Global Strategy to Eliminate Yellow fever Epidemics (EYE)

Document for SAGE – 26 September 2016

Executive summary

The global health community is facing an increased risk of urban outbreaks of yellow fever. Yellow fever's changing epidemiology, a resurgence of mosquitoes and the risk of international spread pose an emerging global threat that requires new strategic thinking.

This document describes the reasoning behind and need for an updated, long-term (2017-2026) and global (Africa and Americas) strategy to "Eliminate Yellow fever Epidemics" (EYE). It includes **three strategic objectives**: (1) protect at-risk populations; (2) prevent international spread; and (3) contain outbreaks rapidly. The strategic approach is comprehensive. In addition to recommending vaccination activities, it calls for building resilient urban centres, planning for urban readiness, and strengthening the application of International Health Regulations

The EYE strategy targets the countries and regions that are considered most vulnerable to outbreaks of yellow fever. The classification of countries' risk has been revised to take into account criteria associated with the changing epidemiology such as environmental factors, population density and vector prevalence.

In all, 27 countries in Africa and 13 in the Americas are considered to be at highest risk and need large-scale, preventive vaccination strategies to establish and maintain high levels of immunity among their populations. In Africa, 5 countries still need to introduce the vaccine into their routine immunization schedules and 12 countries should conduct national mass preventive campaigns. All countries in the Americas have introduced the vaccine into routine vaccination programmes, but 11 of the countries should plan to carry out catch-up campaigns to boost levels of immunity among unprotected pockets among their populations.

Rapid containment of outbreaks is essential to ensure they do not amplify into devastating epidemics. To enhance early detection of cases, surveillance needs to be strengthened. That will require improving laboratory capacity, building on existing surveillance networks and extending the currently limited laboratory diagnostic in-country options.

A revolving mechanism will be put in place to give countries facing emergency needs for yellow fever vaccine access to the internationally managed stockpile. The proposed initial quantity to be held in reserve has been set at 6 million doses and will need to be closely managed in collaboration with vaccine manufacturers. Any outbreak response will include not only reactive vaccination programs, but rapid detection of cases, good case management, vector control and community mobilization -- all elements that need to be strengthened.

Over the coming decade, vaccine manufacturers are expected to be able to meet the global demand of 1.38 billion doses needed to end YF outbreaks. This will require pushing their production to the maximum possible levels, particularly in the first 5 years.

Vaccine needs for the Global Strategy to Eliminate Yellow fever Epidemics, 2017–2026

Routine immunization	Million doses
Africa	465
Latin American and the Caribbean	96
Mass campaigns	
Africa	490
Latin American and the Caribbean	39
Brazil	234
Emergencies	60
Total	**1384**

Cross-cutting core support activities will be initiated from the start of EYE to ensure success through (1) availability of accessible, affordable vaccines procured in a sustained vaccine market, and mechanisms to cope with surges in YF vaccine demand; (2) political commitment at regional and country levels fostered by strong advocacy; (3) robust governance and strong monitoring; and (4) research to support better tools and informed practices.

The EYE strategy will succeed by engaging multidisciplinary partners and coordinating efforts well. But it will require the collaboration of a number of agencies. No country or institution can address this global issue alone.

Acronyms and definitions

ELISA	Enzyme-Linked Immunosorbent Assay
EPI	Expanded Programme on Immunization
FNV	French Neurotropic Vaccine
Gavi	Gavi, the vaccine Alliance
ICG	International Coordinating Group for vaccine provision
IHR	International Health Regulations (2005)
LAC	Latin America and the Caribbean
PCR	Polymerase Chain Reaction
PI	Population Immunity
PMVC	Preventive Mass Vaccination Campaign
PRNT	Plaque Reduction Neutralization Test
RI	Routine Immunization
SAGE	Strategic Advisory Group of Experts on Immunization
TAG	Technical Advisory Group
UNICEF	United Nations Children's Fund
UNPD	United Nation Population Division
VIS	Vaccine Investment Strategy
WHO	World Health Organization
WUENIC	WHO/UNICEF Estimates of National Immunization Coverage
YF	Yellow Fever
YFI	Yellow Fever Initiative

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Part 1: Introduction and context

In 2016, two linked urban yellow fever (YF) outbreaks – in Luanda (Angola) and Kinshasa (Democratic Republic of the Congo; DRC), with wider international exportation from Angola to other countries, including China – have shown that YF poses a serious global threat requiring new strategic thinking.

The world has largely forgotten the threat posed by YF, but little more than a century ago it was a source of terror, decimating the populations of cities, destroying economies and driving political choices. Extensive, repeated epidemics in North American and European port cities during the 18th and 19th centuries spread panic, shutting down the cities and killing hundreds of thousands of people, not just from the disease but also from its economic and other impacts, such as starvation. An estimated 150 000 people died during epidemics in the United States alone, with the then capital Philadelphia losing 10% of its population in the 1793 outbreak, during which the American President, George Washington, fled the city with his government.

The major leaps in biomedical research at the end of the 19th century led to identification of mosquitoes as the source of YF transmission and experiments to identify the infective agent. With the newly opened Panama Canal markedly increasing population movements through YF endemic territory, the Rockefeller Foundation's International Health Commission decided to set up teams to investigate YF eradication, first in South America, then later in Africa. This led to isolation of the YF virus strain in 1927, which in turn led to development of two vaccines, one grown in mouse brain (the "French neurotropic vaccine"; FNV) and later, by the Rockefeller team, the live attenuated 17D vaccine – a version of the safe, highly efficient vaccine still used today, requiring only one shot to confer lifelong immunity and excellent cost–benefit ratios.

The French neurotropic YF vaccine was a good mass campaign vaccine because it was administered by scarification, permitting vaccination of up to 800 people per hour, or about 5000 per day. By 1953, 56 million Africans had been vaccinated. This led to a dramatic drop in cases in the francophone countries of Africa where vaccination was performed, whereas the disease remained epidemic in neighbouring anglophone countries that did not practice vaccination, providing evidence that an effective vaccination strategy can achieve elimination of epidemics. However, the FNV caused some severe neurological adverse effects, which led to discontinuation of its use (production ceased in 1983), including its use in mass campaigns in Africa.

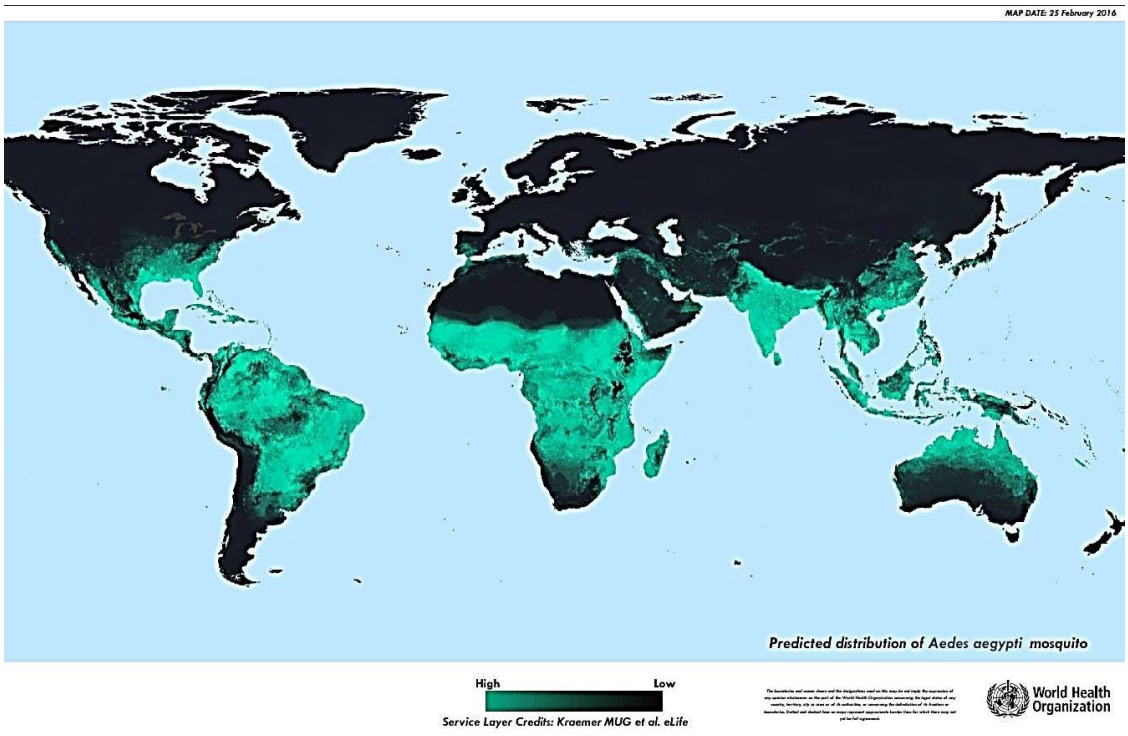
In the early 2000s, an increase in outbreaks in West Africa, with clusters of cases reported in urban settings, led to the launch of the YF Initiative, supported by Gavi, to reduce the risk of urban epidemics. This three-pronged strategy, which began in 2005, included the introduction of the YF vaccine into routine child immunization programmes in endemic countries, mass preventive campaigns in at-risk areas, and the setting up of a global vaccine stockpile to permit rapid emergency mass campaigns in response to outbreaks. This led to vaccination of 114 million people and has prevented epidemics in West Africa since 2010. However, reduction of risk in West Africa did not alter risk in central and eastern African countries, where most recent outbreaks have occurred. A modelling study based on African data sources estimated that the burden of YF during 2013 was 84 000–170 000 severe cases and 29 000–60 000 deaths (Garske T. et al. Yellow fever in

Africa: Estimating the burden of disease and impact of mass vaccination from outbreak and serological data. PLoS Med. 2014;11(5):e1001638).

Changes in outbreak drivers – urbanization and peri-urbanization, ease and speed of population movements, changes in work (e.g. mining and construction), with large numbers of workers being recruited internationally (e.g. Chinese workers in Angola) – have led to large urban outbreaks with international spread. Ebola has already demonstrated graphically what happens when a pathogen – even one not very transmissible – gets into a crowded, mobile, urban population. The West African Ebola outbreak of 2014–2015 began in a remote area but when it arrived in urban areas it spread explosively and was transported internationally.

These are just warnings of much bigger outbreaks to come – including the potential for Asian outbreaks in countries such as India and China, which harbour Aedes mosquitoes and are home to 2 billion people who are immunologically naïve for YF (Figure 1).

Figure 1. Probability of occurrence of the *Aedes aegypti* mosquito under current environmental and land cover conditions



Lessons learnt from recent YF control programmes

Following the early success of the YF investment case, the Gavi Board endorsed additional support for African countries at medium risk of YF outbreaks in December 2013, using a vaccine investment strategy (VIS) process. This was intended to complement mass preventive campaigns and routine

immunization. However, countries have been slow to apply to Gavi for support. Furthermore, in many countries vaccine coverage has stagnated.

Routine immunization: obstacles to progress

Vaccine supplies: A major block to progress has been the limited vaccine supply. Between 2013 and 2015, 15 countries among the 34 that introduced the YF vaccine into their routine immunization programmes reported a YF vaccine stock-out at national level, with consequences for national coverage. The problem is chronic (Table 1).

Table 1. YF vaccine stock-outs in Africa and in Latin America and the Caribbean, 2013–2015

	Number of countries reporting a YF vaccine stock-out at national level	
	Africa	Latin America and the Caribbean
2013	5	4
2014	7	0
2015	6	3

In Latin America and the Caribbean (LAC), all 13 countries considered at risk for yellow fever have routine YF immunization for children aged one year. Vaccine coverage is around 70%. This coverage has been negatively affected by the current global vaccine shortage. Countries receive around 50% of their estimated vaccine requirements (XXIV Meeting of the Technical Advisory Group on Vaccine-preventable Diseases, 13 May 2016, Washington, DC, United States).

To achieve effective YF control, demand and supply must match. Efforts need to be made on both sides. Upstream, manufacturers need to continue ongoing efforts to increase overall production but at the same time, a long-term consistency of demand must be achieved and commitment on number of doses and prices must be obtained. Successive YF vaccine roadmap efforts have not provided enough security to the manufacturers to justify investment and scaling up of production.

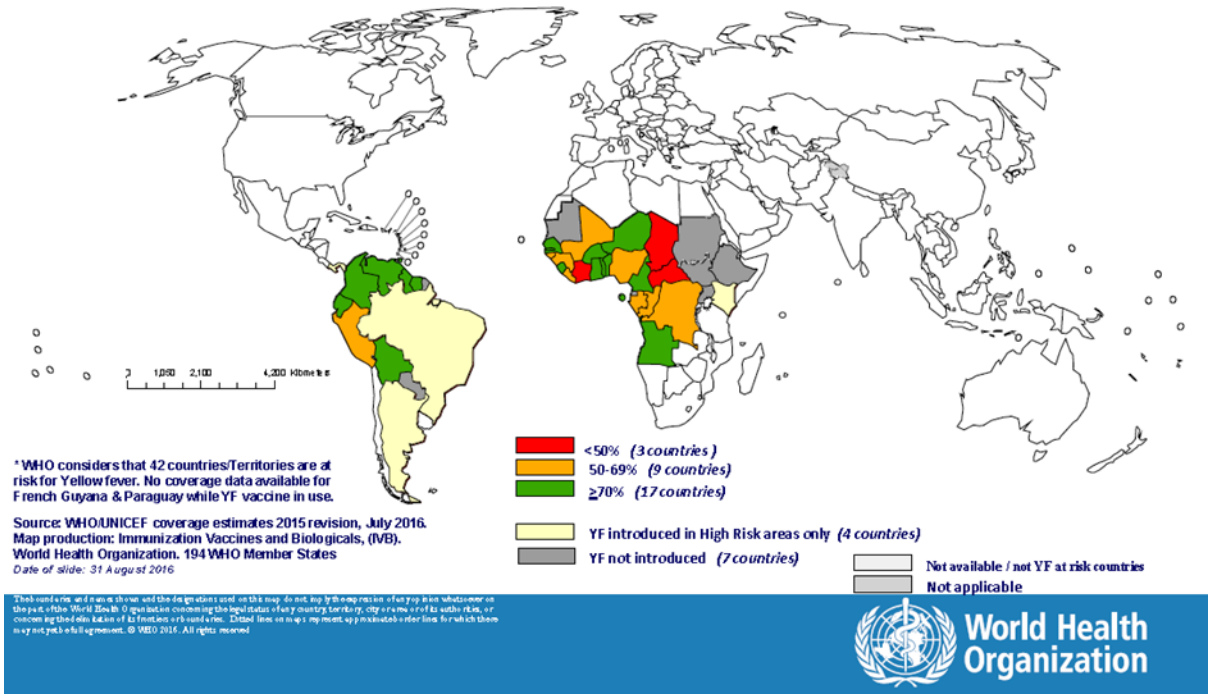
Regional and country buy-in: Due to competing vaccine introduction priorities and limited political will, no new countries have introduced the YF vaccine into their national routine immunization programmes since 2008. The level of YF risk has not been strongly communicated. The absence of a regional goal and well-communicated strategy has left countries without direction on this issue. Regional and national technical advisory groups (TAGs) have a critical role in supporting countries to introduce the yellow fever vaccine into their routine programmes.

