Yellow fever vaccination: The potential of dose-sparing to increase vaccine supply and availability.

April 18, 2013

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Acknowledgments

The authors would like to thank the members of PATH's Vaccine Technologies Group (Birute Curran, Emily Griswold, Erica Jacoby, Courtney Jarrahian, Laura Saganic, and Darin Zehrung) for their comments and guidance during the writing of this report and for reviewing the completed document.

The authors are also indebted to the various company representatives and other key opinion leaders listed at the end of the report for very generously providing information for the report, for reviewing drafts of the report in great detail, and for sharing their data and expertise.

Executive summary

The World Health Organization (WHO) estimates that each year approximately 200,000 people are affected by yellow fever (YF) worldwide and approximately 30,000 die from the disease.[1] Although there is no cure for YF, it can be effectively prevented by one dose of live attenuated YF vaccine.

Over the past 15 years, there have been great successes in controlling the disease by preventive and outbreak-control immunization campaigns, and the introduction of YF vaccination into routine vaccination schedules in at-risk countries. There have, however, also been acute and chronic shortages of YF vaccine, which have delayed or prevented immunization efforts in some regions.

The purpose of this report is to evaluate whether and to what extent YF vaccine supply and demand imbalances could be addressed by delivering reduced doses of YF vaccine via the intradermal (ID) route.

Methodology

The report uses a review of the peer-reviewed and gray literature and also interviews with key opinion leaders to analyze the context and likely impact of a dose-sparing strategy, and to identify the programmatic issues associated with implementing such a strategy, such as changing the route of administration from subcutaneous (SC) to ID delivery. Drafts of this report have been reviewed by a panel of experts with interest and expertise in this area.

Background

Prior to commencing the research relevant to this report, the authors considered YF to be a strong candidate for an ID dose-sparing approach because:

- Chronic and acute supply shortages have limited the use of YF vaccine in the past; examples include:
  - In 2009 the demand for YF vaccine was 105 million (M) but only 75 M doses were produced.
  - In the same year, the Pan American Health Organization (PAHO) requested 20 M doses from manufacturers, who offered 15 M doses but ultimately provided only 7.5 M to PAHO.
  - Planned campaigns have been delayed or phased to match resources including the availability of YF vaccine. In 2010, only one preventive campaign was carried out in West Africa “owing to problems with the availability of vaccine.”
- In 2012, demand for YF vaccine continued to exceed supply, and although there was likely to be sufficient vaccine for the emergency outbreak stockpile and for routine immunization, there was insufficient vaccine for all planned preventive campaigns, with the result that immunization campaigns would have to be delayed.
- The demand for YF vaccine is likely to continue to increase as preventive campaigns are implemented in Africa, particularly in Nigeria, and as countries at lower risk of YF introduce YF preventive vaccination campaigns and routine childhood immunization against YF.
- Recent clinical evidence from a high-income country suggests that a reduced volume of YF vaccine given by the ID route could be non-inferior to the standard SC route and dose in terms of the immune response generated.
- It is possible, therefore, that delivery of reduced volume doses of YF vaccine could increase the availability of this supply-constrained vaccine, particularly when used in preventive and emergency campaigns.

[1] The executive summary does not contain references, but any facts cited are referenced in the main text of the report.

In 2012, the supply of YF vaccine is still constrained; there are only four WHO prequalified (PQ) manufacturers of the vaccine. The production process is relatively inflexible and long lead times are needed to respond to changes in demand. Production issues experienced by several manufacturers mean that supply of YF vaccine has been lower than the demand.

A relatively limited and often uncertain market for YF vaccine means that vaccine manufacturers might be unwilling and/or unlikely to make significant investments to increase production capacity in the short to medium term. Therefore, if the availability of YF vaccine is to be improved in the next decade or so, changes in the way that YF vaccine is used in a population or administered in the clinic might be needed. The administration of reduced volumes of YF vaccine per dose, possibly using the ID route, was identified as one way to have an impact on vaccine availability and also cost.

Main findings

Dose-sparing by the delivery of a reduced volume dose of YF vaccine (0.1 ml per dose, compared with 0.5-ml per standard dose), would be expected to increase the number of doses in current presentations of YF vaccine approximately five-fold. If this was realized, supplies from the existing manufacturing capacity could be "stretched."

