In **Brazil**, YF is detected in sylvatic vectors and to date transmission has only occurred in rural and peri-urban areas. In 2016 the number of annual YF cases increased sharply, associated with epizootic waves (or outbreaks) in non-human primates. The numbers of human cases were much higher than recent years and impacted states not previously assessed as high risk (e.g. São Paulo), representing expanded geographic spread of disease to areas not previously assessed as high-risk. Large numbers of cases were reported in the states of São Paulo and Rio de Janeiro. There was no previous routine immunization in São Paulo, and vaccination coverage has consequently been low. YF transmission continued through 2018 with cases mainly occurring between December and March. Although there is a risk of the re-emergence of urban YF transmission in Brazil for the first time since 1942 due to the presence of *Aedes aegypti* in urban areas, the competency of urban vectors for the YF virus in the country is uncertain.

These epizootic and human cases have primarily occurred in areas bordering the Atlantic coast, indicating the spread of the YF virus to a new biome. From July 2017 to June 2018 a total of 1,266 confirmed cases and 415 deaths (case fatality rate: 32.8%) were reported in Brazil. This represents an increase on the 771 reported cases and 259 fatalities (case fatality rate: 33.6%) over the same period of 2016–2017. There has been significant focus on the emergence of “sylvatic corridors”, or forested areas which extend into peri-urban settings and facilitate epizootic spread occurring in waves from the country’s interior towards the coast which are believed to be linked to migrations of non-human primates.

Although the State of São Paulo previously did not have a recommendation for immunization, this policy was adjusted in mid-2017. The state is undertaking a mass preventive vaccination programme with fractional doses as of January 2018, and 60% of the state’s population were vaccinated as of mid-2018. It is projected that an additional 70 million people will be immunized by 2019 as part of the country’s efforts to expand vaccination into areas which previously did not have a recommendation. This large-scale immunization effort has placed pressure on vaccine supply in other countries, however, and YF vaccine exports from Brazil have been restricted.

Cases were also detected in other countries in the Region. While several YF cases were detected in **Colombia** during 2018, 22 suspected and eight laboratory-confirmed cases were reported in **Peru** during Epidemic weeks 1–9. Another confirmed case of YF was reported in an unvaccinated 47-year-old Swiss man by authorities in **French Guiana** on 10 August 2018.

3. ICG response and performance outcomes

Over January to September 2018, a total of five requests for YF emergency response were made by Nigeria and the Republic of the Congo (Table 1). Three of these were approved and 4,418,486 YF vaccine doses were released from the ICG emergency stockpile. This compares with 2017, when four requests were made by Brazil and Nigeria. All four of these were approved (of which one was partially approved), resulting in the dispatch of 6,795,530 doses.

Table 1. Summary of emergency requests to the ICG for yellow fever vaccines, 2018

Request number and country	Request date	Days for request circulation	Days for additional information	Days decision time	Approval	Days delivery time	Days to campaign	Vaccine doses requested	Vaccine doses approved
#1 Nigeria	01/01/2018	same day	2 days	1 day	Approved	11 days	6 days	3,015,714	3,015,700
#2 Nigeria	01/03/2018	same day	4 days	same day	Not approved	N/A	N/A	N/A	N/A
#3 Nigeria	01/07/2018	5 days	6 days	same day	Approved	8 days	Unknown	169,544	169,544
#4 Republic of the Congo	01/08/2018	same day	3 days	1 day	Approved	14 days	7 days	1,233,242	1,233,242
#5 Nigeria	01/09/2018	3 days	same day	2 days	Not approved	NA	N/A	N/A	N/A

Three requests from **Nigeria (#1 and #3)** and **Republic of the Congo (#4)** were fully approved. Despite being sent on a Friday night at 22:00, the first request (#1) was circulated to ICG members the same day. The delivery of vaccines for a second approved request (#3) was delayed as shipments occurred during the weekend and customs officers were not available to approve their entry into the country. Due to its large size and low availability of cold storage facilities at transit airports, it was necessary to split vaccines destined for the Republic of the Congo (#4) into multiple deliveries. Two requests from **Nigeria (#2 and #5)** were not approved due to a lack of laboratory confirmation of cases while the former (#2) also did not include entomological data.