Implementation issues: In addition to supply insecurity, reasons cited for low vaccine coverage include weak vaccine management, inadequate or overly rigid vaccination practices, such as no vaccination given after 11 months, and unwillingness to open a 10 or 20 dose vial for one child only. Vaccine supply priority is always given to outbreak response.

As a result of these obstacles, childhood immunization coverage is too low to maintain sufficient immunity (Figure 2). Specific reasons for low coverage need to be analysed, addressed and monitored. Differences between measles and YF vaccine coverage (both given at nine months in Africa) also need to be monitored and reasons better understood. In 2015, the median coverage in 22 African countries with both vaccines in national routine immunization programmes was 75% for

the first dose of measles and 70% for YF (Source: WHO/UNICEF Estimates of National Immunization Coverage; WUENIC). Countries reporting a significant difference between the two vaccines also reported a major stock-out of YF vaccine.

Figure 2. Immunization coverage with YF vaccine in infants in at-risk countries, 2015



The global emergency stockpile: Since 2004, the global emergency vaccine stockpile managed by the International Coordinating Group (ICG) for vaccine provision and funded by Gavi is at the level of 6 million doses. Until the epidemic in Angola and DRC, 6 million doses had been sufficient to control YF outbreaks in a one-year period. Only once had the 6 million doses been used (in 2008, to control an outbreak in Brazil and Paraguay). In 2016, the YF emergency stockpile has been replenished twice, bringing it up to 18 million doses. Gavi made an exceptional decision to cover the costs of stock replenishment, and therefore in 2016 the ICG stockpile financed by Gavi was 12 million doses out of the 18 million. Other contributors were the Central Emergency Response Fund, Bio-Manguinhos, the Government of Angola and the ICG revolving fund.

The rapid replenishment and increase of the stockpile has been possible thanks to excellent coordination and collaboration among vaccine manufacturers (reprioritizing their production plans) and the WHO–UNICEF working group, which has worked with affected countries to reprogram Expanded Programme on Immunization (EPI) vaccine routine shipments and thus avoid country stock-outs, while at the same time maintaining 6 million doses in the stockpile, and finally to Gavi who has provide critical financial support for these exceptional requests.

In the future, a plan will be required for rapid scale up of production if demand exceeds the vaccine stocks.

Programme governance: The longer term oversight of the YF initiative was provided to some degree by the YF partnership, made up of key public health partners around the world. The main focus of the group was to assist in the implementation of the preventive mass vaccination campaign, improve adverse event following immunization surveillance within countries conducting the campaign, and discuss YF virus disease activity and need for reactive campaigns. However, the group lack the appropriate authority and infrastructure to address some of the key deficiencies in surveillance, laboratory capacity and case management and to address countries hesitancies to engage in activities to improve their YF vaccination coverage. Although partners within the group often worked together to address gaps (e.g., development of YF risk assessment protocol), the group lacked the ability to systematic identify and address research gaps. A strong, participative governance will be key to the success of the strategy for eliminating YF epidemics.

A global problem: The control programme needs to be global, not only because the risk has gone beyond the classical risk borders but also because the supply issue needs to be addressed globally, for example by supporting Gavi-eligible countries in South America in the VIS. All countries need to be included in the global vision and provided with support, including by having access to the emergency stockpile, which should not be limited to Gavi-eligible countries only.

Current implementation of vaccination in Africa and LAC

LAC countries follow the recommendations of the regional TAG to control YF in the region, which include the introduction of the YF vaccine into national immunization programmes for children aged one year in every country with endemic areas (Table 2).

Table 2. Introduction of YF Vaccine into the routine EPI schedule in at-risk countries/territories in LAC, 2016

Country/territory	Year of introduction into routine EPI	Geographical area	WHO/UNICEF estimates of national immunization coverage, 2015
Panama	1974	Enzootic areas	60%
Trinidad and Tobago	1980	Nationwide	91%
Brazil	1994	Enzootic Areas	99%
Ecuador	2009	Nationwide	78%
Guyana	2000	Nationwide	99%
Venezuela (Bolivarian Republic of)	2000	Nationwide	85%
Peru	2001	Nationwide	67%
Paraguay	2006	Nationwide	71%
Colombia	2002	Nationwide	54%
Argentina	2008	Border with Brazil, Bolivia (Plurinational State of) and Paraguay	60%
Bolivia (Plurinational State of)	2003	Nationwide	88%
Suriname	2005	Nationwide	86%
French Guiana	NA	Nationwide	NA

Twenty-three countries in Africa have introduced the vaccine into routine immunization and 14 countries have conducted a preventive mass vaccination campaign (PMVC) since the beginning of the YF Initiative (Table 3).

Table 3. Implementation of vaccination in Africa, 2016

	Country	Year of introduction into routine EPI	PMVC year(s)	PMVC admin coverage (%)	PMVC survey coverage (%)	WHO/UNICEF estimates of national immunization coverage, 2015
1	Angola	1999	-	-	-	72%
2	Benin	2002	2009	99.8	90.6	79%
3	Burkina Faso	1987	2006	100.2	-	88%
4	Burundi	-	-	-	-	-
5	Cameroon	2004	2009, 2014	100.5, 94.0	89, NA	77%
6	Central African	2000	2010, 2011	90	94.3	45%
7	Chad	1985	-	-	-	84%
8	Congo	2004	-	-	-	80%
9	Côte d'Ivoire	1987	2011, 2012	97.5, NA	90.7, 91.0	58%
10	DRC	2004	-	-	-	88%
11	Equatorial Guinea	2016	-	-	-	-
12	Eritrea	-	-	-	-	-
13	Ethiopia	-	-	-	-	-
14	Gabon	2003	1995	-	-	68%
15	Gambia	1979	1979	-	-	97%
16	Ghana	1992	2011, 2012	98.7, 90.4	73.5, 84.0	88%
17	Guinea	2002	2010	96	89	60%
18	Guinea-Bissau	2008	-	-	-	90%
19	Kenya	2001	-	-	-	20%
20	Liberia	2001	2009	99.3	95.2	56%
21	Mali	1992	2006	98.7	83.3	84%
22	Mauritania	-	-	-	-	-
23	Niger	2005	-	-	-	89%
24	Nigeria	2004	2013	104	76.8	71%
25	Rwanda	-	-	-	-	-
26	Sao Tome and Principe	2003	-	-	-	93%
27	Senegal	1987	2007	99.3	94.2	80%
28	Sierra Leone	2002	2009	96.4, 98.4	94.3, NA	78%
29	Somalia	-	-	-	-	-
30	South Sudan	-	-	-	-	-
31	Sudan	-	2014, 2015	95, 93	NA, 92.8	-
32	Tanzania (United	-	-	-	-	-
33	Togo	1992	2007	98.4	96.8	85%
34	Uganda	-	-	-	-	-
35	Zambia					-

NA = Not available.

Part 2: Public health tools for YF prevention and control

There are several measures that are integral to a long-term strategy aimed at eliminating outbreaks of YF, including surveillance and laboratory testing, vector surveillance and control and vaccination.

1. YF disease surveillance

Sustained YF control strategies must rely on strong surveillance and diagnostic capacities to allow for early detection of outbreaks and rapid implementation of control measures that can help **mitigate the risk of spread and the use of extensive resources**. The recent Angola epidemic highlighted how limited surveillance and laboratory capacity worsen both the epidemic **burden** and spread: by delaying the detection of YF cases and clusters, the outbreak grew uncontained, reached a magnitude that required very resource-intensive containment measures and spread internationally by land and air through unimmunized travellers (workers). Strong surveillance and diagnostic capacity also enable an understanding of where the risk of YF is and to inform the allocation of appropriate resources. Surveillance informs targeting and intervention priorities by providing information on the evolving risk and the impact of preventive and control measures. On the other hand, in the case of YF, insufficient surveillance participated to the limited evidence of risk and lack of interest in controlling the disease.

Appropriate surveillance approaches for YF differ based on the level of risk of urban YF outbreaks, ranging from case- based, sentinel approaches to integrated disease surveillance and response (IDSR) approaches.

The **Integrated Disease Surveillance and Response** (IDSR) program is a population-based surveillance approach using aggregated data counts to compute the incidence of YF cases (suspected, probable and confirmed) at a given level (most often, district), with epidemic investigation and containment measures launched accordingly. In all countries, the IDSR framework can serve as foundation for YF surveillance.

In **case based surveillance**, a standard case definition is used to identify suspected cases, then individual information is collected and each case is sampled for confirmatory testing. Suspected cases are thoroughly documented at the individual level from the epidemiological (incl. vaccination status) and laboratory standpoints. The term “case” implies a focus on “case-level” information, rather than being an antonym to “population-based” surveillance. It can be conducted in a context of population-based surveillance; that is, involving a defined population with a denominator from which cases come and rates can be calculated.

A **sentinel** surveillance approach is a practical and efficient choice, limiting pressure on resources while achieving adequate capacity. The sentinel approach can be location based (i.e. district) or facility based (i.e. hospital); alternatively, it could target a specific part of the population, such as at risk groups (e.g. facilities taking care of high risk workers, or on mining sites). Sentinel surveillance uses data systematically collected in multiple high-quality sites across the country. Ideally, these sites are purposely selected to bring valuable information and answer specific epidemiological questions (e.g., YF virus circulation). The quality of sentinel surveillance is highly dependent on the selection of the sentinel sites. By nature, a sentinel approach cannot answer all the epidemiological

questions associated with YF; however, it is possible to combine different strategies to reach a satisfying level of information and meet the surveillance goals set. In particular, neither the burden of the disease nor the incidence trends of the disease at country level can be reflected. Consequently, whenever a case-based sentinel strategy is implemented, IDSR should still be applied as a basis for this approach, to ensure these information gaps are filled.

2. Vector surveillance and control

Both vector surveillance and control are components of the prevention and control of vector borne diseases, especially for transmission control in epidemic situations. For YF, vector surveillance targeting *Aedes aegypti* and other *Aedes* stegomyia species will help inform where there is a risk of an urban outbreak. By understanding the distribution of these mosquitoes within a country can allow a country to prioritize areas to strengthen their human disease surveillance and testing and consider vector control activities.

There is currently a limited public health arsenal of safe, efficient and cost-effective insecticides. This is mainly due to the resistance of major vectors to common insecticides and the withdrawal or abandonment of certain pesticides for reasons of safety or the high cost of re-registration.[1]

Sylvatic vector control is not feasible and urban vector control has proved challenging. As currently implemented, it has been unable to prevent epidemic dengue, chikungunya and Zika.

Routine vector control

Large-scale attempts to control mosquito populations and breeding sites conducted in the Americas in the 1970s were short-lived due to a combination of factors, such as diminishing awareness and political interest leading to reduced funding, dismantlement of infrastructure, and fewer vector control specialists being trained and deployed; resistance to insecticides, notably reducing the vector control arsenal; and accelerating population growth, rapid unplanned urbanization, and changes in patterns of land use, which made environments even more hospitable for flourishing *Aedes aegypti* populations.[2]

Routine vector control has limited efficiency, and options belong to the areas of long-term development (community engagement to control mosquito breeding sites) or research (genetically modified mosquitoes, requiring further field trials and risk assessment).

Epidemic vector control

The main contribution of vector control in the arsenal of public health measures to control YF epidemics in urban centres where transmission is occurring readily between mosquitoes, namely *Aedes aegypti*, and humans. Control efforts need to target both mosquito **larvae and adults.** Epidemic vector control should be implemented as quickly as possible in neighbourhoods and districts where YF cases live.

[1] http://www.who.int/whopes/questions/en/
[2] http://www.who.int/emergencies/zika-virus/articles/mosquito-control/en/

3. Vaccination against YF

There has been an effective and safe vaccine available to prevent YF since the 1930s. One dose of the vaccine provides lifelong immunity. The YF vaccine is relatively cheap, costing an average of US$ 1.07 per dose in 2016, in 5- and 10-dose presentations.[1]

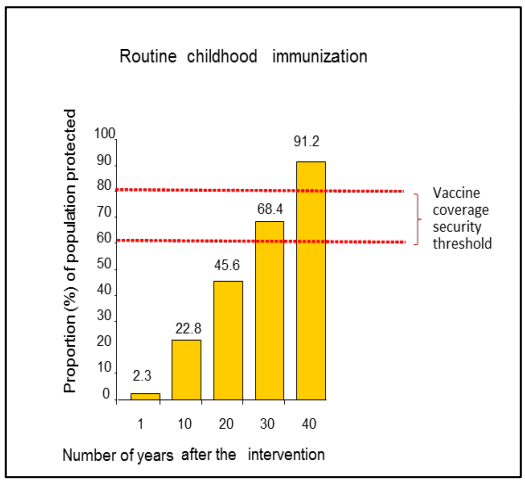
Vaccine coverages greater than 80%, with a 60-80% security threshold, are necessary to interrupt autochthonous transmission (human-mosquito-human) of YF virus within a community and ensure that sporadic unvaccinated cases do not generate secondary cases.

There are several potential ways to improve vaccination coverage in at-risk areas but each of these has potential obstacles and different costs.

3.1. Approach 1: Implementing and strengthening coverage rates of childhood YF vaccination

YF vaccine can be integrated into national routine immunization schedules and delivered through EPI in an integrated approach with other vaccines. Infant YF routine immunization is administered at nine months in Africa and 12 months in LAC, jointly with the first dose of measles-containing vaccines, at low operational costs.

Box 1: Population protected by routine childhood immunization



When well implemented by strong health systems, YF routine immunization in the EPI can provide sufficient population immunity. However, it **takes about 30 years** to build the population immunity to adequate levels to potentially stop large scale outbreaks. Once high level population immunity is established, the continued routine vaccination of new birth cohorts is a **sustainable long-term** approach to maintaining high levels of population immunity. If recently or insufficiently implemented, routine immunization alone does not represent a safe approach to controlling the risk of YF epidemics, as recently demonstrated in **Angola**.

Angola has implemented YF routine immunization since 1999. Between 2004 and 2015, WHO and UNICEF estimated that national vaccination coverages for YF ranged from 40% to 72%, with a 57%

[1] http://www.unicef.org/supply/files/Yellow_Fever.pdf

average.[1] No preventive mass campaign has been conducted. At the time of the 2016 epidemic crisis, with international spread, the average population immunity against YF was very low among the 25 million people living in the country.