Because YF vaccine for use in endemic areas is usually supplied in multi-dose vials (typically 5- and 10-doses per vial), dose-sparing by administering fractional doses is likely to be most appropriate for those immunization settings where large numbers of vaccinations are given per session. Campaigns in which hundreds of individuals are immunized per day by a single immunization team would perhaps benefit the most.

Within routine YF immunization settings, with low numbers of people to be vaccinated per immunization session, a reduced-volume dose-sparing approach would most likely lead to large volumes of unused, reconstituted vaccine being discarded at the end of the immunization session.

The Mantoux technique is currently used to deliver ID injection of vaccines. This technique is generally regarded as being unsuitable for use in mass immunization campaigns. If ID delivery of reduced doses of YF vaccine is to be used in this setting, then devices designed to facilitate ID delivery of vaccines are likely to be needed. Devices being developed to aid ID delivery include adapters fitted to needles to control the depth and angle of ID injections, disposable-syringe jet injectors (DSJIs), intradermal "mini" needles, and hollow microneedles.

To evaluate the potential impact of using reduced-volume dose-sparing, the authors conducted preliminary modelling using a forecast of future demand for YF vaccine provided by the WHO. Using this model, the authors determined that the introduction of reduced-volume dose-sparing in all preventive immunization campaigns (but not routine immunization or outbreak-control campaigns), in Africa, Brazil, and South America could save up to a maximum of 24 to 42 M 0.5-ml doses of YF vaccine each year between 2011 and 2022, with a cumulative savings of approximately 420 M 0.5-ml doses. This would bring the estimated global demand for YF vaccine within the expected level of supply.

In addition to increasing the amount of YF vaccine available, the results of the preliminary modelling in this report suggest that dose-sparing by reduced volume could reduce the cost of "vaccine plus delivery device" for each YF vaccination by approximately 67 percent, even if novel devices to facilitate ID delivery, such as DSJIs, are used.

Programmatic issues

The authors identified a number of programmatic issues that would need to be addressed before the ID delivery of reduced-doses of YF vaccine could be introduced, including:

- Clinical evidence demonstrating non-inferiority of the reduced dose compared with standard dose in terms of immunogenicity and safety will be needed. This is likely to be required for each of the manufactured YF vaccines of interest.
- Clinical trials to determine whether a change of route of administration to ID is required to achieve dose-sparing. It is possible that, because YF vaccines are generally more potent than the minimum level recommended by the WHO, the SC route could still be used but with a lower dose; this would simplify introduction of dose-sparing and might also reduce some of the possible safety issues associated with a change of route.
- Data from a clinical trial published while this report was being finalized show that reduced doses of YF vaccine delivered via the standard SC route can induce satisfactory immune responses.
- The safety of a reduced dose and/or change of route would need to be shown. There might be increased reactogenicity with an ID vaccine and/or changes in live vaccine virus behavior if the virus targets different antigen-presenting cells. However, it is difficult to address safety concerns in small clinical trials and further discussion of clinical trial design will be required.
- A regulatory strategy to support reduced-volume ID delivery would need to be developed. Changing the dose and/or route would ideally be accompanied by a label change for the new dose, route, and ID device (if required). A change to a "dual label" to support delivery of reduced-volume doses in campaign settings and full-volume doses in routine immunization is an option that is both feasible and could be attractive. Further discussions with manufacturers and regulatory agencies will be required to elaborate on this.

Conclusion

Following a comprehensive review of the evidence, the authors believe that a reduced-volume dose-sparing strategy for YF vaccine:

- Is a pragmatic, relatively low-risk strategy for increasing YF vaccine supply, possibly without the need for reformulation of vaccine or large investment in vaccine manufacturing capacity.
- Could be implemented in the short to medium term, as soon as the clinical evidence for non-inferiority, safety, and dose levels has been generated.
- Could potentially be used in all settings in which YF vaccine is used, but is likely to be of most benefit in settings where many individuals are vaccinated in a single session, thereby reducing wastage of unused, reconstituted vaccine (i.e., preventive and mass campaigns and high-throughput routine childhood vaccination).
- Could be particularly useful in situations when there might be an acute shortage of YF vaccine.
- Has the potential to increase access to vaccines (the equivalent of 24 to 42 M 0.5-ml doses could be saved per year during 2011 to 2022), and reduce vaccine purchase costs by up to approximately 67 percent per individual, according to preliminary estimates in this report.
- Could benefit:
    - People of all ages at risk of YF infection, who currently do not have access to vaccination because of supply constraints.
    - Vaccine manufacturers interested in meeting demand for YF vaccine without having to invest in increased capacity or reformulation of YF vaccine.
    - Vaccine manufacturers with limited seed stocks.
    - Vaccine purchasers, because vaccine purchase costs could be reduced.
    - Vaccination planners, because acute supply constraints could be eased.