Regarding the ICG's key time performance indicators, the mean decision time for the five requests was 0.6 days (range: 0–2) (Table 2). The mean delivery time for the three approved requests (#1, #3 and #4) was 11.0 days (range: 8–14). This resulted in a mean ICG process time, from receipt of requests to arrival of vaccines in requesting countries, of 17.0 days (range: 14–19) for approved requests. Mean time to campaign start in-country was only available for two of the approved requests (#1 and #4, missing information for #3), and this was six and seven days respectively (mean: 6.5 days). By comparison, in 2017, there were four requests of which all were approved. Mean time to decision on approval was 0.3 days (range: 0–1), mean delivery time was 11.0 days (range: 8–14) and mean ICG process time, from initial submission of requests to arrival of vaccines in country, was 11.3 days (range: 8–14).

Table 2. Summary of ICG performance indicators for emergency yellow fever vaccine requests, 2018

Number of requests	Number additional information requested (%)	Number approved (%)	Mean days decision time (range)	Mean days delivery time (range)*	Mean days ICG process (range)**
5	5 (100%)	3 (60%)	0.6 (0–2)	11.0 (8–14)	17.0 (14–19)

*approved requests; **approved requests.

The ICG currently has three key performance targets: requests are circulated to ICG members within one working day; the ICG decision-making body reaches a decision on approval of requests within two working days; and UNICEF-SD delivers approved vaccines to the requesting country within seven days.

Three out of the five requests (60%) in 2018 were circulated to ICG members the same day. This compares with 100% in both 2016 and 2017. Decisions were reached within two days for all five requests (100%) in 2018; as in the previous two years. The delivery time from approval to arrival of vaccines in country was below seven days for none (0%) of the three approved requests. This compares with 33% in 2016 and 0% in 2017.

Although the need for rapid emergency response to contain outbreaks is less severe than for meningitis and cholera, any factor that prolongs the period between the start of an outbreak and arrival of vaccines in the field can significantly impact the effectiveness of emergency vaccination campaigns. One such factor, which is currently not captured by the current ICG performance indicators, is the delay between the identification of first suspected cases in a country and the confirmation of the outbreak. This delay has an impact on the delay in submitting a request to the ICG. Countries are faced by ongoing challenges for surveillance including limited capacity for carrying out entomological investigations and insufficient logistics for transporting samples to laboratories which may delay submission of ICG requests. Countries may also face competing priorities, such as measles and polio control, which can strain capacity and divert surveillance resources. Requests for emergency vaccines cannot be approved by the ICG without laboratory confirmation of an outbreak, and laboratory capacity (encompassing facilities, availability of key reagents, and range of diagnostic tests offered) particularly in the AFRO Region, remains a significant bottleneck. This is especially the case for Nigeria, where the impact is pronounced given the large population, low immunity and re-emergence of YF cases. Nigeria currently does not have the capacity to independently confirm a YF outbreak. In the Republic of the Congo, several weeks elapsed between detection of the index cases and laboratory confirmation of the outbreak; significantly delaying the preparation of the emergency request (#4). The AFRO Region currently hosts a single reference laboratory (the Pasteur Institute in Dakar), resulting in delays in confirmation due to time needed for transportation of samples from national laboratories to the reference laboratory and the latter's limited capacity and large area of responsibility.

One area of discussion was the criteria for approving vaccine requests and the content of the country request form for YF. Although entomological investigations are vital for assessing underlying YF risk, particularly in urban areas, participants questioned whether submission of entomological data should no longer be mandatory for making emergency vaccine requests

(and whether alternative or proxy measures may be used). Although advantageous to obtain, participants considered that submission of entomological data need not be a necessity for determining whether emergency vaccination should go ahead once cases have been laboratory confirmed, nor a cause for delays in emergency response activities. It was agreed that the ICG Secretariat and members should review the content of the YF country request form over the coming year, including the requirement for entomological data, and ensure request forms are as clear and user-friendly as possible while including all necessary information fields.