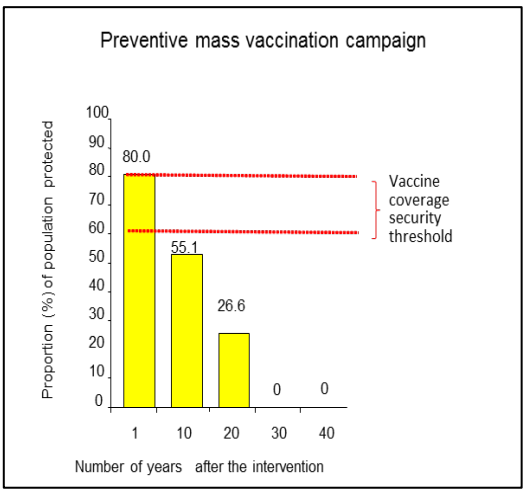
Current patterns of population movements, with frequent exchanges between sylvatic and rural areas, are such that subnational approaches to risk control might not be adequate in all countries specifically if vaccination of travellers within a country is suboptimal. In these countries, a national approach might be more appropriate in a comprehensive risk mitigation strategy

3.2. Approach 2: Conducting preventive mass vaccination campaigns

PMVCs are **the most efficient** approach to **rapidly increasing population immunity** levels in high-risk areas and controlling the risk of YF epidemics on a **short-term** basis, but the protection provided wanes rapidly, becoming inexistent after 25 to 30 years.

Preventive mass campaigns target the at-risk population older than nine months. They have low wastage rates of around 10%. These one-time transversal campaigns are associated with operational costs of approximately US$ 0.65 per dose delivered. They are fairly resource-intensive and require strong commitment at all levels (political to community) and intense coordination between partners. By actively seeking to reach everyone and attaining high vaccine coverages, preventive mass campaigns participate in strengthening **health equity**. Most countries are used to campaign implementation and usually reach high coverages (>90%; see Table 3). However logistic challenges remain, particularly regarding waste management and monitoring of adverse effects following immunization. The capacity of a system to overcome these challenges directly affects the quality of a mass campaign.

Box 2: Population protected by preventive mass campaigns



Current patterns of population movements, with frequent exchanges between sylvatic and rural areas, are such that subnational approaches to risk control do not seem reasonable and only national approaches provide comprehensive risk mitigation. The situation of Cameroon illustrates the importance of planning **nationwide** rather than subnational mass campaigns in countries

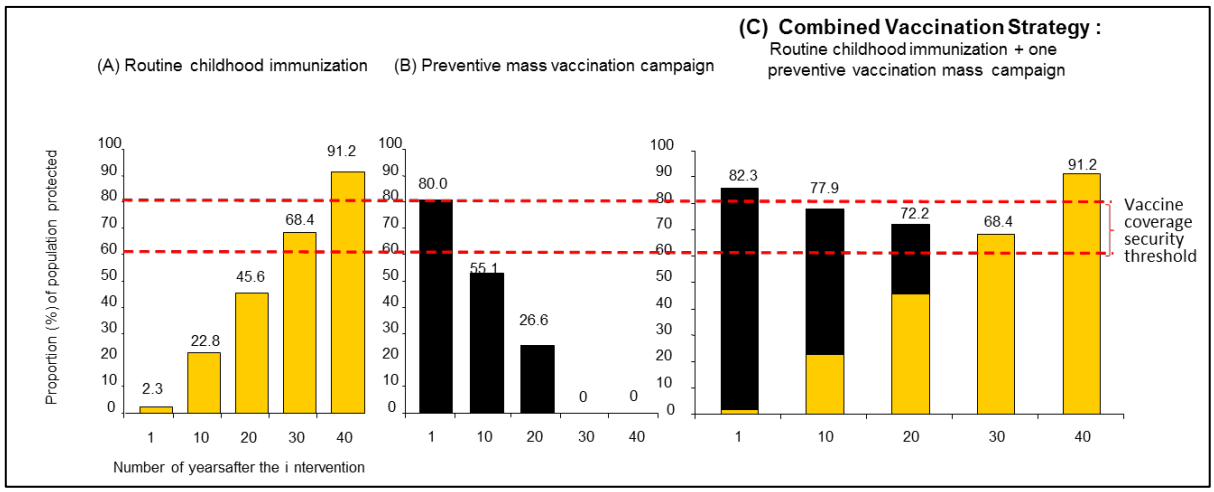
[1] http://www.who.int/immunization/monitoring_surveillance/data/ago.pdf

deemed at risk. In 2009, subnational preventive mass campaigns were mounted in a "patched approach" that protected only the districts at highest risk. In 2011, a YF outbreak hit unimmunized areas located between district "patches" where preventive mass campaigns had been conducted. The "patched approach" ultimately caused greater morbidity and required more resources and coordination to address the consequences than if a comprehensive plan had been formulated in the first place.

An optimal, sustained public health impact can be achieved when PMVCs are combined with routine immunization. **Combined vaccination strategies** are estimated to have reduced the burden of YF by more than half in countries at highest risk for YF epidemics – by up to 92% in some areas – and averted almost half a million YF cases.

Large-scale vaccination campaigns conducted in West Africa from the 1940s to the 1960s were successful by themselves in eliminating the risk of YF epidemics from the region; but in the absence of associated routine immunization or catch-up campaigns, YF epidemics resurged in the 1980s due to low vaccination coverages. Most recently, vaccination strategies combining preventive mass vaccination campaigns and routine immunization were successful at eliminating the risk of YF epidemics on a long-term basis. More than 150 million individuals were protected against YF between 2007 and 2015 in the 13 countries at highest risk for YF in Africa. No YF epidemic has been recorded in those countries.

Box 3: Population protected by combined vaccination strategy



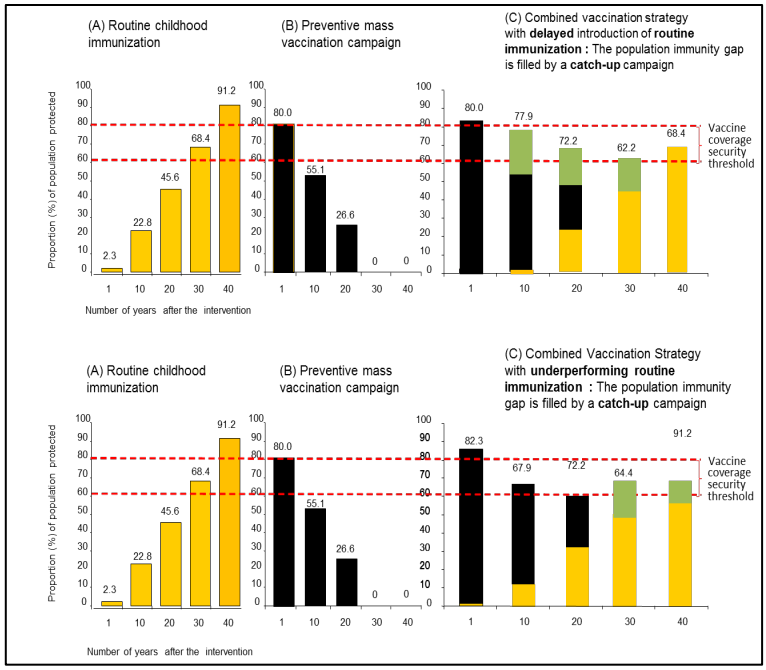
3.3. Approach 3: Implementing catch-up campaigns

Where low routine vaccination coverage and potential dilution of preventive vaccine campaign vaccine coverage due to population movements, mounting targeted "catch-up campaigns" would enable reaching under-vaccinated cohorts or pockets. These may target age-specific vaccination gaps, or geographic areas where population immunity is low.

Catch-up campaigns are a reasonable **risk mitigation** measure in high-risk areas to **close immunization gaps.** They are resource-intensive, particularly as vaccination coverage surveys might need to be performed to determine areas with low coverage, and require the same amount of coordination and fixed costs as large-scale preventive mass campaigns. Catch-up campaigns are **not**

a substitute to well-functioning routine immunization systems. Countries should be engaged though to perform periodic assessments of their vaccination coverage in areas at risk for outbreaks of disease in order to identify gaps in coverage and response proactively. Assessments could be performed at regular intervals (e.g., every 5-10 years) or in response to large population movement or other factors that might impact coverage.

Box 4: Population protected by delayed or underperforming routine childhood immunization combined to preventive mass campaigns



3.4. Approach 4: Maintaining a stockpile for reactive campaigns

A large supply of readily available YF vaccine can be kept for any future emergency response. Vaccine stockpiles enable a rapid access to a limited supply of vaccines, allowing countries to **respond to YF outbreaks** in a timely fashion. In a limited vaccine supply context, the international management of vaccine stockpiles is necessary to ensure an **equitable distribution**. Until optimal vaccination strategies are implemented to control the risk of YF and prevent epidemics, YF vaccine stockpiles will be necessary.

4. Targeting travellers and improving IHR adherence

The recent Angola epidemic highlighted how YF can spread internationally by land and air through unimmunized travellers (workers from China and DRC). In the country there are 400 000 migrant workers from DRC, at least 220 000 Portuguese, and about 260 000 Chinese (2008 estimates). In LAC, unimmunized “eco-tourists” lodging in sylvatic areas are a recognized source of introduction of YF virus into non-forested areas.

The YF immunization status of travellers needs to be confirmed upon arrival into and departure from areas at risk for YF to prevent YF exportation to immune-naïve populations where the potential for local transmission exists.

Although little data is available, the International Health Regulations (2005) (IHR) are inconsistently applied in countries at risk for YF, including upon airport arrival. As experienced during the 2015 Ebola epidemic, points-of-entry personal data and health checks are difficult . Yet lessons can be learnt from that experience that could inform a strengthening of IHR application.

The recent Angola–DRC YF epidemics also highlighted the need for uniform vaccination cards that are cheap but hard to counterfeit: viraemic unimmunized migrant workers used counterfeited cards to cross land borders and spread YF into immune-naïve populations.

No cost figures are available, but they should be fairly low compared to vaccination and surveillance activities.

In summary, YF cannot be eradicated but epidemics can be eliminated if population immunity levels are effectively raised through mass vaccination and *sustained* by routine infant immunization. Different approaches enable detection of YF and mitigation or prevention of the risk of YF epidemics. They can be used alone or in combinations, with different impacts. The appropriate (cost-effective) combinations of approaches depend on the risk level of a country.

It is important to emphasize that immunization programmes must maintain high levels of immunity, and that cessation of routine immunization will eventually lead to a return of outbreaks, as happened in Senegal in 1965, about five years after routine immunizations were stopped.

In West Africa, the three-pronged approach – including YF vaccine in routine immunization, performing mass vaccinations in at-risk countries/populations, and responding rapidly to outbreaks – has successfully controlled the disease. This three-pronged approach works and still provides the basic ingredients needed for an effective strategy. However, the change in risk both in vulnerable, fragile countries and internationally, and the resurgence of vectors, means the way in which these tactics are strategically applied needs to be scaled up and tackled globally.

This strategic document focuses on activities recommended in Africa and LAC, where the disease is endemic. Many experts worry that the disease will reach other continents, such as Asia. This risk is difficult to estimate. We assume, however, that by protecting populations in areas currently endemic for YF and by protecting travellers who could spread the disease, the risk of exportation will be contained.

The following risk-driven combination of strategic options to detect and control YF is proposed:

Table 4. Public health goal and combination of strategic options for YF detection and control by risk level

Country Risk level	Public health goal	Combination of strategic options
High	Protect at risk population Contain outbreaks rapidly Prevent international spread	• Three-pronged vaccination approach to maintain high population immunity levels (routine immunization, catch-up campaigns, preventive mass campaigns) • Monitoring of population immunity • Rapid response to outbreaks • Case-based surveillance and laboratory testing • Targeting travellers and improving IHR adherence (upon entry and departure) • Readiness and health systems strengthening
Moderate	Contain outbreaks in high risk areas Prevent international spread	• Sentinel surveillance and laboratory testing • Rapid response to outbreaks • Improving IHR adherence • Readiness and health systems strengthening
Currently not considered at risk but potential for YF transmission	Early detection of suspected cases Prevent introduction of YF	• Integrated surveillance and laboratory testing • Improving IHR adherence • Readiness and health systems strengthening

Part 3: Evolution of the global YF risk

Recent changes in transmission dynamics

In the latter half of the 20th century the most frequent YF virus transmission patterns were either: (1) sylvatic – where the animal reservoir (non-human primates living in the forest or jungle) – infects tree-dwelling mosquitoes which in turn bite humans who enter the forest to hunt or work; or (2) intermediate – where the mosquitoes moving between the forest and human settlements are implicated, with humans serving as the hosts in the transmission cycle. In Africa, virtually all intermediate type outbreaks have led to outbreaks involving the *Aedes aegypti* (urban) vector. This cycle can occur in rural villages and small towns, but large outbreaks have occurred when infected people from these rural settlements travelled to urban centres. More recently, however, although YF virus transmission patterns *per se* have not changed, the sequence has been increasingly short-circuited from sylvatic directly to urban, inter-human transmission. Urban outbreaks are particularly deadly and disruptive and are more likely to cause international spread. In contrast to Africa, YF cases in LAC have been nearly exclusively sylvatic, with very few small outbreaks of the urban type, although large, unvaccinated coastal populations are at potential risk. There is no recognized intermediate cycle.

Vectors: The worldwide resurgence of the primary vector responsible for urban outbreaks – *Aedes* species mosquitoes – means that globally, more cities and countries are at risk. The current global outbreak of Zika virus disease and continuing outbreaks of dengue fever and chikungunya disease, all caused by viruses primarily transmitted by *Aedes aegypti*, are indicative of the success of, and threat posed by, *Aedes aegypti*. Wherever and whenever Zika, chikungunya and dengue virus occur, this should alert countries to the possibility that YF virus could also be successfully transmitted in their communities.

Environmental risk: Deforestation, climate change, more incursions into forests and jungles for mining, construction and to clear land for agriculture are all increasing contacts between humans, the animal reservoir and the mosquitoes transmitting YF virus. Humans no longer stay at the edge of forests but move in, work there and move rapidly back to cities or large settlements (in a matter of hours), thus contributing to the potential rapid spread of YF virus. All these risk-amplifying factors – urbanization, large population movements, climate change and increasing exposure of workers to infected mosquitoes in jungles and forests (particularly those working in mining and forestry) – are driving the change in YF epidemiology.

Human risk: Movement of populations for commerce and due to civil unrest can often lead to lower population immunity, particularly in urban centres, as previously unvaccinated persons move to areas that might have benefited from vaccination campaigns earlier (e.g. Abidjan in Côte d'Ivoire experienced outbreaks several years apart with a notable decrease in population immunity between outbreaks).

Risk specific to urban outbreaks

In urban outbreaks, population density, crowding, low levels of population immunity, daily population movements in and out of, and around, the city, and conditions conducive to high vector

density such as plentiful breeding sites in and around houses, increase transmissibility, raising the risk of large-scale outbreaks.