The authors hope that this report will stimulate interest among a wider group of key stakeholders involved with YF vaccination.

Contents

Abbreviations and acronyms

AD ..... autodisable
AE ..... adverse event
BCG ..... Bacille Calmette Guerin
CAR ..... Central African Republic
CDC ..... Centers for Disease Control and Prevention (USA)
CERF ..... United Nations Central Emergency Response Fund
DSJI ..... disposable syringe jet injector (needle-free)
DTP ..... diphtheria, tetanus, and pertussis (vaccine)
ECHO ..... European Commission Humanitarian Aid Office
EPI ..... Expanded Programme on Immunization
GAR ..... Global Alert and Response
GMT ..... geometric mean titer
HepB ..... hepatitis B (vaccine)
Hib ..... *Haemophilus influenzae* b (vaccine)
HIC ..... high-income country
ID ..... intradermal(ly)
IFFIm ..... International Finance Facility for Immunisation
IPV ..... inactivated poliovirus vaccine
IU ..... international unit
JE ..... Japanese encephalitis
KOL ..... key opinion leader
LMICs ..... low- and middle-income countries
LNI ..... log neutralization index
M ..... million
MCV ..... measles-containing vaccine
MLD_{50} ..... 50-percent mouse lethal dose
MMR ..... measles, mumps, and rubella vaccine
MSF ..... Médicins Sans Frontières
NHP ..... nonhuman primate
N&S ..... needle and syringe
N ..... population size
n ..... sample size
PAHO ..... Pan-American Health Organization
PATH ..... Program for Appropriate Technology in Health

PFU ..... plaque-forming units
PQ ..... prequalified (by WHO)
PRNT ..... plaque-reduction neutralization test
RBV ..... ribavirin
RCT ..... randomized controlled trial
SAE ..... serious adverse event
SAGE ..... Strategic Advisory Group of Experts (WHO)
SC ..... subcutaneous(ly)
SPF ..... specific-pathogen free
VDTG ..... Vaccine Delivery Technology Group (at PATH)
WHO ..... World Health Organization
YF ..... yellow fever
YFI ..... Yellow Fever Initiative
YFV ..... yellow fever virus

1. Introduction

1.1. Project background

One of the objectives for PATH's Vaccine Delivery Technologies Group (VDTG) is the completion of a "report on intradermal (ID) delivery of reduced doses of vaccines using disposable syringe jet injectors (DSJI), from the supply, demand, and manufacturing perspectives, highlighting key programmatic issues." Yellow fever (YF) vaccine was selected as a model vaccine for this study. An earlier report focussed on ID delivery of inactivated poliovirus vaccine.[2]

Concurrently, there has been growing interest from at least one manufacturer of YF vaccine and one vaccine-delivery device manufacturer to test clinically the ID delivery of YF vaccines, especially in low- and middle-income countries (LMICs). This interest partly followed on from the publication of two reports of ID delivery on YF vaccine in travel clinics in a high-income country (HIC; Roukens et al., 2008; Roukens et al., 2009), which suggested that reduced-volume doses of YF vaccine given by ID delivery might ease some supply issues and reduce vaccine costs for the end-user/purchaser.

The purpose of this report, therefore, is to analyze in more detail whether or not ID delivery of reduced-volume doses of YF vaccines could play a role in addressing supply/demand imbalances. The report also aims to inform the planning and design of clinical trial programs to evaluate the potential of ID delivery of YF vaccine to generate useful data for the international public health community.

1.2. Intradermal delivery of vaccines and aim of this report

Delivering vaccines by the ID route can be more immunologically efficient than injection into muscle or subcutaneous (SC) tissue, for some but not all vaccines (reviewed in PATH 2009; Hickling et al., 2011). For this reason, the use of the ID route has been suggested as one way to reduce the amounts of vaccine antigen required to induce protection. This is commonly known as dose-sparing, and is generally achieved by delivery of smaller volumes of vaccine (also known as fractional doses). Typically the volumes of liquid vaccine are 20 percent, or sometimes 10 percent, of the standard dose and are administered by ID delivery. Dose-sparing has been demonstrated best with inactivated rabies, inactivated poliovirus, and influenza vaccines (PATH 2009; Hickling et al., 2011).