According to UNICEF-SD, another major constraint on timeliness of delivery is the need to secure approval for importation of vaccines from national customs authorities.

The ICG and UNICEF-SD agreed to establish a working group on delivery lead times and to identify and evaluate bottlenecks in the procurement and delivery process. Its work will focus on reducing the potential delays related to unregistered products with priority countries, encouraging proactive or pre-emptive waivers for import and reducing the time taken for customs to give the green light. It was highlighted that manufacturers can play a role in reducing delays in vaccine delivery by sharing information on their product registrations and the progress of applications for product registration.

Although UNICEF-SD highlighted that the seven-day delivery target may not be realistic for all requests due to limited transport connections and infrastructure, participants agreed that seven days is both an achievable and appropriate target in the majority of cases, and that performance targets should be driven by the need to achieve timely vaccine delivery to contain outbreaks rather than by constraints or available logistics capacity.

The ICG and partners have identified that there is scope for improvements in provision of information and guidance for personnel at the country level, both on preparation of emergency vaccine requests and implementing emergency campaigns once vaccines have arrived. Gaps in campaign planning, particularly at the micro level, have also been recognised. Participants agreed that the ICG Secretariat should consider sending representatives to attend in-country Expanded Program on Immunization (EPI) manager meetings to provide guidance on submitting vaccine requests, and increase its efforts to gather more information on campaign implementation on the ground and vaccine use to identify lessons learned.

4. Vaccine supply, procurement, forecasting and deployment

During the 2018 annual meeting, the ICG members and partners reaffirmed their commitment to maintaining a stockpile of 6 million YF vaccine doses. Although the ICG YF emergency stockpile was exhausted and replenished a total of six times in 2016, no stockouts were reported in 2017 and 2018. The ICG's YF vaccine partners (WHO, UNICEF and UNICEF-SD) have consistently been able to maintain the stockpile at the required level. This was achieved through global efforts with measures including scaling back vaccine orders destined for Expanded Program on Immunization EPI programmes, delaying scheduled preventive campaigns and securing commitments from manufacturers to increase vaccine output. All of this was possible due to effective implementation of ICG procedures and strong collaboration with vaccine manufacturers. The availability of 6 million YF vaccine doses for the emergency stockpile not only facilitates rapid emergency vaccine response to contain outbreaks, but can also limit disruption of routine and preventive mass immunization when outbreaks occur.

Vaccine procurement and deployment

UNICEF-SD has supply agreements in place for 2018–2020 with all four manufacturers to maintain the emergency stockpile at 6 million doses. In addition to doses contracted to replenish the stockpile, it is projected that 39 million doses will have been supplied to UNICEF-SD for preventive campaigns by the end of 2018. Four manufacturers with WHO prequalified products currently supply vaccines for the ICG stockpile. Availability has increased over the past four years thanks to growing production capacity at all four vaccine suppliers. It was noted that there is also scope to increase availability to UNICEF-SD beyond the supplies already contracted for 2019 and 2020.

UNICEF-SD manages doses held in the ICG stockpile on a "first-in, first-out" basis. As doses near expiry they can be redirected to mass preventive campaigns supported by the EYE Strategy. Demand for YF vaccines over the coming years will be driven both by the need for new doses to replenish the ICG stockpile, but also to supply ongoing and future mass preventive campaigns—particularly in high-risk countries such as Nigeria and the DRC. UNICEF-SD will work closely with the EYE Programme Management Group (PMG) on improving the process of contracting for vaccines.

Currently, YF vaccines supplied for use in the ICG stockpile come in five-, 10- and 20-dose presentations. Although countries may also have preferences on vaccine presentations for mass preventive campaigns, they are likely to accept whichever are available during an outbreak emergency. Different presentations may be associated with tradeoffs; some of which may pose issues for certain receiving countries. Although use of presentations with fewer doses may result in lower wastage, these may be less suitable for emergency campaigns as they require more packing materials, space for storage and transport, and cold chain capacity per dose. Participants agreed that the presentation of the YF vaccines included in the stockpile should be reviewed by the ICG Secretariat in the coming year.