Urban outbreaks are characterized by their rapid amplification, capacity for international spread, and impact not only on public health but also on economic, social and political life. The West African Ebola outbreak showed that when a pathogen spreads to capital cities it can amplify into a major epidemic on scale never observed before. The public health impact of such outbreaks is huge and so too are the economic losses: in the Republic of Korea, an outbreak of Middle Eastern respiratory syndrome in June 2015 caused only 185 cases but paralysed Seoul for several weeks, precipitating losses of millions of dollars in a matter of days.

Responding to outbreaks in large urban settings is challenging and costly and, in a globalized world, such outbreaks have impacts on travel and trade beyond the health consequences alone.

Risk classification of countries

While the YF virus has caused outbreaks in many countries in past decades, it is still difficult to assess the risk of re-emergence. Such re-emergence depends on a convergence of factors, requiring virus circulating in the animal reservoir, infection in mosquitoes, and transmission to humans. Many unknowns remain. In this challenging context, we reviewed the available information and applied specific criteria to classify the countries and propose preventive strategies accordingly. In a context of growing concern and perception of globalized risk, we decided to be inclusive in the number of reviewed countries.

Forty-seven countries (34 in Africa and 13 in Central and South America) are either endemic for, or have regions that are endemic for, YF[1]. In addition to these 34 African countries, we added Zambia, as a working group of international experts included north-western and western provinces as areas of low exposure (Jentes ES et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for YF. Lancet Infect Dis. 2011; 11:622–32).

Africa

For Africa, we used a **three-step approach** to reclassify the 35 countries into different risk categories and propose preventive strategies accordingly.

- **Step 1.** Estimation of ***crude risk*** for YF transmission. Crude risk represents the likelihood for YF disease cases to occur if the population is inadequately vaccinated. Crude risk was established to identify countries that are naturally at higher risk and should be targeted to achieve sustained, high level of vaccine coverage.

[1] : Yellow fever: Fact sheet. Geneva; World Health Organization; updated May 2016; http://www.who.int/mediacentre/factsheets/fs100/en/

- **Step 2.** Estimation of ***actual risk*** for YF disease cases and urban outbreaks. Among countries determined to have a high crude risk of YF virus transmission, their population immunity was assessed to further highlight which countries are most at risk for outbreaks.

- **Step 3.** prioritization of countries based on their perceived level of risk. The prioritization is meant to guide further implementation of preventive activities.

Step 1. Crude risk estimation

The crude risk for YF virus transmission in a country was estimated based several key factors:

(1) Timing and intensity of YF virus circulation in the country.
   - Assessed using both direct evidence of YF circulation (i.e., serosurveys in vaccination-naïve populations) and proxies for current (recent reports of YF cases) and historical active YF virus circulation and human disease cases; we used mass immunization campaigns in the 1940s–1960s as a proxy for intense virus circulation. We used the following definitions and cut-offs:
     - number of reported YF outbreaks in the last 25 years
     - serosurvey from the recent comprehensive risk assessments – see Table 3 – demonstrating YF-virus specific neutralizing antibodies prevalence >3% in at least one zone[1]
     - presence of YF cases reported between and 2011–2016
     - national mass immunization campaign prior to the Yellow Fever Initiative.

     Any country positive for one of these criteria was initially classified as being at high risk (Table 5). This analysis enabled identification of **27** "**high-risk**" and **eight "moderate-risk**" countries.

(2) Estimate of the transmission potential in terms of the basic reproduction number
   - A working group from Imperial College, London, developed a model to assess the geographically varying transmission potential and resulting disease burden of YF in the endemic zone in Africa. They considered a wide range of environmental factors as potential covariates, with the final (best-fitting) model including population size, longitude, the enhanced vegetation index and land cover type. The model was used to estimate the transmission potential in terms of the basic reproduction number, Ro. The Ro model was fitted to outbreak data between 1984 and 2013.

   The Ro were used to verify if the categorization of countries based on the timing and intensity of YF virus circulation in the country (see point 1 above) needed to be adapted. We used a cut-off point for Ro.≥1.25, being the median (P50) value of the Ro distribution.

[1] Risk assessment on yellow fever virus circulation in endemic countries, available from http://apps.who.int/iris/bitstream/10665/112751/1/WHO_HSE_PED_CED_2014.2_eng.pdf

Table 5. Risk of YF virus circulation of 35 African countries

	Country	Numbers of YF outbreaks 1990–2016	Recent report of YF cases[1]	National PMVC prior to the YFI	High seroprevalence[2]	Ro≥1.25	Risk level
1	Angola	1	Y				High
2	Benin			Y		Y	High
3	Burkina Faso	5		Y		Y	High
4	Cameroon	5	Y	Y			High
5	C. A. R.	3				Y	High
6	Chad	1	Y	Y			High
7	Congo	2	Y			Y	High
8	Côte d'Ivoire	7	Y	Y		Y	High
9	DRC	4	Y		Y		High
10	Eq. Guinea		Y				High
11	Ethiopia	1	Y		N		High
12	Gabon		Y[3]	Y		Y	High
13	Gambia			Y		Y	High
14	Ghana	1	Y			Y	High
15	Guinea	10		Y		Y	High
16	Guinea-Bissau		Y[4]			Y	High
17	Kenya	2			N		High
18	Liberia	5		Y		Y	High
19	Mali	2				Y	High
20	Niger					Y	High
21	Nigeria	3				Y	High
22	Senegal	5	Y	Y		Y	High
23	Sudan	4	Y		Y[5]		High
24	South Sudan	1			Y[6]		High
25	Sierra Leone	3				Y	High
26	Togo			Y		Y	High
27	Uganda	2	Y		Y		High
1	Burundi					N	Moderate
2	Eritrea					N	Moderate
3	Mauritania					N	Moderate
4	Rwanda				N	N	Moderate
5	Sao Tome and P.					NA	Moderate
6	Somalia					N	Moderate
7	Tanzania (United Republic of)					N	Moderate
8	Zambia				N	N	Moderate

Ro = basic reproductive number; PMVC = preventive mass vaccination campaign; YFI = Yellow fever Initiative; Y = yes; N = no; NA = not available.

- In Ethiopia, the YF risk assessment found evidence of risk and virus circulation limited to the south-western part of the country. South-western Ethiopia only is therefore considered to be at high risk.

- PMVCs conducted in the 1940s–1960s, except for Gabon and the Gambia, which conducted national mass campaigns in response to epidemics in 1995 and 1979, respectively.

[1] 2011–2016.

[2] Serosurvey demonstrating neutralizing antibody prevalence >3% in at least one zone (multidisciplinary risk assessment).

[3] Cases were recently laboratory confirmed.

[4] Imported cases were recently confirmed (area of origin unclear).

[5] In Sudan, the national average was 5.1%, ranging from 2.1–7.3%.

[6] In South Sudan, the national average was 7.2%, ranging from 4.5 to 8.6%.

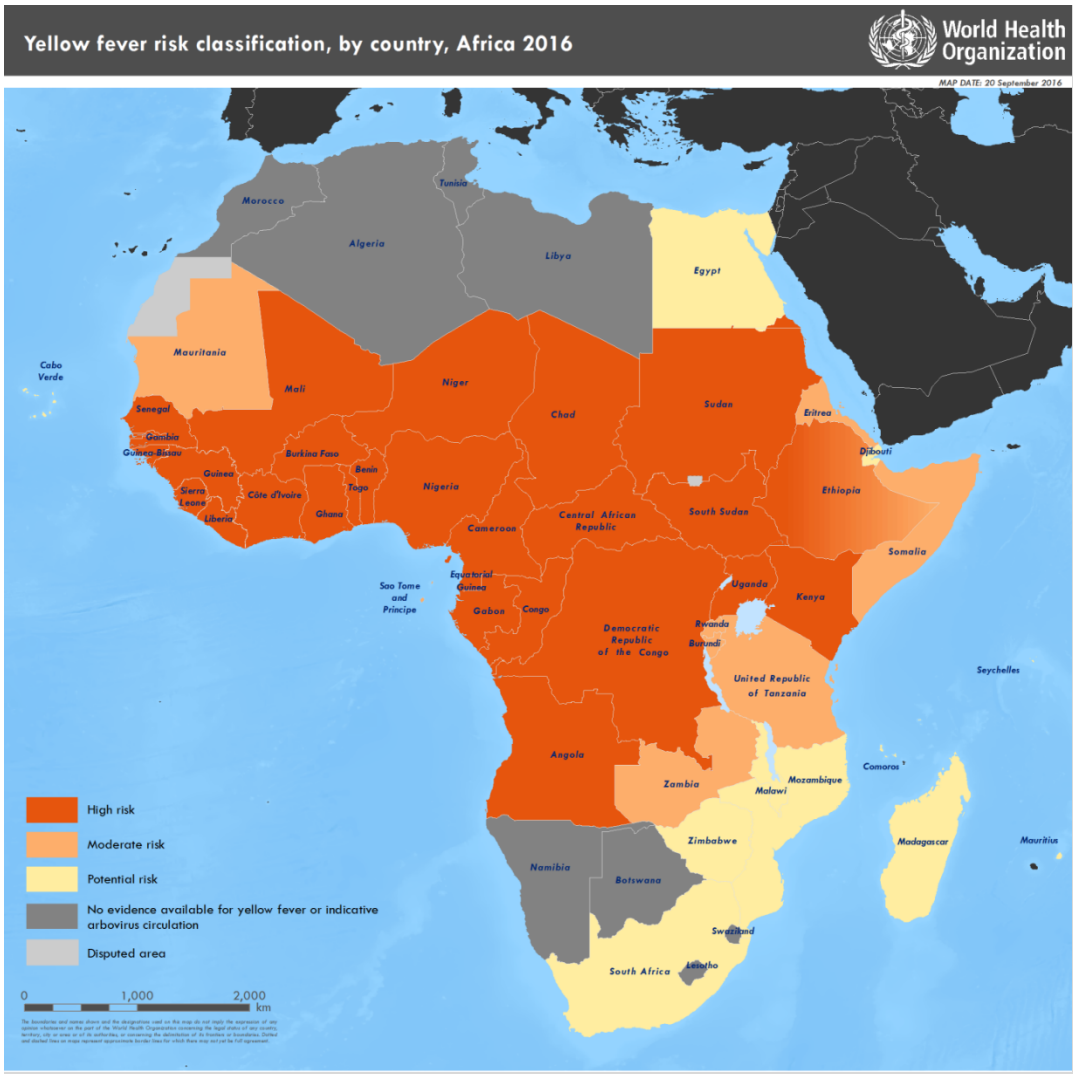
(3) Assessment of urban outbreak risk based on reports of recent or current outbreaks of *Aedes aegypti*-transmitted viral diseases

Recent or current outbreaks of dengue fever, Zika virus disease, and chikungunya were assessed in the 35 countries in Africa and 13 countries in Americas where YF is considered endemic. In addition, these criteria were also applied to countries in Africa that neighbour areas with risk of YF and outbreaks to define **"potential for YF virus transmission"** (Figure 3)**.**

(4) Determination of countries with no risk of YF virus circulation and limited potential for outbreaks of disease

Last group of countries were limited to those who had no risk of YF virus circulation and also reported no evidence of arbovirus circulation (e.g., dengue, chikungunya, or Zika virus disease cases) (Figure 3). Although countries are generally felt not to be significant risk for outbreaks of YF disease, several of these countries could be at risk for a sustained urban outbreak of YF given the predicted distribution of the *Aedes aegypti* mosquito.

Figure 3. Risk of YF outbreaks in Africa by country, 2016



Step 2. Actual risk estimation to inform immunization activities

Based on the crude risk of YF virus circulation, we then assessed countries by the current proportion of the population that is likely protected against YF to determine the actual risk of YF disease and outbreaks. We used vaccine-acquired population immunity, as calculated by the working group from Imperial College, London, in 2016 and focused on the 27 high risk countries based on YF virus transmission patterns (i.e., crude risk). Population immunity is the proportion of individuals protected against YF in a given population (non-susceptible). In each country, population immunity was calculated at district level from cumulative data on preventive mass campaigns, routine immunization, outbreak response and catch-up campaigns. The computation accounted for target population, vaccine coverage and the year of the respective activity. District-level coverages were averaged across each country to provide a national estimate.

Among the high-risk countries, a number have already conducted immunization activities and show a higher population immunity (Table 6).

Table 6. Vaccine-acquired population immunity for high-risk countries, Africa 2016

	Country	Pop. immunity
1	Côte d'Ivoire	0.9
2	Togo	0.888
3	Benin	0.884
4	Liberia	0.873
5	Burkina Faso	0.869
6	Sierra Leone	0.857
7	Central African Republic	0.839
8	Guinea	0.808
9	Mali	0.788
10	Cameroon	0.721
11	Ghana	0.720
12	Senegal	0.719
13	Gambia	0.687
14	Gabon	0.675
1	Angola	0.508
2	Sudan	0.455
3	Niger	0.354
4	Nigeria	0.337
5	Congo	0.319
6	Chad	0.314
7	DRC	0.285
8	Kenya	0.270
9	Guinea-Bissau	0.173
10	Uganda	0.017
11	South Sudan	0.015
12	Ethiopia	0.005
13	Equatorial Guinea	0

Thirteen countries show a population immunity below 60%, indicating that herd immunity is not sufficient to prevent outbreaks. These countries need large-scale preventive approaches. Two countries, Gabon and the Gambia, lie between 60% and 70% and should consider methods to improve their vaccination coverage to prevent outbreaks of disease.

Ghana is a special case: PMVCs were conducted in 2011 and 2012 (two phases) but large areas of the country were not covered; the approach was "patched", as described above. It is therefore recommended that the campaigns be completed and full coverage achieved in remaining districts.

Step 3. Prioritization among the countries perceived to have the high risk of outbreaks given YF virus circulation and low vaccine immunity

The prioritization exercise was completed (Table 7), based on:

- History of arbovirus outbreaks: History of arthropod-borne virus (arbovirus) outbreaks also transmitted by Aedes species (dengue, Zika, chikungunya). Presence of dengue was given 1–3 grading points based on the quality of documentation. Presence of chikungunya and Zika virus was graded with one point each. A grading of 0 denotes absence of all documented arboviruses.
- Expert opinion. Based on experience and practical considerations, subject matter experts provided input on the prioritization. Some of their considerations are included below:
    - Nigeria is the only one of the 12 countries originally approved by Gavi under the YF investment case which has not yet finalized its national PMVC. Nigeria was affected by one of the largest YF epidemics in the last 35 years, with the estimated number of cases being greater than 116 000, with 24 000 deaths. It remains a major gap in West Africa and was identified as a top priority by the experts.
    - Ghana and Sudan also need to ensure that the whole country is covered – to complement the 2011–2012 campaign in Ghana and phase 2 in Sudan.
    - Angola and DRC also need ensure that the whole country is covered after various campaigns organized in 2016 in response to the outbreaks.
    - Uganda had YF outbreaks in 2010 and 2016 affecting three areas in distinct locations of their country and have minimal to no population immunity except in the areas targeted by the reactive campaigns
    - Ethiopia had a sizeable outbreak in 2013.
    - Guinea-Bissau remains an unprotected space in West Africa.
    - For the remaining countries, the difference is small, but a slightly higher priority was given to Congo and Equatorial Guinea because of the reporting of recent cases in neighbouring countries.