The aim of this report is to assess whether the approach of ID delivery could play a role in improving the availability of YF vaccines.

The report aims to:

- Briefly review the YF virus and global burden of disease caused by YF virus.
- Review the four settings in which YF vaccine is used: routine childhood vaccination, preventive vaccination campaigns, outbreak response, and travel vaccination.
- Assess the current and near-future situations regarding need, demand, and supply of YF vaccines, using nonconfidential information.
- Review the possible short-to-medium and long-term strategies for addressing supply–demand imbalances of YF vaccine, including their probability and impact on different market clusters.

[2] http://www.path.org/publications/files/TS_IPV_econ_analysis.pdf

- Evaluate whether dose-sparing by use of reduced volumes of reconstituted YF vaccine, which might be delivered intradermally, represents a useful strategy to improve access to YF vaccines, including:
    - A review of the clinical evidence for this approach.
    - A review of settings in which a reduced-volume dose-sparing strategy would be most useful.
    - A preliminary assessment, based on data from the World Health Organization's (WHO) forecasting of YF vaccine demand, of the potential impact of dose-sparing on the availability of YF vaccine, and possible savings in vaccine purchase costs.
    - Modeling of some of the incremental costs associated with the use of various vaccine-delivery devices (needle and syringe [N&S] Mantoux, DSJIs, and syringe-mounted microneedle array) that might be required if reduced-volume immunization with YF vaccine necessitated a change to the ID injection.
    - A review of some of the programmatic issues involved in implementation of dose-sparing for YF vaccine, including regulatory issues.
    - An outline for the development of a clinical evidence base to establish whether a reduced-volume dose can be non-inferior in terms of immunogenicity and adverse events, if the vaccine needs to be delivered by the ID route, with what delivery devices, and which sub-groups of vaccinees might benefit.

2. Background: yellow fever virus, disease and global burden

Yellow fever virus (YFV) is a positive-strand ribonucleic acid (RNA) flavivirus (Mutebi and Barrett, 2002). The transmission cycles of the virus are complex, can be seasonal (for example due to rainfall patterns and density of vectors), and can involve nonhuman primates (NHPs) and specific species of mosquito vectors, which either live in forests, jungles ("jungle cycle"), savannahs ("intermediate cycle"), or urban areas ("urban cycle"; WHO UNICEF, 2010).

Vectors of the jungle cycle include *Aedes africanus* (in Africa) and *Haemogogus* and *Sebethese* species (in South America). There are several mosquito species involved in the African intermediate cycle (Mutebi and Barrett, 2002). In urban settings, urban-dwelling mosquitoes (such as *Aedes aegypti*) can maintain human-to-human transmission and cause "the most deadly form of YF, potentially involving thousands of human cases" (Mutebi and Barrett, 2002).

2.1. Burden of YF disease and major threats

WHO estimates that each year approximately 200,000 people are affected by symptomatic YF disease and approximately 30,000 people die (WHO UNICEF, 2010). Under International Health Regulations (WHO, 2008f), there is mandatory reporting (within 24 hours) of any suspected case of YF, with the expectation of full follow-up (PAHO, 2005).

The true rates of YFV transmission, YF disease, and case fatality are unknown, due to inherent and practical problems with surveillance of this complex disease, which is often asymptomatic or misdiagnosed (Staples et al., 2010), leading to underreporting of cases. It has been suggested that the true incidence of YF infection in Africa might be 10- to 50-fold higher than reported (WHO, 2008a). The estimate of 200,000 cases and 30,000 deaths per year is based on a "static model" that uses data from a serological study conducted in Nigeria in the 1950s to 1970s. The WHO Quantitative Immunization and Vaccines Related Research (QUIVER) advisory committee recently suggested that a working group should be established to estimate better the burden of YF disease (WHO, 2012).

At particular risk of YF epidemics are densely populated cities, which provide environmental conditions for the larvae development of the urban vector of YF, *Ae. aegypti* (WHO UNICEF, 2010). The GAVI Alliance (GAVI) considers the major threats to be "large uncontrollable" urban outbreaks, particularly in 12 GAVI-eligible African countries (GAVI, 2008).