Challenges for vaccine deployment were also identified. Limited facilities for cold storage at transit airports have also been cited as an issue. In Nigeria, lack of capacity for aircraft refueling at regional airports closer to outbreak sites necessitates that aircraft must carry sufficient fuel for their return flight. Stockpiled vaccines are held by manufacturers and dispatched to sites of YF outbreaks. This may entail that vaccines must travel long distances, for example when manufacturers' production facilities are based in Europe.

Vaccine supply and the Gavi Roadmap

In previous years, global vaccine supply had been insufficient to meet demand, and reasons cited included low investment in production capacity, the lack of a concerted effort at market shaping, and poor visibility of vaccine demand. Furthermore, three of four manufacturers experienced production issues or had products retested for prequalification from 2010–2014. Thanks to investments by manufacturers and concerted market-shaping efforts by Gavi, global YF vaccine output has increased from 50 million doses annually in 2008 to around 140 million in 2016–2018. According to the global supply and demand predictions by Gavi, it is expected that global YF vaccine demand will remain within the upper and lower global supply estimates over the period 2019–2024. There are also countries who would like to implement their preventive mass vaccination campaigns earlier, but have been informed that they must wait or reduce the scale of their campaigns due to global supply constraints. Going forward, although global supply is set to increase and will likely meet the vaccine demand scenario set out in the Gavi Yellow Fever Vaccine Roadmap 2017, there is still the potential for stockouts and disruption of routine campaigns if the world is faced with outbreaks in multiple countries or a single large-scale outbreak. Total global YF vaccine supply is expected to increase from 75 million doses in 2015 to approximately 150 million in 2020 and 175 million in 2025. Should this be achieved, there is the potential for 1.2–1.5 billion people to receive vaccinations over the next decade including 0.9–1.1 billion in Africa. Long-term commitment and continuing investment from vaccine manufacturers will be key to making these projections a reality.

Gavi also reported on the progress towards meeting its supply and procurement objectives set out in its 2017 Yellow Fever Vaccine Roadmap. **These objectives were:**

- Manufacturers are to increase their supply offer to UNICEF-SD to over 80 million doses by 2018 and to over 105 million doses in 2021, and to over 440 million doses for the period 2017–2021.

- During the 2017–2021 period, no manufacturer experiences a disruption of more than 15% per year on its expected supply output, and no vaccine is suspended from prequalification.

- The UNICEF-SD weighted average price in 2020 is ≤ the target value (confidential).

- The overall YF vaccination wastage rate is well understood and less than 25% by 2020 (≤40% routine, ≤10% campaigns), without reducing coverage.

The first target of increasing available vaccine supply is on track to being achieved, and, based on current trends, annual supply offer to UNICEF-SD is expected to increase in the coming years and exceed 105 million doses by 2021. The second and third targets of have now been met. Further progress is still needed towards the target of reducing vaccine wastage, however.

Manufacturer updates

Four manufacturers, Bio-Manguinhos (Brazil), Sanofi Pasteur (Belgium), Chumakov (Russia) and the Pasteur Institute in Dakar (Senegal), currently supply vaccines to UNICEF-SD for use in the ICG YF stockpile.

Bio-Manguinhos produces YF vaccines in both five- and 10-dose presentations. Production fell in 2018 compared with 2017 due to increased demand for MMR vaccine and the company's practice of sharing production lines between different vaccines. The company is optimizing its production processes and investing in increased production capacity not only for bulk product, but also labels and packaging. YF vaccine output is expected to increase in 2019, and will total 10% more than in 2017. The majority of YF vaccine output over the next two years will be deployed in Brazil, and restrictions on exports continue as mass preventive YF campaigns continue in the country. Bio-Manguinhos is developing a proposal for a new campus including production facilities. The company is seeking investment partners for the USD 9 million project, which is expected to be completed in 2021. It is also pursuing other avenues for increasing available vaccine supply, and is advocating for legislative action from the Brazilian government to allow scientific institutes receiving public funding to manufacture vaccines for commercialization. Bio-Manguinhos plans to submit the results of a study on the potential extension of its YF vaccine's shelf life from 12 month to 24 months in December 2018. A two-dose presentation is also under development, and Bio-Manguinhos plans to submit an application for approval to Brazil's national regulatory authority by the end of 2019. These product improvements have the potential to give UNICEF-SD greater flexibility in managing the ICG stockpile and to reduce vaccine waste after delivery.