Table 7. Proposed priority for African countries at high risk of YF

	Country	History of arbovirus outbreaks	Expert opinion
1	Nigeria	5	Complete investment case – West Africa Gavi approved
2	Ghana	3	Complete investment case – West Africa Gavi approved
3	Sudan	4	Last phase – finish campaign Gavi approved Recent outbreak
4	Uganda	4	Recent outbreaks Commitment to introduction into routine EPI
5	DRC	4	Recent outbreak response – country to be finalized
6	Angola	3	Recent outbreak response – country to be finalized
7	Guinea-Bissau	4	West Africa higher risk
8	Ethiopia	3	Recent outbreak
9	South Sudan	3	Recent outbreak
10	Congo	2	Recent confirmation of cases
11	Eq. Guinea	2	Recent confirmation of cases
12	Chad	2	
13	Niger	1	

This ranking should be considered preliminary as it has to be discussed with the respective countries and at the regional level.

Latin America and the Caribbean

For **LAC**, YF continues to be a significant public health problem for the 13 countries with endemic areas, and all are considered to be at high risk. Over the last 30 years, YF virus activity has been restricted to the enzootic area shared by the Plurinational State of Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Panama, Peru, Suriname, Trinidad and Tobago, and the Bolivarian Republic of Venezuela.

Since late 2007, the region has experienced intense circulation of the YF virus with extensive epizootics and outbreaks of human cases. 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 LAC had occurred in 1942 in Brazil. This event, in addition to the proliferation of *Aedes aegypti* in the Region, shows the high risk of re-urbanization that still exists in LAC. The endemic area was extended to include Paraguay and northern Argentina, because of human cases and epizootics detected in 2008.

In 2013, the regional TAG reviewed the YF problematic in countries of Latin America. The TAG reaffirmed that the strategy to control YF should include surveillance and YF vaccination through a combination of routine immunization strategies and large-scale disease-prevention campaigns. Campaigns in response to outbreaks should be conducted if vaccine coverage is inadequate in the population.

As of 2016, every country in the region with enzootic areas has added the YF vaccine to its national immunization schedule. In Argentina, Brazil and Panama, the vaccine is only administered in areas of potential risk (Table 2).

Population immunity could not be estimated for at-risk countries in LAC. However, mass preventive campaigns were usually conducted long ago and, as described earlier in this document, routine immunization has achieved suboptimal levels. Experts have estimated that most countries need to conduct mass campaigns, to be targeted at the very specific high-risk zones or according to the remaining susceptible population. Among the 13 countries with endemic areas, experts have prioritized Peru (recent outbreaks), Colombia and the Bolivarian Republic of Venezuela.

YF circulation was never identified in the Caribbean countries and territories, which are not endemic for the disease, except in Trinidad and Tobago. Yet the intense and rapid spread of both the chikungunya and Zika viruses and recurrent dengue epidemics in large, densely populated regions of South America, Central America and the Caribbean outside the enzootic zone make them countries with **"potential for YF transmission"**, on the same basis as the risk categorization proposed for Africa.

Figure 4. YF risk areas in South America, Panama, and Trinidad and Tobago

Part 4: EYE goal and strategic objectives

To respond to the increased risk of large urban outbreaks with international spread that could threaten global health security, a comprehensive long-term strategy has been developed, able to target the most vulnerable countries and regions, while addressing global risk by building resilience in urban centres and readiness in areas with potential for outbreaks, and at the same time ensuring reliable vaccine supply to predict needs and shape vaccine production.

EYE goes beyond immunization activities to address the increased risk and adapt to changing YF epidemiology. An efficient surveillance system and the control of international dissemination are essential pillars complementing population protection. This can only be achieved through strong partnerships and collaborations across agencies, disciplines and sectors.

EYE goal: To eliminate the risk of YF epidemics globally by 2026

The EYE strategy has three strategic objectives:

1- protect at-risk populations;
2- prevent international spread;
3- contain outbreaks rapidly.

The EYE strategy will only be successful if core activities are initiated from the very beginning to provide cross-cutting support to the three central objectives. These activities are:

- continued availability of accessible, affordable vaccines through a sustained vaccine market;
- political commitment at regional and country levels;
- robust governance and strong partnerships for EYE implementation;
- research to support better tools and practices.

Strategic objective 1: Protect at-risk populations

Action 1: Where risk is high, vaccinate everyone

Preventive mass vaccination campaigns

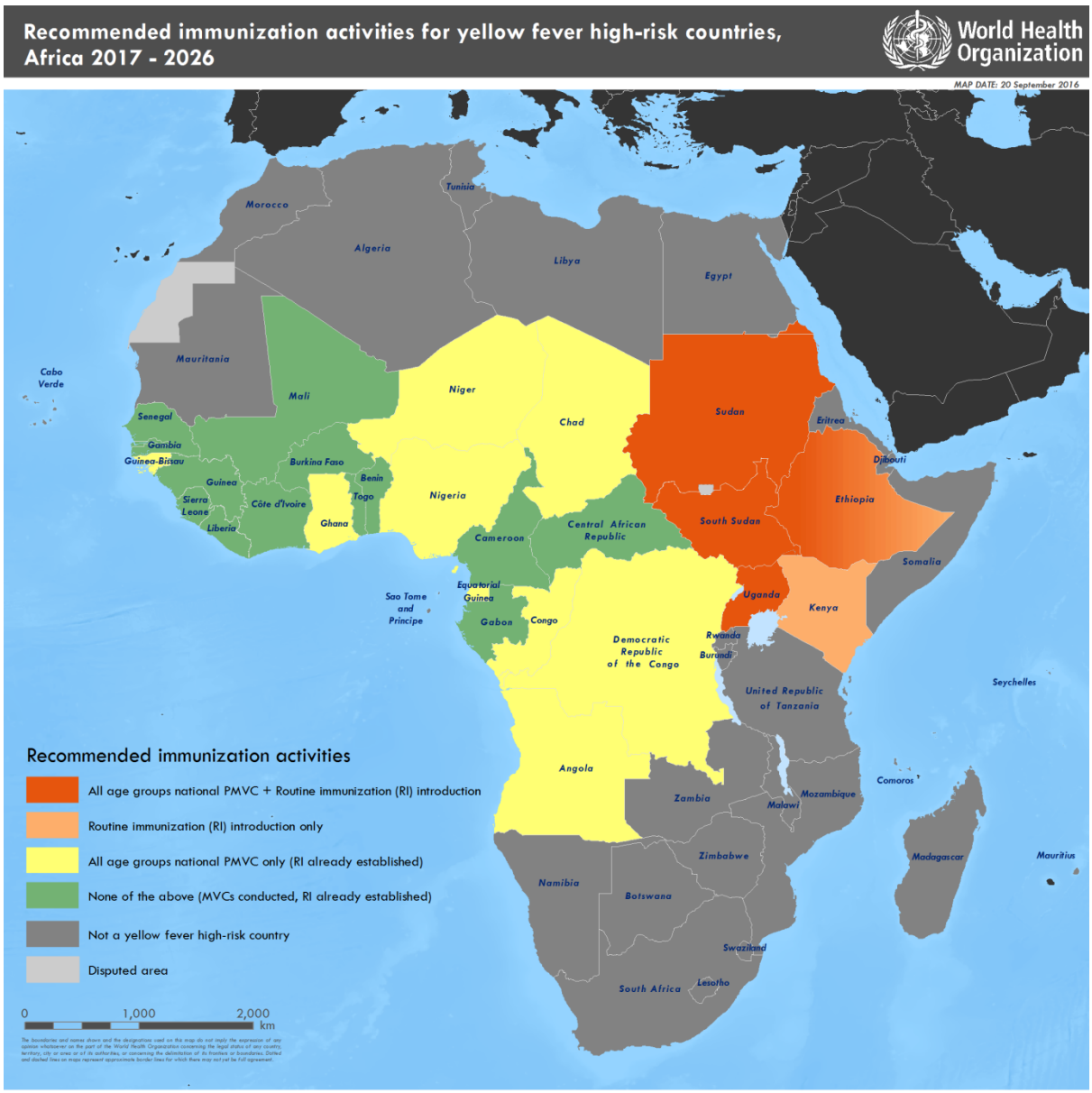
To rapidly reduce the risk of outbreaks, it will be important to target areas at high risk of YF virus transmission and inadequate population immunity.

Africa. As previously noted, there are 13 countries in Africa identified as high risk where PMVC would be considered to increase the inadequate levels of immunity rapidly (Figure 5): Angola, Chad, Congo, DRC, Ethiopia, Equatorial Guinea, Ghana, Guinea Bissau, Niger, Nigeria, South Sudan, Sudan, and Uganda.

While the primary goal is to build a barrier of human immunity in sylvatic areas and protect populations in the zone of emergence, the preventive strategies have to be national in scope to account for the reality of frequent and rapid population movements and to prevent urban outbreaks. The exception is Ethiopia, for which the south-western part of the country is scheduled for a PMVC as seroprevalence surveys and confirmed epidemics have indicated virus circulation in this area only.

Kenya is another special case: it is included as a high-risk country, has experienced various outbreaks in the 1990s and borders Uganda and the south of Ethiopia where outbreaks have been reported. However, the risk assessment conducted in 2014 did not find evidence of virus circulation, and the antibody seroprevalence in particular was very low. For this reason, Kenya is not included in the list of planned PMVC countries, consistent with the north-eastern part of Ethiopia.

Figure 5. Recommended immunization activities to be completed by country, EYE strategy, 2017–2026



The total target population for Africa is approximately 440 million, requiring 490 million doses of vaccine over 10 years (Table 8).

Sequencing of vaccination activities

Following the prioritization exercise, PMVCs were sequenced based on available vaccines by year. For this we used global vaccine production forecasts for 2017–2026 (see Part 5), deducted estimated needs of countries in LAC and for routine immunization in Africa, and assigned the remaining vaccines to PMVCs in priority order.

According to the proposed schedule, all recommended PMVCs can be completed with the available vaccines within the 10-year time frame of the strategy (Table 8).

Table 8. Proposed sequencing of preventive mass vaccination campaigns over time, Africa

In number of doses (1000s)

Country	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	total
Nigeria	30 694	31 480	32 280	33 093	33 920	0	0	0	0	0	161 467
Ghana	3 057	9 370	3 190	0	0	0	0	0	0	0	15 616
Sudan	0	9 215	14 159	0	0	0	0	0	0	0	23 374
Uganda	0	0	0	14 674	30 285	0	0	0	0	0	44 959
DRC	8 773	0	0	0	0	30 638	31 558	21 664	0	0	92 633
Angola	0	0	0	0	0	9 947	0	0	0	0	9 947
Guinea-Bissau	0	0	0	0	0	0	2 354	0	0	0	2 354
Ethiopia	0	0	0	0	0	31 242	31 940	0	0	0	63 182
South Sudan	0	0	0	0	0	0	8 112	8 310	0	0	16 422
Congo	0	0	0	0	0	0	0	6 221	0	0	6 221
Equatorial Guinea	0	0	0	0	0	0	0	1 147	0	0	1 147
Chad	0	0	0	0	0	0	0	19 762	0	0	19 762
Niger	0	0	0	0	0	0	0	30 402	0	0	30 402
Gabon	0	0	0	0	0	0	0	664	0	0	664
Sum (Africa)	**42 523**	**50 065**	**49 629**	**47 767**	**64 206**	**71 828**	**73 965**	**88 171**	**0**	**0**	**488 153**

Notes:

- Population figures taken from UNPD projections for anticipated year(s) of campaign implementation.
- Initial target population = 96% of total, corresponding to >1-year-old population.
- In Nigeria, initial target population is 80% of total, corresponding to 1–45 year-old population. In Ghana, target population is 67% of total, corresponding to those aged 10 years and above.
- For Nigeria, Sudan, DRC, Angola and Ghana, the remaining target population takes into account previous PMVCs.
- The assumed vaccine wastage rate is 10%.
- For DRC, the 2017 number of doses is estimated to be provided as a booster dose to the fractioned dose used in Kinshasa. The need for this strategy will be confirmed with immunological studies.

Catch-up campaigns

Reported immunization coverage will be monitored and the overall vaccine-induced population immunity (PI) (taking into account routine EPI, reactive and preventive campaigns), will be calculated each year, indicating which countries should be targeted for catch-up. The recommended PI

threshold for protection is 70% (being the midpoint of the consensus threshold range for YF herd immunity of 60–80%).

In **Africa**, based on current assessments at the time of drafting the strategy (September 2016), a catch-up campaign is recommended for Gabon only. Gabon was also identified in the middle range PI category (Table 6). It is estimated that 677 000 doses of vaccine will be required, covering in particular the unprotected population currently aged between 10 and 20 years, in order to vaccinate the susceptible population not reached during the national mass vaccination campaign in 1995 and routine EPI since the introduction of YF vaccine in 2003.

In LAC, mass preventive vaccination campaigns have been conducted in 10 countries: the Plurinational State of Bolivia (2007), Brazil, and earlier in Colombia, Ecuador, Guyana, Panama, Paraguay, Peru, Trinidad and Tobago and the Bolivarian Republic of Venezuela. Most of these campaigns have targeted populations living in enzootic areas and areas from where migrants originate to enzootic areas. The Plurinational State of Bolivia is the only country to have conducted a national campaign targeting the population aged between 2 and 44 years. Suriname and Panama have not conducted a national campaign, in addition to Argentina where virus circulation is very limited geographically.

Brazil has implemented a unique vaccination schedule, including periodic re-vaccination in endemic areas. This special case falls outside the regional strategy. The total vaccine demand for Brazil, including such campaigns, has been estimated at 30 million doses per year. The particular situation of French Guyana, as a special territory, is not included in the strategy.

It is proposed that catch-up campaigns will be conducted in the 11 remaining countries with enzootic circulation of YF virus (Table 9). Initial vaccine demand is estimated at approximately **39 million doses** (Brazil and French Guyana not included) (Table 10).