2.2. Geographic areas in which humans are at-risk of exposure to YFV

Most human YF cases occur in the "YF belt" from 15° North to 10° South (Huhn et al., 2006). In these endemic areas, there are intermittent epidemics of YF, including periodic urban epidemics in sub-Saharan Africa and sporadic outbreaks in South America (Staples et al., 2010).

The "at risk" status of countries has been defined by the WHO as "areas where YF has been reported currently or in the past, plus areas where vectors and animal reservoirs exist" (Staples et al., 2010). In 2011, an expert group published its four-level classification of risk of YF by geographic areas as (Jentes et al., 2011):

- Endemic (with a high risk for infection).
- Transitional (with a moderate to high risk for infection).
- Low potential for exposure (with a low risk for infection).
- No risk (with no risk for infection).

Data (or lack of data) from countries, including elevation and vegetation, has been systematically reviewed, and countries have been reclassified within a "vaccination map" (WHO 2011d). The revised maps include:

- In Africa, countries with endemic areas include Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad (in the south only), Cote d'Ivoire, Democratic Republic of the Congo (all but the south), Ethiopia (west only), Equatorial Guinea, Gabon , Gambia, Ghana, Guinea, Guinea Bissau, Kenya (not east), Liberia, Mali (in the south only), Mauritania (in the far south only), Niger (in the southern half only), Nigeria, Rwanda, Senegal, Sierra Leone, Sudan (mainly in the south), South Sudan, Uganda, and Togo.
- In Africa, countries with low potential for exposure or no risk include Algeria, Botswana, Egypt, Eritrea, Libya, Madagascar, Malawi, Morocco, Mozambique, Namibia, Sao Tome and Principe, Somalia, South Africa, Tanzania, Tunisia, Western Sahara, Zambia, and Zimbabwe.
- In South America, countries with endemic or transitional areas include Bolivia (in the eastern side only), Brazil (all but the coastal strip to the east), Colombia (most areas), Ecuador (except the central region), French Guiana, Guyana, Panama, Paraguay (transitional), Peru (in the eastern side only), Suriname, Trinidad and Tobago, and Venezuela (all but the far north).
- In South America, countries with low potential for exposure or no risk include Argentina, Chile, and Uruguay (Jentes et al., 2011).

It is difficult to predict future trends in the geographic spread of mosquito vectors and nonhuman animal reservoirs for YFV:

- Dengue virus has been proposed as a useful model, because it shares (some of) the same mosquito vectors. It is surprising, therefore, that to date there has only been one recent urban outbreak (around 24 cases) of YF in the Americas (Asunscion, Paraguay in 2008; WHO 2008c), despite widespread reinfestation of *Aedes aegypti* mosquitoes in large cities, which has been sufficient for urban outbreaks of dengue.
- Dengue and YF coexist in Africa and in South America but not in Asia (Amaku et al., 2011). Dengue, however, has a longer-lasting viremia (in humans) and a shorter extrinsic incubation period in mosquitoes (Massad et al., 2003).

Since the 1930s, people have raised concerns about the spread of YF to Asia but, so far, this area has remained free from YF. The reasons for this are unclear and, although there is very little supporting evidence, several theories have been proposed (Tomori, 2002; Amaku et al., 2011):

- Absence (or very low risk) of introduction of YFV from YF-endemic areas.
- Lack of human genetic susceptibility factors.
- Different vector competence or behavior, which might be due to competition with other flaviviruses within vectors.
- Cross-protection following exposure to other flaviviruses; for example, recovery from dengue infection (or after antidengue vaccination) might reduce susceptibility to YF; the "Asian hypothesis" (reviewed in Amaku et al., 2011).
- "Absence of a non-human maintenance cycle" so the virus is not able to sustain transmission outside humans.

3. Strategies for YF vaccination

YF disease can be prevented by one dose of the live attenuated vaccine, which has been in use since the 1930s. Since that time, approximately 500 million (M) doses have been used in human populations (Lindsey et al., 2008). The current vaccines are generally considered to be "safe and affordable" (WHO UNICEF, 2010; WHO, 2010a), but vaccine coverage in a given population needs to be at 60 to 80 percent to prevent YF outbreaks (WHO UNICEF, 2010).

There are very rare serious adverse events (SAEs) following use of YF vaccine, which is why some populations at higher risk of SAEs (including very young infants and persons with immuno-compromising conditions, such as AIDS) are contraindicated for vaccination, and why YF vaccine is only prescribed for a population and an individual in that population after a risk-benefit analysis has been performed.