Chumakov, which achieved WHO prequalification for its YF vaccine in 2008, produces for export only. Its output has doubled since 2015, with around half of this increase occurring since 2017. Although not exclusively designated for YF vaccine production, the company is renovating its primary manufacturing campus with support from the Russian government. The project, which is expected to be completed in 2026, will occur in four stages and involve the construction of warehouses, laboratories, education and research facilities, and three new buildings housing production lines. The company is flexible in scaling up production quickly, if required, by adding additional shifts and running production lines on Saturdays.

The Pasteur Institute in Dakar has recently secured a grant of USD 1.7 million from the Bill and Melinda Gates Foundation to facilitate a significant facility upgrade. This will include replacement of critical equipment and improvements to the facility's power supply and the production process including measures to increase automation. Together, these upgrades will result in a 20% increase in production capacity by 2021 with a further expected increase by 2023.

Sanofi has been proactive in expanding production capacity, and its ongoing investment programme, which commenced in 2013, is on track and near completion. The company's capacity to produce bulk product has doubled since 2016 following the major outbreaks in Angola and DRC. Further investments are expected to result in increases in total capacity of 5% from 2018 to 2019, and another 5% from 2019 to 2020. Sanofi is also committed to increasing the number of countries in which its products are registered.

Manufacturers were in agreement on the utility of more regular and routine communication with UNICEF-SD and the EYE PMG, and the proposal to hold quarterly conference calls was raised at the EYE Strategy Partners Meeting in Dakar the previous week. They also highlighted the need for reliable, longer-term vaccine demand forecasting, and for information on preferred

presentation to be provided in advance to inform future production schedules and plans for expanding production capacity.

Manufacturers' progress to date on product registration in a wider range of high-risk countries has been relatively slow overall, as they do not know where the next significant YF outbreak will occur. They highlighted that forecasts should reflect "credible demand" based not only on need, but also countries' ability to implement preventive campaigns and roll out routine immunization, in order to give a more accurate reflection of the number of doses which will be both procured and deployed. Although there is the possibility of new manufacturers entering the market, this does not seem likely in the near future. Although companies in China may possess the necessary technology and expertise, none have as yet expressed an interest in supplying vaccines to UNICEF-SD or pursuing WHO Prequalification for their products.

EYE Strategy Update

EYE is a comprehensive global strategy developed by WHO and partners to build a global coalition that will tackle by 2026 the increased risk of YF epidemics in a coordinated manner.

The EYE has three Strategic Objectives:

- Protect at-risk populations
    - Preventive mass vaccination campaigns
    - Vaccinate every child
    - Risk analysis to allocate resources

- Protect at-risk populations
    - Protect high-risk workers
    - Apply the international health regulations
    - Build resilient urban centres

- Contain outbreaks rapidly
    - Strengthen surveillance and laboratory capacity
    - Ensure availability of emergency vaccine stockpiles
    - Immediate outbreak response.

During the previous ICG annual meeting, participants identified the need to improve coordination and communication between the EYE governance structures and ICG. The ICG's efforts are critical for achieving the EYE's third objective of outbreak containment, and the EYE has the potential to improve timeliness of vaccine delivery and effectiveness of emergency vaccine campaigns in a number of key areas.

Issues at the country level include lack of resources for gathering information of sufficient granularity for assessing YF risk and identifying clusters of cases. By supporting in-country surveillance capacity building and the strengthening of national and regional laboratory networks, particularly in the AFRO Region, outbreaks can be detected earlier and confirmed faster.

In addition, the EYE Strategy is finalizing its new Country Guidance Toolkit as part of efforts to address the sub-optimal provision of information and guidance for personnel at the country level.