Table 9. Needs estimates for preventive mass vaccination against YF targeting high-risk groups in Latin America

Country	Type of campaign	Target population (% country total)	Target population
Argentina	Subnational	1%	433 020
Bolivia (Plurinational State of)	Catch-up	20%	2 217 273
Colombia	Catch-up	20%	9 535 186
Ecuador	Catch-up	5%	832 243
Guyana	Catch-up	5%	37 766
Panama	Subnational	5%	203 085
Paraguay	Catch-up	40%	2 745 865
Peru	Catch-up	20%	6 175 963
Suriname	Subnational	5%	27 308
Trinidad and Tobago	Catch-up	5%	66 211
Venezuela (Bolivarian Republic of)	Catch-up	40%	12 603 443
TOTAL			**34 877 363**

Table 10. Proposed sequencing of preventive mass vaccination campaigns over time, LAC countries

In number of doses (1000s)

Country	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	total
Peru	5 147	1 736	0	0	0	0	0	0	0	0	6 883
Colombia	0	2 638	5 318	2 679	0	0	0	0	0	0	10 635
Venezuela (Bolivarian Republic of)	0	0	3 491	3 532	3 573	3 614	0	0	0	0	14 210
Argentina	0	0	0	0	490	0	0	0	0	0	490
Bolivia (Plurinational State of)	0	0	0	0	2 499	0	0	0	0	0	2 499
Brazil	0	0	0	0	0	0	0	0	0	0	0
Ecuador	0	0	912	0	0	0	0	0	0	0	912
French Guiana	0	0	0	0	0	0	0	0	0	0	0
Guyana	0	0	42	0	0	0	0	0	0	0	42
Panama	0	0	222	0	0	0	0	0	0	0	222
Paraguay	0	0	0	0	1 525	1 543	0	0	0	0	3 069
Suriname	0	0	0	0	30	0	0	0	0	0	30
Trinidad and Tobago	0	0	0	0	74	0	0	0	0	0	74
Sum (LAC excl. Brazil)	**5 147**	**4 375**	**9 985**	**6 211**	**8 192**	**5 157**	**0**	**0**	**0**	**0**	39 066

In-country prioritization:

In countries with large target populations, national PMVCs will be mounted in multiple phases of subnational increments over several years, in a similar way to the introduction of the meningococcal meningitis A vaccine. In those circumstances, in-country prioritization will be required. Campaign phasing will be developed with the countries themselves, on a country-by-country basis, based on the following principles:

- *ecological criteria*: areas of moist savannah, which are the zones of YF emergence, should be given priority;
- *PI*: areas with low PI should be prioritized;
- *pragmatic considerations,* such as:
    - vaccination activities are not feasible in sylvatic areas during the rainy season;
    - the YF vaccine being live attenuated, preventive mass campaigns should be conducted at least one week apart from other live attenuated vaccine campaigns, such as the oral polio vaccine or the measles vaccine, to avoid vaccine immunogenicity reduction;
    - capital cities located near the YF emergence zone (moist savannah) have an increased risk of urban outbreaks and should be prioritized.

In-country prioritization will not be necessary in countries where PMVCs will be conducted within a year (even if conducted in successive phases).

Action 2: Vaccinate every child

Including YF vaccination in routine immunization schedules

The best way to maintain high levels of immunity in high-risk countries is to ensure that all new cohorts are immunized in infancy. High coverage in successive cohorts of children will gradually ensure that the PI does not decrease after mass vaccination campaigns.

In Africa, all 27 countries at high risk need to protect all infants against YF by introducing the vaccine into the national routine vaccination schedule and ensure that high coverage is achieved. Most

countries at high risk have introduced the vaccine into the national routine immunization schedule already. However, as of September 2016, five out of the 27 countries had not yet done so (Ethiopia, Kenya, South Sudan, Sudan and Uganda). It is expected that these countries will have introduced the YF vaccine into their routine immunization schedules by 2020.

Approximately **20 to 30 million children** (counts increasing from 2017 to 2026 due to natural population growth) will need to be immunized **annually**, representing an annual demand of 35 to 50 million doses. The total vaccine demand for the next 10 years has been estimated at 465 million doses (Table 11). In this forecast, a 40% vaccine wastage rate has been assumed. The proposed year of introduction for the five countries will need to be confirmed. It is assumed that for year 1 of introduction, the demand is 50% of the infant cohort.

Table 11. Annual needs estimates (vaccine doses in 1000s) for routine immunization against YF in the 27 high-risk countries, Africa

Country	VaccDs17	VaccDs18	VaccDs19	VaccDs20	VaccDs21	VaccDs22	VaccDs23	VaccDs24	VaccDs25	VaccDs26
Nigeria	11,371	11,538	11,710	11,887	12,070	12,258	12,449	12,643	12,840	13,040
Ghana	1,415	1,420	1,424	1,430	1,436	1,443	1,450	1,458	1,466	1,476
Sudan	1,069	2,164	2,191	2,220	2,248	2,278	2,307	2,335	2,363	2,391
Democratic Republic of the Congo	5,213	5,325	5,436	5,547	5,659	5,771	5,883	5,995	6,107	6,220
Angola	1,788	1,829	1,871	1,913	1,956	1,999	2,042	2,086	2,130	2,174
Uganda	1,367	2,794	2,855	2,915	2,975	3,036	3,097	3,158	3,219	3,279
Guinea-Bissau	105	106	107	108	109	110	111	112	113	114
Ethiopia	0	2,599	5,243	5,285	5,323	5,358	5,389	5,417	5,441	5,460
South Sudan	0	0	375	763	774	785	795	804	814	822
Congo	272	276	280	284	289	294	300	305	311	317
Equatorial Guinea	47	48	49	49	50	51	51	52	52	53
Chad	1,000	1,023	1,046	1,068	1,090	1,112	1,133	1,155	1,176	1,196
Niger	1,667	1,729	1,792	1,856	1,922	1,988	2,056	2,125	2,195	2,266
Senegal	935	947	960	973	987	1,001	1,016	1,031	1,047	1,064
Cameroon	1,346	1,362	1,378	1,394	1,410	1,426	1,443	1,459	1,475	1,491
Sierra Leone	355	357	360	362	364	366	367	369	371	372
Central African Republic	254	256	258	260	262	263	264	265	266	267
Guinea	747	758	769	779	790	801	812	823	833	844
Côte d'Ivoire	1,353	1,378	1,402	1,425	1,448	1,470	1,492	1,514	1,535	1,556
Liberia	253	257	261	265	269	273	277	281	285	289
Gambia	138	141	144	146	149	152	155	158	161	164
Togo	419	424	430	435	441	446	452	458	464	471
Burkina Faso	1,163	1,185	1,207	1,228	1,251	1,273	1,296	1,319	1,342	1,365
Mali	1,210	1,235	1,260	1,286	1,313	1,341	1,369	1,399	1,428	1,458
Benin	623	633	642	651	660	669	678	686	694	703
Gabon	83	83	84	84	85	85	86	87	87	88
Kenya	0	0	1,296	2,619	2,647	2,677	2,708	2,740	2,773	2,808
Sum (Africa)	**34,194**	**39,867**	**44,827**	**47,234**	**47,977**	**48,726**	**49,478**	**50,232**	**50,988**	**51,746**

In LAC, all countries have already introduced the vaccine into the routine schedule. The annual vaccine demand for the 13 countries with enzootic circulation of YF virus is approximately **12 million doses**. The total vaccine demand for the next 10 years has been estimated at 119 million doses (Table 12).

Table 12. Annual vaccine needs estimates (Vaccine doses in 1000) for routine immunization against YF in LAC countries

Country	VaccDs17	VaccDs18	VaccDs19	VaccDs20	VaccDs21	VaccDs22	VaccDs23	VaccDs24	VaccDs25	VaccDs26
Peru	998	992	986	981	975	969	962	956	950	944
Peru (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Colombia	1 202	1 190	1 179	1 167	1 155	1 143	1 131	1 120	1 110	1 099
Colombia (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Venezuela (Bolivarian Republic of)	982	979	976	973	969	965	961	957	953	948
Venezuela (Bolivarian Republic of) (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Argentina	185	185	185	184	184	184	183	183	183	182
Argentina (travellers)	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250	1 250
Bolivia (Plurinational State of)	410	411	413	414	415	416	416	417	417	417
Brazil	2 921	2 900	2 879	2 857	2 835	2 813	2 790	2 767	2 743	2 719
Ecuador	541	540	539	539	538	536	535	534	532	531
French Guiana	11	11	11	12	12	12	12	12	12	13
Guyana	25	25	25	26	26	26	26	25	25	25
Panama	37	37	37	37	37	37	37	37	37	37
Paraguay	229	230	230	230	230	229	228	227	226	225
Suriname	16	16	16	16	16	15	15	15	15	15
Trinidad and Tobago	30	29	28	28	27	26	26	25	25	25
Sum (LAC excl. Brazil)	**9 665**	**9 646**	**9 626**	**9 605**	**9 582**	**9 558**	**9 534**	**9 509**	**9 485**	**9 460**

For Argentina, Colombia, Peru and the Bolivarian Republic of Venezuela, workers and travellers (eco-tourists in particular) to endemic zones are a special consideration.

For Argentina, Brazil and Panama, according to the national schedule, the proportion of the targeted child or infant cohort is 15%, 50% and 30%, respectively, corresponding to the proportion of endemic areas.

To avoid re-vaccination practices, a reliable information system (electronic registry) would be needed, including the adult population.

Improving routine immunization performance

Introducing the vaccine into routine immunization programmes is not enough. In many countries routine immunization coverage is low. Exploration of, and an effective response to, reasons for this poor coverage – which are likely to vary between localities – will be key to successfully implementing this element of the EYE strategy.

Some potential approaches include ensuring that the YF vaccine stock is reliable and that health facilities are well supplied, increasing political will to ensure that children are vaccinated, improving the knowledge and awareness of health care workers about the importance of childhood YF vaccination, linking prevention of measles and YF, and clearly defining targets and indicators. Demand creation has to be particularly strengthened, in liaison with stronger community engagement at all levels, communication and social mobilization efforts.

Special attention must be paid to reaching vulnerable and marginalized populations (e.g. street children, displaced populations and refugees).

Action 3: Risk assessments

A comprehensive risk assessment methodology has been designed and applied in a number of countries in the last five years[1]. Country results have been successfully used to guide preventive interventions and recommend – or not – preventive campaigns or introduction of YF vaccine into the routine EPI.

In Africa, given the current EYE plan to conduct national preventive campaigns in the remaining 13 high-risk countries, it is currently not recommended to conduct such a risk assessment in those countries systematically.

The risk assessment exercise has value, in case of:

- perception of changing risk in countries at moderate risk;
- assess vaccine needs and prioritization of roll out;
- country or regional request for revised classification, in particular for the IHR.

In addition, countries outside the current at-risk country list might also benefit from such an assessment, for the same reasons. It is recommended that the risk assessment methodology be revised according to these specific objectives.

In LAC, a risk assessment is recommended for Panama, to inform an IHR reclassification. In addition, in the Plurinational State of Bolivia, Guyana and Trinidad and Tobago, a risk assessment would also be useful to provide orientations on the current risk, and take into account recent population dynamics (migration and urbanization) and evolving ecological conditions.

Strategic objective 2: Prevent international spread

The Angolan outbreak showed that a large urban outbreak in a transport hub can rapidly spread to distant countries (11 cases were exported to China). Fortunately, this occurred during a period when temperatures in China were too low for YF vector activity but it demonstrated that there is a serious risk of international spread. Actions needed to prevent this include:

Action 1: Protect high-risk workers

Applies to the 27 countries at high risk for YF outbreaks in Africa and the 13 countries in LAC

Globalization means that workers in a wide range of extractive industries (such as the oil and mining industries) and other sectors (such as construction and forestry) move into and out of YF endemic areas regularly and are at risk of both developing the disease and spreading it internationally. These workers are particularly exposed to sylvatic transmission when the activity is in forests or recently deforested areas.

Within the EYE governance mechanism (see Part 5), a working group involving companies from the major sectors affected (e.g. the extractive, construction and forestry industries, and the transportation sector) and public health experts is needed to develop strategies ensuring that all

[1] http://www.who.int/csr/disease/yellowfev/risk_assessment/en/

international workers are protected. The private sector should be involved in this effort and ensure that staff and their families are protected.

Action 2: Apply the International Health Regulations

Because epidemic risk might exist through imported cases, strict implementation of the IHR for travellers in and out of countries at-risk for YF, as well as increased surveillance and preparedness, will be paramount to prevent, detect and respond to potential epidemic threats. YF vaccination requirements are clearly stated in the IHR, but are not being fully applied. Port and border control authorities need to be engaged to identify gaps and ensure that the vaccination status of all travellers entering and leaving endemic areas is known and appropriately managed. This is particularly important at points of entry in the at-risk countries.

All countries need to engage transportation agencies (e.g. the International Air Transport Association), airlines and border control agencies/customs to strengthen the control of YF immunization status, in line with the IHR, based on area of origin and destination, at entry and departure.

A particular problem is the production of falsified immunization cards or certificates as well as non-official card selling points. In addition to specific country control measures, a solution needs to be proposed at the global level to move towards a unique registration system and the creation of non-falsifiable cards.

Action 3: Build resilient urban centres

Large cities are vulnerable to epidemics: viruses are more likely to be introduced and dense populations enable rapid amplification of transmission. Epidemics in urban settings are particularly disruptive. Building resilience to epidemic risks in large cities is essential for global health security.

Readiness plans

Reducing the risk of epidemics in urban centres can be achieved through increased readiness (e.g. development of urban readiness plans) and the development of risk assessment and intervention plans for transportation hubs.

Urbanization has led to rapid demographic growth in capital cities where the risk of YF urban outbreaks is very high. Some countries have already identified this risk of epidemics and have developed emergency management plans. These are led by specialized agencies (such as the Lagos State Emergency Management Agency[1]), with possible focus on high-risk infrastructures such as airports and other transportation hubs,[2] or health care centres.[1]

[1] https://www.facebook.com/permalink.php?story_fbid=488494674631290&id=325518144262278
[2] "Preparing and responding to a public health event: Montreal Airport", Public Health Agency of Canada, available from http://www.icao.int/Meetings/CAPSCA2015/Presentations/DAY%201/Session%204/02%20Capsca%202015%20Public%20health%20preparedness%20and%20planning.pdf

Large urban centres at risk for YF outbreaks or at potential for YF transmission should be prepared to respond to YF outbreaks and develop readiness plans focusing on rapid implementation of an emergency vaccination campaign and control of transmission in transportation hubs (bus and railway stations, airports, ports). These plans should identify key resources and a highly trained core team of health care professionals (public health officers, laboratory experts, patient care and vector control specialists) who will be prepared to manage the entire outbreak response – including rapid risk assessment – and to tap into appropriate networks of experts and resources (e.g. the ICG). Plans will detail coordination between agencies (roles and responsibilities, communication channels) in the preparedness phase (e.g. maintaining an appropriate pool of trained health care workers) as well as during the epidemic (e.g. leadership roles, decision-making, and engagement with partners).

Mass vaccination campaigns have proved to be particularly challenging in urban settings due to the size and logistic challenges of the operation, as well as the mobility of the population. Specific preparedness efforts are needed to ensure timely and rapid vaccination during urban outbreaks.