The primary control measure for YF infection in endemic areas is a three-prong vaccination strategy, to induce immunity in 60 to 80 percent of the population. This strategy comprises:

- Routine childhood immunization, which builds the level of immunity in a nonimmune population in the long term by vaccinating once each child in a birth cohort. It is also used in an immune population to ensure that new entrants to the population become immune.
- Preventive (mass) campaigns, which are usually "one-off" immunization activities, aimed at plugging gaps in immunity in a population. Generally, the aim is to immunize all those in a given territory who have not had a vaccination in the past and who do not have a contraindication for vaccination based on risks for SAEs.
- Emergency (outbreak response) campaigns, which are similar to preventive campaigns but are triggered by the need to control an acute YF outbreak. This can be triggered by just one confirmed case.

Who receives vaccine in each of these strategies depends on a risk analysis and knowledge of where "immunity gaps" are in a population. For example, a population might have had very high coverage by routine childhood immunization but have no immunity in those aged over 10 years. In this case, a preventive campaign might be only in those aged over 10 years.

A fourth strategy is the use of YF vaccine for travelers. This can be to protect travelers, both foreign and domestic, from acquiring the disease when entering endemic areas, or to prevent travelers from introducing virus into nonendemic areas.

3.1. YF vaccine in routine immunization

A single dose of YF vaccine is included in routine childhood immunization schedules in countries at medium or high risk of YF (see Appendix Table 6 for details). Some countries are at risk of YF only in circumscribed areas and only infants in those areas will be vaccinated; these decisions follow risk analyses but can also be influenced by the availability of YF vaccine.

The single dose of YF vaccine is often administered at the same time as the first measles (or measles-containing) vaccine dose, which can be planned for ages 9 or 12 months, or as children first present or are contacted (see Appendix Table 6 for details). If these live vaccines are administered at separate visits, an interval of 30 days is recommended by the WHO to prevent interference between the immune responses to the live viruses, which can lead to reduced immune responses.

If given at the same time as measles-containing vaccines (MCV), YF vaccine and MCV are given as separate injections at different anatomical sites (Veras et al., 2010).

No interference has been found between YF and measles vaccines, but studies from Brazil suggest that simultaneous immunization of measles, mumps, and rubella (MMR) vaccine and YF vaccine at either age 9 months (cited in Veras et al., 2010) or 12 to 23 months (Nascimento Silva et al., 2011), reduced the response to YF vaccine, and also the response to mumps and rubella but not to measles.

In its recent YF factsheet, the WHO concluded that children aged less than nine months (or less than six months during an epidemic) should not be vaccinated with YF vaccine (WHO, 2010a) due to increased risk of SAEs in young babies (Veras et al., 2010). For outbreak control and/or in populations at very high risk of YF, YF vaccine can be given as young as age six months (Veras et al., 2010).

In routine immunization, YF vaccine is currently administered:

- In most African endemic countries, at age nine months (Veras et al., 2010).
- In South American countries (other than Brazil), aged older than 12 months (Veras et al., 2010).
- In Brazil, approximately aged nine months[3] (range of 5 to 24 months; Veras et al., 2010).

3.1.1. Booster doses of YF vaccine

It is assumed that one dose of YF vaccine will protect the individual for an extended period of time, possibly for life, although the evidence for this is not yet very strong.

In Brazil, in endemic areas, booster doses are mandatory every 10 years after routine childhood immunization (Ferguson et al., 2010), although in the Pan American Health Organization's (PAHO) field guide to YF, it states there is "no need to re-vaccinate" (PAHO, 2005).

In African countries, routine booster doses are not policy, but during mass prevention campaigns repeat doses can be delivered deliberately or inadvertently to those already vaccinated or immune as a result of natural YF exposure (Ferguson et al., 2010).

For travelers, the YF vaccination is repeated every 10 years, according to International Health Regulations (WHO, 2008f).

The requirement for booster doses of YF vaccine is under review by the YF working group of the WHO's Strategic Advisory Group of Experts (SAGE) and the outcome could impact demand for vaccine globally.

3.2. YF vaccine in preventive (mass) campaigns

For most of the "at-risk countries," a policy of routine childhood immunization alone is considered unlikely to control YF outbreaks due to vaccination gaps in older populations. Preventive campaigns are therefore also required to vaccinate all susceptible (nonimmune) people within a population (GAVI, 2008).