Its objectives are:

- To provide “ready-to-use” practical guidance to personnel involved in planning, coordinating and implementing YF campaigns at the country level

- To promote awareness of sources of support for YF prevention and outbreak response

- To highlight examples of best practice in campaign planning, preparedness, implementation and monitoring.

Important topics covered by the Toolkit include YF surveillance; investigation; procedures for making emergency vaccine requests to the ICG; and guidance on implementing response activities, including reactive vaccination, once an outbreak has occurred including logistics. Country-level representatives gave comments on the Toolkit’s clarity, suitability for their needs and possible areas for improvement following the EYE Strategy Partners Meeting. ICG meeting participants were also invited to give their comments and input on the Toolkit by the end of October 2018. The Toolkit is expected to be published in early 2019.

The EYE Strategy is currently on track to meet its targets. The EYE Strategy’s four working groups are to set out their milestones for the next 6–12 months. The EYE and partners will continue to support the implementation of ongoing mass vaccination campaigns in the fourth quarter of 2018 in Nigeria, Ghana and Sudan to reach over 35 million people by the end of 2018. Six preventive mass vaccination campaigns are expected to have been completed in Nigeria, the DRC, Uganda, South Sudan, Ethiopia and the Republic of the Congo by the end of 2020, targeting over 80 million people. Together, these campaigns will drive YF vaccine demand over the next two years. The EYE and partners will also continue their progress towards establishing a network of three regional reference laboratories in the AFRO Region, (Institut Pasteur Dakar was the only laboratory approved at the time of meeting and the Uganda Virus Research Institute has been added as of early October 2018) and are supporting an application to Gavi for funding for enhancing laboratory capacity in the Region. Importantly, the EYE Strategy will leverage its critical mass of expertise to support countries in expanding preventive and routine immunization while stepping up engagement with individual countries to secure political commitment, promote country ownership of vaccination campaigns and push for comprehensive health system strengthening.

5. Evaluation of the ICG

In 2016 the ICG commissioned an independent external evaluation of its activities by the consultancy Hera. The results of the evaluation were presented to the ICG Secretariat in October 2017 at a high-level meeting on the evaluation of the ICG. Specific recommendations included the need for a clear definition of roles and responsibilities among key actors in the ICG; to more formally involve UNICEF-SD during the decision-making process to ensure the decisions take the context of the global stockpile situation and production capacity better into account; and to share a more standard response with the countries on how the criteria were applied during decision-making on whether to approve requests for emergency vaccines. In addition, the evaluation report highlighted both how the ICG's links with the EYE Strategy and the Global Task Force on Cholera Control (GTFCC) are complementary at the programmatic level, and the need to enhance coordination between the ICG and these disease control initiatives. For example, rapid detection and response for YF outbreaks is a key pillar of the EYE Strategy (Strategic Objective 3: contain outbreaks rapidly). Importantly, the evaluation proposed that the role and responsibilities of requesting countries' governments should also be formalized with regards to the promptness of request submissions following confirmation of cases, resolving issues around licensing and customs, and ensuring effective implementation of vaccination campaigns with adequate reporting. In terms of the ICG's governance, the evaluation proposed the formation of a new body for managerial oversight, consisting of senior staff from stakeholder organizations.

The ICG Governance and Oversight Committee

An action plan for implementation of improvements to the ICG process was drawn up following the high-level meeting on the evaluation of the ICG in October 2017, and called for changes in three key areas.

In response to the recommendations of the external evaluation to improve its **governance**, the ICG launched the Governance and Oversight Committee in February 2018. Its objectives, set out in its terms of reference, are:

- To provide strategic direction to the ICG mechanism to review performance of the process against agreed performance indicators.
- To ensure alignment of the mechanism with ICG's founding principles, such that the mechanism provides vaccines in a timely manner based on technical needs assessment and according to principles of equitable access.
- To advise on linkages between activities and decisions in other disease control initiatives for YF, cholera and meningitis.

Committee members will not be directly involved in the work of the ICG mechanism and will comprise senior staff drawn from the WHO, IFRC, MSF, UNICEF and Gavi. Its functions are set out in its terms of reference, which also set out specific guidelines for its areas of competence, composition, and decision-making process.