For Africa: A list of priority cities for readiness plans will be established. A first attempt to identify densely populated cities with low PI and increasing risk of importation or exportation (e.g. with harbours or other transportation hubs) is proposed: Nairobi, Mombasa, Kampala, Khartoum, Lagos, Abuja, Juba, Dar es Salaam, Brazzaville and Libreville.

Sustained vector surveillance and control programmes in cities

Aedes aegypti indices should be calculated regularly in cities at-risk or with potential for YF. This monitoring should be integrated into urban emergency planning and trigger activities based on the estimated level of risk. These measures should be part of broader arbovirus surveillance and readiness in countries at-risk for dengue, Zika, and chikungunya as well.

Vector control requires sustained efforts to maintain low mosquito density, particularly *Aedes* vectors which are well adapted to humans. Qualitative research should be used to understand what does and does not work for *Aedes* control. Strategies involving all parties practically and effectively need to be developed.

Strategic objective 3: Contain outbreaks rapidly

The risk of large urban YF outbreaks has increased due to a combination of factors including rampant informal urbanization. The fast pace at which African cities grow is challenging the capacity of health systems to provide adequate services such as timely epidemic detection and response and prevention of international spread. The recent Angolan outbreak illustrated the heavy demand on international resources and capacity imposed by responding to large YF urban outbreaks.

Outbreaks are unusual events that require additional resources and partners. Planning is essential for a successful response as well as a good coordination of partners.

Rapid containment of an outbreak is essential to prevent amplification into devastating epidemics. It is dependent on:

[1] https://www.health.ny.gov/environmental/emergency/

(i) early detection;
(ii) emergency vaccine stockpiles; and
(iii) rapid response.

Action 1: Early detection. Strengthen surveillance and laboratory capacity

As work proceeds to raise population immunity levels, outbreaks will continue to occur. Strengthened surveillance and improved laboratory capacity should be in place to detect outbreaks early and contain them rapidly. In addition, better surveillance and diagnostic capacity provides more information to permit assessment of the evolving risk as well as the impact of preventive and control measures.

In Africa, a network for detection and laboratory confirmation of YF cases in the WHO African Region was established in 2001, with 21 Member States currently participating. This has enabled surveillance objectives, case definitions, investigation and laboratory methods, and other tools to be standardized across the network and to use the same information flow. However, the laboratory capacity in some countries is still too low to ensure early detection of initial cases. **In LAC**, the regional network of laboratories is integrated with arbovirus surveillance (Red de Laboratorios de Dengue de las Américas).

Current challenges include:

- The suspect case definition (fever and jaundice) is sensitive but not very specific; from there very few suspected cases turn out to be true yellow fever cases (less than 2%). This is costly and might discourage the health workers.
- The first level of diagnostic, IgM detected in serum, is not specific enough to confirm a case:
    - The current test / assay used at national level (IgM detection) is based on in-house ELISA for IgM from US-CDC and Institut Pasteur Dakar, Senegal.
    - The IgM detection test is generally performed by the national laboratory (usually in the capital city) meaning that samples may need long transportation times thus affecting specimen quality and timely investigation. This causes delays, is cumbersome (cold chain, etc) and is associated with the risks of bad conservation.
    - For the diagnosis of cases in the *first* phase of disease, the IgM is often negative and therefore detection of YF genome would be the method of choice.
- Because of the lack of national laboratory capacity for confirmation, specimens that give a positive IgM result in any African country has to be shipped to the regional YF reference laboratory for confirmation (neutralization, PCR, etc.), which considerably delays the final diagnostic decision.
- The current laboratory quality control – quality assurance scheme is limited.
- Countries with no laboratories participating in the laboratory network have no recognized laboratory capacity
- Data management is compartmentalized: yellow fever case information is collected in three different databases (epidemiological, laboratory and reference laboratory) but are not linked to each other.

Recommended surveillance strategies

All high-risk countries should be part of the regional surveillance networks. The eight African countries considered at moderate risk should raise their detection and confirmation capacities. A sentinel surveillance approach is the most practical and efficient choice, limiting pressure on resources while achieving adequate capacity.

The countries in the "potential for YF transmission" group are not required to join the regional network but they should, as part of the country control plan, ensure that severe suspected cases (e.g. people with haemorrhagic symptoms) are detected and investigated for YF.

In all countries, the IDSR framework should be the foundation for YF surveillance. Means of optimizing YF detection and confirmation and integrating activities (training, sample transportation, laboratory confirmation, etc.) should be explored and defined in each country. Community-based surveillance through initiatives such as community risk management and early warning social networks should be promoted. YF surveillance and testing capacities need to be integrated with those of other systems, such as for other arboviruses (e.g. Zika and chikungunya), viral haemorrhagic fevers (e.g. Ebola) or other diseases for which stronger capacity was built over time (e.g. HIV).

Strengthening surveillance

To strengthen and extend surveillance, **two axes** will be developed in parallel:

1. **Strengthen rapid detection capacity**

Adaptation and strengthening of existing case based surveillance

Priorities include:

- Revision of regional surveillance guidelines including the revision of case definition: testing the usefulness and feasibility of additional symptoms or tests to improve the specificity of the suspected case definition.
- Revision of national YF surveillance guidelines taking into account local needs and differential diagnosis in areas with circulation of other arboviruses;
- Providing specific health worker training to improve differential diagnosis and the collection of vaccination information
- Design and use a regional database management structure to ensure that the epidemiological and laboratory information for each suspected case of YF is linked. Elements needed to achieve this include:
    - build an Information Technologies (IT) platform permitting the information to be entered and consulted;
    - the IT platform should allow the visualization of YF cases in space and time, and link the information with immunization activities;
    - train the various actors involved accordingly.

2. Increase diagnostic capacity

Regional and subregional laboratory confirmation capacity

In Africa, currently there is only one functional reference laboratory in the Institut Pasteur, Dakar. It is necessary to develop additional facilities in the region with genome detection (PCR), and serology (ELISA, PRNT to detect antibodies and neutralising antibodies for YF, respectively) capacity according to international standards. The region will develop a plan to progressively identify and support an increasing number of reference laboratories that will serve neighbouring countries.

Building national laboratory capacity

At the same time, all countries will be supported to increase their own capacity, in particular PCR. A specific issue needs to be addressed concerning sample transportation, particularly cross-border shipping of specimens. Standard Operating Procedures describing the flow of specimen and data must be established and/or enhanced (for the national and, more challenging, international level). It is critical to ensure that those laboratories have sufficient reagents and appropriately trained personnel.

External quality assessment (EQA)/quality control (QC)

Strengthening and expansion of the EQA programme for laboratories performing YF diagnostics (genome detection and serology) should be fully functional for both serology and genome detection. Laboratories need to be accredited and operationalized for standardized laboratory procedures and data management.

New methods to accelerate diagnostic

- Introducing bedside (point-of-care) laboratory techniques to test for other pathogens that cause symptoms and illness similar to YF and meet the same case definition (malaria, leptospirosis, hepatitis A, B, C, D, E).
- development of a robust and rapid diagnostic test for YF genome detection;
- development of new specimen sampling methods (serum, saliva, urine), sample stabilization and transport;
- development of additional serology tests for differentiating between cross-reacting viruses;

Action 2: Ensure emergency stockpile vaccines

Emergency stockpiles ensure timely and equitable access to vaccines during emergencies. It is a critical element to contain outbreaks. In the VIS approved by the Gavi Board, the emergency stockpile estimation was a reducing number of doses over the years from 6 million to a minimum level of 2 million doses in 2022. This estimation was made under the assumption that after mass preventive vaccination campaigns in the 12 highest-risk countries and the decreasing number of YF outbreaks in the period 2011–2015, the need for a large stockpile would decline.

After the large urban outbreak in Luanda and the risk of spread, the ICG members met in July 2016 to review the vaccine needs for the emergency stockpile and discuss a forecast for the next 10 years. Taking in consideration the rapid change in YF the epidemiology in Africa and Latin America, and the current situation in Angola and DRC, the option of increasing the size of the stockpile has been considered. Maintaining a large stockpile was not considered as a the best investment given the low frequency of large outbreaks, therefore the ICG decided to retain the emergency stockpile at the level of 6 million doses. The main difference with the previous stockpiles is in the availability of vaccine: the new stockpile model is to maintain a stock of 6 million doses at any time over a given year – a **Revolving Emergency Stockpile.** The stockpile will be immediately replenished after its use to respond to an outbreak. This strategy will allow the ICG to respond to large urban or long-lasting outbreaks. Vaccine manufacturers should always have a constant level of vaccine in stock ready for shipment. UNICEF Supply Division (SD) will closely work with the vaccine manufacturers to ensure and monitor the fact that 6 million doses of vaccine are always in stock.

The stockpile of 6 million doses will be part of the annual demand for preventive vaccination campaigns; therefore, UNICEF SD and vaccine manufacturers will rotate the stocks between the emergency, the vaccine for preventive campaigns and routine EPI stocks in order to ensure that there is always a minimum of 6 million doses ready for in shipment within 48 hours. With this revolving concept, there will be no wastage due to expiration of vaccine since the vaccine will be used for preventive campaigns.

If a larger outbreak occurs and the demand exceeds 6 million doses, UNICEF and WHO will work together with the vaccine manufactures to reprioritize the vaccine still under production in order to give primacy to the replenishment of the stockpile to return as soon as possible to the level of 6 million doses. To rapidly replenish the stock during long emergencies, of over 3 months, WHO and UNICEF SD will also work with the vaccine manufacturers to optimize/prioritize vaccine supply in 20 dose vials presentation, which could later be used in mass preventive campaigns.

The ICG also decided to continue reviewing the stockpile forecast every year since it is expected that in the context of the EYE strategy the risk of large epidemics will be eliminated, and therefore the need for vaccine for emergency response will be reduced to a minimum stock.

Short- and long-term options to cope with a surge in emergency demand

The 6 million doses in the emergency stockpile should be enough to respond to most urban epidemics in the current endemic countries in Africa and LAC. In case of a larger unexpected outbreak, including in India or China, there is a need for alternatives to enable a rapid increase in production or shorten the production and release lead times.

In the short term, EYE partners will explore with vaccine manufacturers and national regulatory authorities ways of optimizing bulk production capacity, reviewing potency and stability requirements, and increasing the shelf-life of the bulk and the finished product. These will give the manufacturers greater flexibility to stock bulks for long periods, and thus to quickly fill/finish production in case of emergencies and/or vaccine shortages. Extending the shelf-life of the final product will provide manufacturers with more flexibility to rotate the stock and countries with more flexibility in using the vaccine.

In the mid to long term, WHO will also work with vaccine manufacturers to explore and encourage novel vaccine production technologies, such as YF vaccine production based cell-culture or a DNA vaccine (Table 13).

Table 13. Short- and long-term options to cope with a surge in emergency demand

Time frame	Strategy	Advantage
Short term	Expand the shelf-life time of the 5, 10 doses of YF vaccine from 3 years to 5 years	This will give greater flexibility in using stockpiles and will reduce the outdating of still usable YF vaccine
	Expand the shelf-life time of YF bulk material	This will give manufacturers greater flexibility to rapidly fill/finish vaccine in case of unexpected emergencies or long outbreaks
	Long-term storage (1–2 years) of unlabelled or naked vaccine vials at -20°C for immediate approval in case of shortage	This will give manufacturers greater flexibility in preparing vaccine in case of emergencies and vaccine shortage
	Prioritizing 20-dose vials, which might be more suited to mass vaccination campaigns than 5–10-dose vials	This will facilitate rapid replenishment of the stockpile by enabling easy duplication of production capacity
Medium term	Define an upper limit of potency per YF vaccine dose	This will improve the homogeneity of vaccine between the different manufacturers
Long term	Review and revise the YF manufacturing process regarding thermal stability testing (14 days, 37°C ► 7 days, 37°C)	This will allow optimization of vaccine preparation
	Revise the testing of the YF working seed in monkeys by replacement with a molecular analysis.	This will replace animal trials and reduce lead time of QC and costs

Action 3: Rapid outbreak response

An effective yellow fever outbreak response revolves around rapid detection of cases, reactive vaccination, good case management, vector control and community mobilization.

Strengthened outbreak response capacity can be achieved through:

1. streamlined YF investigation with an emphasis on assessing the risk of spread in relation to transportation hubs and population movements, PI and vector density. Streamlined YF investigations should include the following:
   - documentation of the geographical extent of the outbreak (transportation hubs, population movements, markets);
   - identification of where and how the epidemic is spreading;
   - systematic, rapid entomological investigations (vector density):
     - it is critical to understand the possible spread of the YF virus (as Aedes spp. only travel 100–1000m).

2. rapid laboratory confirmation and adaptation of the case definitions if needed;
3. control interventions
    - efficient reactive vaccination campaigns (achieving high coverage and quality);
    - good case management and increased access to health care centres in order to reduce mortality and improve diagnosis;
    - vector control:
        - elimination of all potential breeding sites or control
            - cleaning campaigns (tyres, empty cans, etc.)
            - covering of reservoirs
            - larvicide
        - spraying to kill adult mosquitoes during an epidemic
            - fogging is most effective when conducted in the hours around dawn and dusk, when mosquito activity is most intense.
        - capture" of the eggs of survivors
            - Ovitrap

4. Partnership and coordination
    - Involvement of multidisciplinary teams to conduct investigation and response interventions (e.g., with the support of the regional GOARN network, development partners, other UN agencies).

Fractional doses

In emergencies, when vaccine supplies are limited, use of a "fractional dose" – one fifth of the normal dose – may be considered. In October 2016, the evidence-base for the use of this strategy will be submitted to the Strategic Advisory Group of Experts (SAGE) for validation. In addition, the evaluation of its use during the current DRC outbreak will guide further practice, and follow-up studies (such as immunogenicity studies) will also provide further evidence.

Part 5: Keys to success

1. Availability of accessible, affordable vaccines and a sustained vaccine market

Since the inception of the YF investment case supported by Gavi, YF vaccine supply has improved significantly. In 2001, only two manufacturers were producing WHO-prequalified YF vaccine. This has now increased to four manufacturers: Sanofi Pasteur (France), Institut Pasteur de Dakar (Senegal), Bio-Manguinhos (Brazil), and Chumakov Institute (Russian Federation). Vaccine production capacity has quadrupled from 20 million to 80 million doses annually.

However, vaccine supply has remained one of the major obstacles to implementing mass vaccination campaigns, especially in countries with large targeted populations. Vaccine supplies available for preventive campaigns have been limited to 15 million people per year, and therefore some countries have had to phase their campaigns over two or three years, slowing down the risk reduction strategy.

Vaccine supply has been continually challenged, mainly by: (i) a sharp increase in demand after the YF investment case; (ii) regulatory and prequalification suspensions; and (iii) production problems, leading to a situation in which supply has been below demand.