Vaccination is prioritized to those most at risk of exposure to infected vectors, for example people working or living in forested areas. The aim is to protect all people in a population who are at risk, to reduce the need for emergency vaccination (WHO UNICEF, 2010), and to achieve greater than 90 percent coverage of eligible children and adults.

These campaigns vary in scale; examples of previous campaigns include:

[3] Fiocruz: Brazilian Basic Child Vaccination Schedule: http://www.fiocruz.br/bio_eng/cgi/cgilua.exe/sys/start.htm?sid=168 (accessed 8 October 2012)

- From January 2007 to December 2009, the Yellow Fever Initiative (YFI) vaccinated approximately 41 M people, including in Benin, Burkina Faso, Cameroon, Liberia, Mali, Senegal, Sierra Leone, and Togo, (WHO UNICEF, 2010).
- In Bolivia, a PAHO-supported program vaccinated 5.8 M people over two years of age from 2000 to 2006 (WHO, 2008b).
- In Brazil, approximately 63 M children over the age of two have been vaccinated since 1997 (WHO, 2008b).

3.2.1. Targeting of preventive campaigns

Increasingly, preventive campaigns are highly targeted to specific "at-risk" regions within a country. Accurate targeting of vaccine to susceptible individuals or subgroups requires knowledge of anti-YF immunity within the population, which is not always available.

Sometimes the whole population, of all ages greater than approximately nine months (including pregnant women), has to be vaccinated to reduce the risk of YF infection. An upper age limit, such as "aged 60 years," for campaigns has also been proposed to reduce the risk of SAEs (GAVI, 2008).

3.3. YF vaccine in emergency (mass) campaigns

The WHO has stated that "In high-risk areas where vaccination coverage is low, prompt recognition and control of outbreaks through immunization is critical to prevent epidemics. To prevent outbreaks throughout affected regions, vaccination coverage must reach at least 60 to 80 percent of a population at risk (WHO website)."[4]

Details of outbreak responses that have been conducted in Africa and the Americas are provided in Appendix Table 7 and Appendix Table 8. Since 1992, the number of countries that reported outbreaks via WHO or PAHO each year ranged from 1 to 14 in Africa and 0 to 5 in Central and South America, although not all of these outbreaks will have been followed by emergency campaigns. The size of an individual outbreak response campaign can vary between approximately 60,000 (Guinea, 2009) to 30 M (Nigeria, 1986) individuals vaccinated (Appendix Table 7).

An example of a relatively recent outbreak response was the emergency campaign to control the 2001 outbreak in urban Abijan the capital of Ivory Coast. This campaign involved 200 teams, each having four vaccinators plus supervisors, delivering 2.6 M doses of Sanofi Pasteur's YF vaccine to all people aged greater than nine months, including those known or unknown to be HIV positive and also to pregnant women. Vaccine was delivered using autodisable (AD) syringes at a rate of 1,325 people per day per vaccinator, with daily distribution of vaccine and consumables; it achieved 91 percent coverage (Fitzner et al., 2004). From active adverse events (AE) surveillance, 12 AEs were due to programmatic errors, including three severe local reactions and nine abscesses from nonsterile handling of syringes or multidose vials (Fitzner et al., 2004).

3.4. Vaccination of travelers

YF vaccine is the only vaccine that is included specifically in the International Health Regulations (WHO 2008e); other diseases are listed but there is no suitable preventive vaccination available for them. Vaccination, documented by certification, is a requirement for entry into certain countries. Vaccination of travelers against YF is important for two reasons:

[4] Accessed March 5, 2012: http://www.who.int/mediacentre/factsheets/fs100/en/

- Travelers into endemic areas require YF vaccination to protect their own health and to prevent them from bringing YF back to their home country.
- Travelers from endemic areas need to receive YF vaccine to prevent them from introducing YF into areas with susceptible mosquito vectors and a susceptible population.

Annually, about 9 M people travel from Asia, Europe, and North America to countries where YF is endemic, and probably more than 3 M travel to areas where YF transmission occurs (Jentes et al., 2011).

The international travel market for YF vaccine is small and has little impact on global YF vaccine demand or supply. It does have some relevance as a driver of the development of novel vaccines of lower risk of SAEs than current live attenuated YF vaccine. It is also potentially a more attractive market to manufacturers than the use of YF vaccine for public-sector use because the price of vaccine for travelers is much higher than the price for public-sector use.