In terms of the ICG's **mechanisms and processes**, the action plan called for the ICG Secretariat to attend biweekly meetings of the EYE Secretariat and GTFCC Secretariat to enhance complementarity of the ICG's activities with these initiatives, and for the ICG Secretariat to attend meetings with manufacturers together alongside UNICEF-SD and Gavi.

To improve **communication and transparency**, the ICG Secretariat will continue to give regular updates on vaccine availability, the size of the stockpile versus doses contracted, and the outcomes of requests for emergency vaccines. Going forward, the ICG will disseminate information through the following channels:

- Online ICG dashboard
- ICG decision summaries
- Regular conference calls between the ICG Secretariat and UNICEF-SD
- ICG annual meeting reports
- Annual reporting of ICG performance indicators
- Publications and conference presentations.

To date, the committee has published its performance outcomes for 2016 and 2017, and will continue to do so on an annual basis with the addition of new indicators.

The ICG Accountability Framework

The activities of the Governance and Oversight Committee will be guided by the ICG Mechanism Accountability Framework, which sets out the actions and responsibilities of the ICG and each partner, including individual country governments, at each stage of the ICG process. These encompass request preparation, decision and review, vaccine procurement, campaign cost review, communication on request status, vaccine deployment, vaccine delivery, campaign implementation, monitoring and evaluation of campaigns, campaign funding, payment and reimbursement for Gavi eligible and non-eligible countries, financial reporting, vaccine supply and demand forecasting, vaccine market shaping, and communication and coordination with WHO disease control programmes.

The Accountability Framework includes a Monitoring and Evaluation Framework, setting out expected results and performance indicators for each stage of the ICG process, along with associated targets and frequencies of reporting for each. Importantly, performance indicators are assigned to a specific organization or ICG partner to which they will be accountable going forward. The ICG Secretariat will report on each indicator on an annual basis. A draft of the accountability framework was circulated among members for written feedback, and the three days of ICG meetings provided an opportunity for participants to give their final input and comments.

Specific to YF, time between detection of suspected cases and outbreak confirmation, and time required to provide additional information, are of particular importance both for improving timeliness of emergency vaccine response and an area of responsibility for individual countries.

Finally, going forward, the ICG will hold biannual meetings with partners to review the progress of the implementation of the evaluation report's recommendations. The ICG will also continue to examine its future role, and whether there is scope for the mechanism to encompass new vaccine stockpiles (for example, Ebola).

6. Discussion

Although it is not possible to eradicate YF, the risk of epidemics can be effectively controlled using YF vaccine, which, unlike the oral cholera vaccine, provides long-term immunity following a single dose. Market shaping activities, informed by robust assessments of YF risk and reliable demand forecasting, hold promise for improving visibility of YF vaccine demand and driving further increases in output. This will both ensure the necessary supplies are available in the event of a major outbreak, and allow for the expansion of mass preventive campaigns and routine immunization. While global YF vaccine output has increased substantially in recent years to the point where it is approximately sufficient to meet global demand, the ICG, the EYE Strategy and partners require confidence in reliability of supply. This positive trend in vaccine availability can only be sustained through commitment and investments from manufacturers.

Although the scope of mass preventive campaigns and routine immunization is set to expand over the next eight years under the EYE Strategy, the ICG YF stockpile, which is to remain at its current size of 6 million doses, will continue to play a crucial role in achieving the Strategy's objective of outbreak containment. Areas of complementarity with the EYE Strategy were also highlighted. Not only can stockpiled doses be redirected to preventive campaigns as they near expiry, but the Strategy has encouraged significant improvements in surveillance and laboratory capacity in the AFRO Region which are expected to materialize in the coming years. Both the ICG and EYE Secretariats have observed the need for improving information and guidance for countries in submitting vaccine requests and implementing reactive campaigns. While the EYE Country Guidance Toolkit is expected to be published in early 2019, the ICG Secretariat is to consider attending in-country meetings to provide guidance on submitting vaccine requests.