Global demand for YF vaccines has increased from approximately 20 million doses in 2001 to 90 million doses on average from 2012 onwards. This growth is mainly due to the demand generated by the resurgence of YF epidemics in Africa and the support provided by Gavi to endemic countries to access the vaccine.

The change in risk shows that the need for YF vaccine has increased. However, the EYE will be successful only if demand and supply are aligned to allow a timely and effective risk reduction strategy. This will require the sustained engagement of the various stakeholders as well as robust mechanisms for need forecasting and market shaping.

Production capacity

The market for YF vaccine is not very attractive for manufacturers: it is small compared with that for other vaccines and the profit margin is low, providing little incentive for manufacturers to produce it. The vaccine is only used in endemic countries and only one dose is needed. The demand for YF vaccine is also unpredictable and very much driven by outbreaks, another disincentive for vaccine manufacturers.

It is not expected that any new manufacturers will begin production in 2017, although production by existing suppliers is expected to increase.

In 2017, global production capacity is expected to rise to between 105 and 132 million doses. There is considerable uncertainty around these figures. However, a rise in capacity is linked to one of the manufacturers being able to increase production through contracting out filling/freeze-drying capacity. There are also uncertainties around yields.

Reliable production

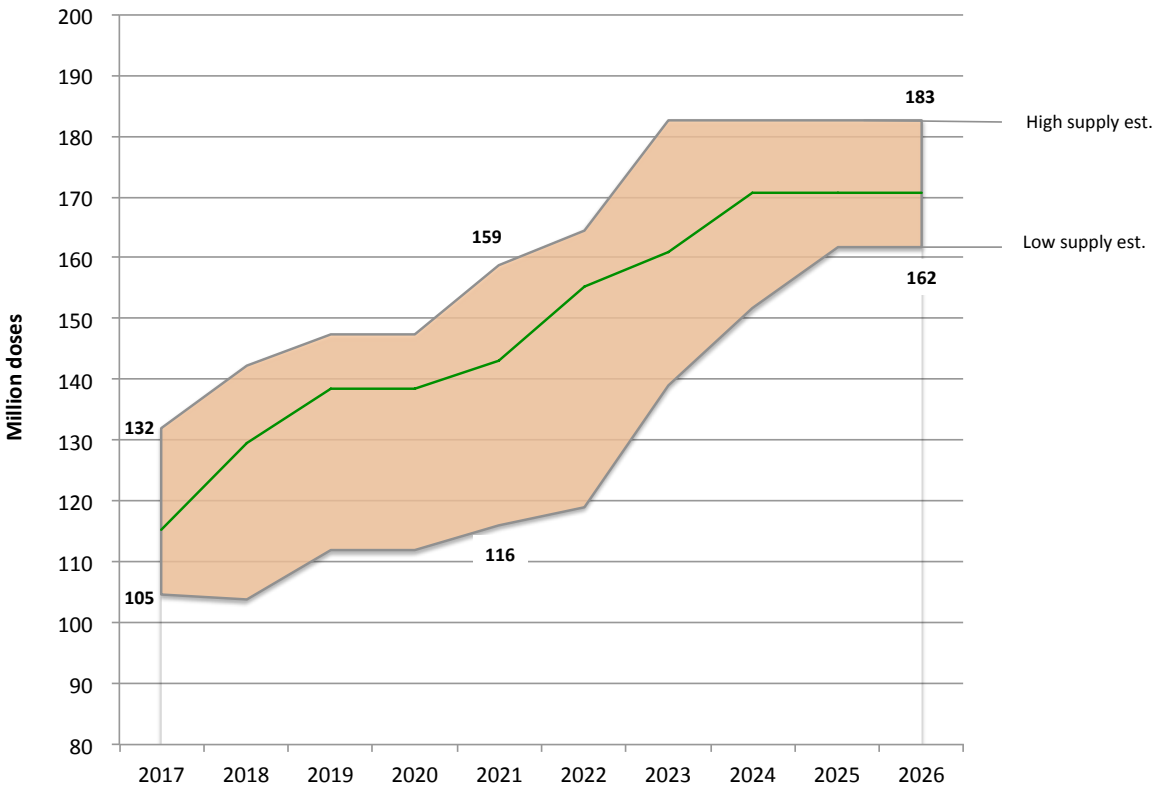
Over the past five years, actual supply has been significantly lower than theoretical production capacity. This was due to quality issues for some manufacturers and/or upgrading work on the production units. As a result, supply was 10–20% below demand. In 2017, reliability is expected to improve because all manufacturers have made investments in production equipment and facilities between 2012 and 2016. However, the YF vaccine production process remains the same and will continue to be technically challenging and prone to unexpected quality or yield issues. It will also remain relatively inflexible to increased demand.

Global supply outlook 2017–2026

The global supply of YF vaccines is expected to increase to between 105 and 132 million doses in 2017, to between 116 and 159 million doses in 2021, and to between 162 and 183 million doses in 2026 (Figure 6).

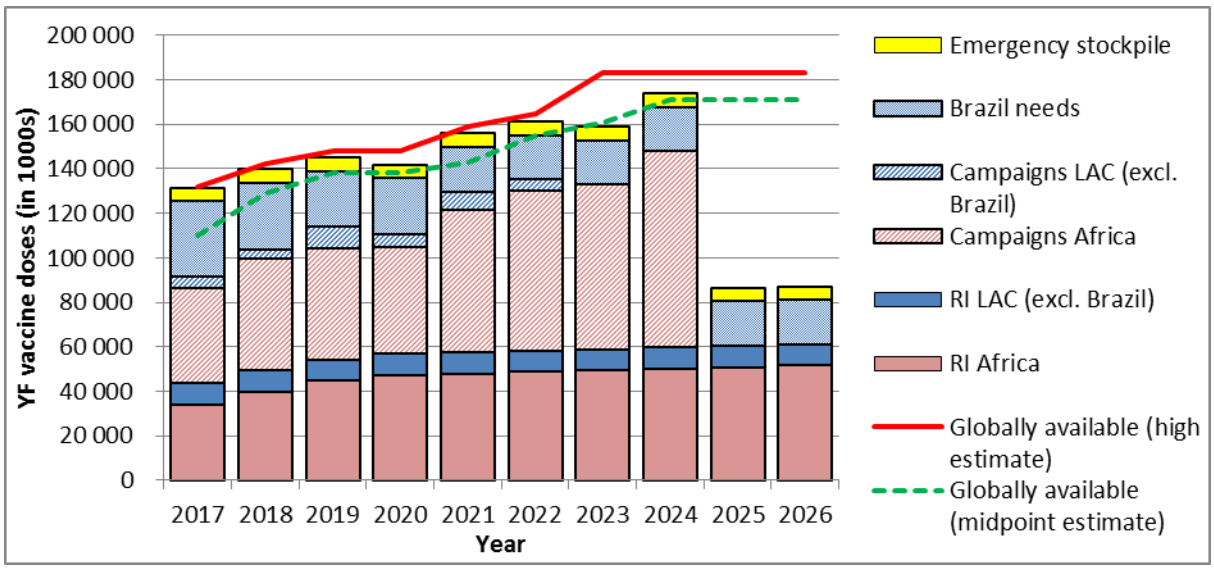
The increased capacity expected during 2017–2020 should be achieved by prioritizing and optimizing YF vaccine production and contracting manufacturer operations for filling and freeze-drying. New production capacity is mainly expected after 2021, when new facilities in two manufacturers will start production.

Figure 6. Estimated global yellow fever vaccine supply (high to low risk-adjusted estimates), 2017-2026 (Source: Gavi. Supply and procurement roadmap Yellow fever vaccine, update August 2016)



When comparing the planned production with current estimates for global demand as presented in this document, the demand fits into the high estimates of the projections (Figure 7). However, the current picture does not include catch-up campaigns for Africa and does not take into account changing risk, as well as production issues, a problem that, as noted above, has occurred regularly in the last five years.

Figure 7. Global YF vaccine demand, by type, 2017–2026



2. Political commitment and sustainable national and regional YF control strategies

In countries at greatest risk of YF epidemics, it is essential that the leadership is committed to preventing epidemics and embraces the need to establish new synergies by providing local expertise and resources to implement EYE. Campaigns and strategies can only work if country ownership is genuine. Where public health strategies, including vaccination, are successful, it is primarily because local people have worked hard to improve the health of their communities and are committed to improving the nation's health. EYE will only achieve its goal of eliminating epidemics if it is the people in affected countries who "lead the charge" against YF epidemics. EYE is a global strategy with regional and country representation.

To achieve political commitment and country buy-in, the EYE strategy must include raising awareness at all levels, from the community to national and international leaders and partners. Understanding of the potentially devastating nature of YF epidemics should increase the eagerness of countries and communities to adhere to the opportunity that EYE offers to prevent this once and for all.

At regional level, the political (regional committee) and technical (TAG) bodies will be requested to endorse the strategies and way forward.

3. Governance and partnerships

The development and the implementation of a YF long-term strategy require the coordination of a number of partners and countries as well as a transparent and effective mechanism for decision-making on strategic tactical and operational issues. This mechanism should be flexible enough to adapt to the evolution of the risk, whether it increases due to external factors such as urbanization, or decreases due to factors such as successful implementation of control interventions.

Based on the existing mechanism in place, such as the YF partnership and the lessons learnt from the past in YF and other disease programmes, EYE:

- Will be led by a **steering committee** composed of a core group and members. The core group of three multilateral stakeholders – UNICEF, WHO and Gavi – guides the overall effort and ensures that members who play a critical role in the effort are engaged and represented. The members are institutions, partner agencies or countries that play a significant role in the implementation of the strategy. The initial list of members will be based on the existing members of the YF partnership (http://www.who.int/csr/disease/yellowfev/yfvaccine/en/), but will be open to new members as well. The steering committee will be broad enough to provide expertise relevant to the many areas involved and flexible enough to integrate new partners as needed (e.g. the African Union and private sector partners from the extractive, construction and forestry industries, and the transportation sector).
- The EYE **secretariat** based at WHO will support the steering committee and will propose terms of reference and governance principles for the steering committee (appointment of the chair, criteria for membership, frequency of meetings, relationship between steering committee and working groups and so on).
- In addition to the steering committee, **working groups** will be established as resource groups to address issues within a particular area and to mobilize external expertise for answering specific questions. The working groups will be defined by the steering committee at the inception phase of the strategy. Members of the steering committee are also expected to contribute to the working groups. The working groups will report to the steering committee on a regular basis. There will two types of working groups:

  (i) **technical working groups** addressing technical and tactical issues in specific areas (e.g. laboratory and surveillance, vaccine market shaping, vector control and so on); and

  (ii) **regional/subregional working groups** addressing operational issues in implementation of the strategy. Regional immunization TAGs and countries that are to be targeted for the next round of vaccinations should also be included in working groups.

The steering committee will:

- support the design and implementation of the global strategy;
- provide a forum for technical exchange, coordination, and cooperation on YF-related activities;
- coordinate the implementation of EYE strategic approaches and activities;
- continuously monitor and evaluate implementation;
- disseminate information about YF prevention and control;
- encourage continuous engagement of partners, donors and countries;
- support the development of a research agenda taking into account the public health needs.

The secretariat will:

- run stakeholder analyses and maintain a stakeholders list;
- organize meetings of the EYE steering committee;
- organize regular working groups on a planned and emergency basis;
- monitor and evaluate EYE implementation;
- engage with appropriate networks of experts, agencies and sectors, including the private sector and transportation and border control/customs agencies.;
- review EYE progress towards targets and assess public health impact;
- advocate at high level;

4. Acceleration of research and development for new tools and better practices

A broad global coalition of experts with stakeholders, including public health agencies (particularly those in affected countries), academia, the biotech sector, industry, regulators, funding agencies and ethics committees will be formed as a specific working group under the umbrella of the governance body. The group will identify public health research priorities and activities, and ensure that the identified priorities and activities are considered within the WHO R&D Blueprint for Action to Prevent Epidemics.

Specific steps:

- assess the current public health measures for YF prevention and control, and identify the current challenges and knowledge gaps;
- review gaps in key activities at all levels (global, regional and country), minimize unhelpful overlaps, and stimulate priority activities to maintain momentum;
- organize expert consultations to prioritize R&D options to guide control of and response to YF outbreaks.

Current priority research areas include vaccine, vector control, diagnostic and case management issues.

Part 6: Monitoring and evaluation

The EYE governance body will be in charge of monitoring the implementation, performance and impact of EYE activities. The secretariat will liaise with the Decade of Vaccine/GVAP working groups.

Key milestones

By the end of 2017:

- EYE governance body is fully operational
- The implementation plan including indicators and deliverable is ready
- At risk countries are engaged in the EYE implementation

By the end of 2018:

- Three African subregional reference laboratories are fully functional with confirmation

By the end of 2019:

- All African high-risk countries have introduced the YF vaccine into routine immunization;

By the end of 2020:

- Six African subregional reference laboratories are fully functional and an EQA/QC is fully functional for both serology and molecular diagnostic procedures.

By the end of 2021:

- All LAC countries have completed mass immunization campaigns.
- Campaigns have been completed for Nigeria, Ghana and Sudan.

By the end of 2022:

- Seven of the 13 of high-risk countries of Africa have completed national preventive mass vaccination campaigns.

By the end of 2025:

- All African high-risk countries have diagnostic capacity to confirm YF.

By the end of 2026:

- All high-risk countries have completed national preventive mass vaccination campaigns.

Key indicators

The following indicators will be measured on a regular basis:

Implementation and performance

- **Preventive mass campaigns**:
  - number of preventive mass campaigns conducted;
  - number of persons vaccinated;
  - district-level coverage;
  - vaccine wastage rate.
- **Routine immunization**:
  - number of persons vaccinated;
  - proportion of districts with coverage level >80%;
  - difference between YF and measles coverage (WUENIC);
  - number of vaccine stock-outs.
- **Laboratory capacity:**
  - average time for a suspected case to be confirmed (date of confirmation – date of sample taken).
- **Vaccine supply:**
  - ratio annual YF vaccine production/annual projected capacity
- **Readiness:**
  - number of cities that have an Urban Readiness Plans in place, including response to the YF risk.
- **Outbreak response:**
  - number of days in each year during which the emergency stockpile level is at level zero.

Impact

- number of outbreaks, size and spread;
- number of urban outbreaks;
- number of internationally imported cases.

Regular updates

Assessing risk and setting priorities

Risk and priorities for implementation of the strategy will be reviewed annually: it is expected that risk of YF epidemics will evolve throughout the 10-year implementation of EYE as a result of a combination of factors reducing risk, such as increased PI, and factors increasing risk, such as major population movements, state collapse, or climate change. As risk changes, immunization activity priorities will need to be adjusted accordingly.

Learning as we go

Experience gained from EYE's development, implementation, monitoring and evaluation at all levels should be recorded, analysed, and made available on a regular basis, to **build knowledge** and serve as a source of inspiration and resources for other programmes and initiatives.