A number of bottlenecks which can delay delivery of emergency vaccines were noted, including cold chain and logistics capacity, surveillance and laboratory confirmation capacity, product registration and customs clearance. The ICG and UNICEF-SD agreed to set up a working group to address these issues. Participants also agreed on the need to ensure the ICG request process is as streamlined and user-friendly as possible, and discussed whether, going forward, submission of entomological data should no longer be mandatory for making emergency vaccine requests.

Finally, the ICG has established its new Governance and Oversight committee and is moving forward with the implementation of the Accountability Framework. These developments will improve the transparency of the ICG mechanism and ensure the ICG and partners' roles (including that of requesting countries) are clearly defined and that they are accountable for meeting their respective responsibilities.

7. Action points

Several common themes and issues were raised over the three consecutive days of ICG meetings. Common action points identified from all three meetings included:

- The ICG and UNICEF-SD are to set up a working group on delivery lead times and to identify and evaluate bottlenecks in the procurement and delivery process.

- Among these, this group will examine delays related to product registration, delays in providing waivers and time it takes for customs to give the green light.

- If possible the ICG indicators will include time from index case confirmation by regional reference laboratory to submission of emergency vaccine request, and time from declaration of outbreaks to submission of emergency vaccine requests and time required for laboratory confirmation of cases as performance indicators in future years. The ICG Secretariat will report on this indicator annually going forward.

In addition, the ICG for Yellow Fever also identified the following actions specific to the YF stockpile:

- The YF vaccine stockpile is to be maintained at its current size of six million doses at all times.

- UNICEF Supply Division is to work with the EYE PMG on improving the process of contracting for vaccines.

- The presentation of the YF vaccines included in the stockpile is to be reviewed by the ICG Secretariat and UNICEF-SD.

- The ICG country request forms are to be reviewed. Specifically, in relation to YF, the ICG Secretariat is to consider whether submission of entomological data should no longer be mandatory for making emergency vaccine requests (and whether alternative/proxy measures may be used).

- ICG Secretariat is to consider attending in-country EPI manager meetings in collaboration with EYE Secretariat to provide guidance on submitting vaccine requests.

- The ICG is to gather more information on campaign implementation on the ground and vaccine use to identify lessons learned.

- The ICG Secretariat and member agencies will provide letters of support to the Bio Manguinhos addressed to the Ministry of Health of Brazil to help resolve the ongoing issues surrounding exportation of YF vaccines.

All participants agreed on the action points by consensus and expressed their commitment to moving forward with their implementation over the coming year.

Annex 1: Meeting agenda

20 September 2018, Salle C

DRAFT AGENDA

Objectives:

1. Review epidemiological situation in 2017 and 2018 (including ICG requests), discuss lessons learned and propose recommendations for improvement
2. Review the emergency stockpile for 2019 and beyond (size and speed of replenishment)
3. Review the articulation of EYE-ICG secretariats and governance

Time	Topic	Presenter
9h00 – 10h30	Arrival and welcome of participants	
	Opening Remarks	WHO, ICG Secretariat
	Yellow fever epidemiological situation in 2017-2018 (Brazil and Nigeria)	WHO HQ, AFRO and PAHO
	Vaccine shipments, 2017-18 ICG performance – review of key indicators Revised ICG form	UNICEFSD ICG Secretariat All participants
10h30 – 10h45	Coffee break	
10h45- 11h45	Update on EYE strategy and anticipated needs for the coming years Coordination between EYE and ICG secretariats	WHO
11h45 – 12h30	Stockpile management (availability, volumes, timings) Reserve for emergencies/ICG versus global stock Discussion on lessons learned Stockpile 2019-21: tender update and availability timeline	UNICEF-SD
12h30 – 13h30	Lunch break	
13h30 – 14h30	Gavi roadmap and market shaping – update	Gavi
14h30 – 15h30	Manufacturers production forecast	Vaccine manufacturers
15h30 – 15h45	Coffee break	

15h45 – 16h15	Implementation of ICG evaluation recommendation	All participants
16h15 – 17h00	Discussion and wrap up	All participants

Annex 2. List of participants

International Coordination Group (ICG) on Vaccine Provision for Yellow Fever
Annual Meeting
WHO Headquarters, 20 September 2018

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* excused