3.5. Summary

- There are four well-established vaccination strategies within which YF vaccine is used worldwide: routine childhood immunization, preventive campaigns, emergency outbreak response campaigns, and vaccination of travelers.
- For the routine childhood vaccination strategy, the market is relatively stable (annually) compared with mass campaigns, and it is predictable for each country based on birth cohort. Use is directed by WHO recommendations and national policies, which vary between countries in terms of requirements for boosters and national versus subnational coverage. Very high coverage can be obtained for YF in routine immunizations.
- Mass campaigns can involve any age group and can be triggered by an outbreak (emergency outbreak response) or they can be preplanned to plug an immunity gap at the population level to prevent future outbreaks (preventive campaigns). In general, session sizes can be very large for mass campaigns (100 to 1,300 per vaccinator per day). Very high coverage rates can be obtained for mass campaigns, “eliminating” YF from whole countries.
- For the travel vaccination strategy, the market is very small and stable and does not have much impact on supply–demand imbalances for public-sector use in endemic countries. Use is directed by International Health Regulations, which require booster doses every 10 years.

4. The need for yellow fever vaccine

Since the 1980s, YF has increased in public health importance within low- to high-risk endemic countries, endemic regions, and globally (WHO UNICEF, 2010), and new populations of humans are becoming at risk of infection by YFV.

The "total market" for YF vaccine could be as high as 900 M people in 45 endemic countries, comprising the total populations of:

- 32 countries in Sub-Saharan Africa (WHO UNICEF, 2010; WHO, 2010a).
- 13 countries in (tropical) Central and South America, especially Bolivia, Brazil, Colombia, Ecuador, and Peru (WHO UNICEF, 2010; Veras et al., 2010; WHO, 2010a; WHO, 2008a).

Not all the people within these countries, however, will be "at risk."

4.1.1. Relationship between need and demand for YF vaccine

The relationship between need and demand for YF vaccine is complex; "only people at risk should be vaccinated:"[5]

- Only a proportion of the total population of people living in YF "at risk" countries has an immediate epidemiologically defined need for YF vaccine; individuals have to be both at risk of exposure to the YF virus and susceptible (without a past history of YF vaccination).
- Only some of those in immediate need for vaccination are actually represented by the immediate demand for YF vaccine, due to reasons of inequality of access to YF vaccine.
- Some of the demand for YF vaccine is not from people with actual need for vaccine, according to global guidelines (e.g., the demand for vaccine for booster doses).

4.1.2. Is the need for YF vaccine increasing?

There are many reasons for the increasing prevalence of YF virus transmission and incidence of YF disease including climactic, demographic, economic, social, and political changes. Most of these factors are not within easy human control (Tomori, 2002; Mutebi and Barrett, 2002; Briand et al., 2009; WHO UNICEF, 2010). As a result, some countries are likely to enter the high- and medium-risk categories and start to trigger the need for preventive campaigns in at least some areas.

Another risk factor for increasing incidence of YF cases, which could be addressed by vaccination, is the immunity gap in the population in endemic areas as a result of the cessation of preventive campaigns with YF vaccine in most countries from the 1960s to 1980s.

4.1.3. Why might global need for YF vaccine decrease?

As countries at risk of YF complete their preventive campaigns (for example, The Gambia) their need (and demand) for YF vaccine decreases. Eventually, greater than 90 percent of their populations will be protected by YF vaccine, which should prevent outbreaks and the need for mass emergency vaccination. Then the only need for YF vaccine for these countries will be to protect new nonimmune entrants to the population, mainly by immunising infants in the birth cohort, but also those people migrating into the areas from countries that have not already provided them with YF vaccine.

[5] Alejandro Costa, WHO, written communication, March 5, 2012.

4.2. Summary

- The need for YF vaccine underlies, but is not a perfect match for, the demand for YF vaccine, but is difficult to derive for all populations from current epidemiological knowledge.
- The need for YF vaccine in some countries is likely to increase as new populations become at risk of YF infection due to climactic, ecological, socioeconomic, and demographic change.
- In other countries, the population's need for YF vaccine will decrease as preventive campaigns are completed and as the coverage of YF vaccine in routine childhood immunization increases. The risk of YF infection in these countries will probably remain, but the susceptibility to infection and symptomatic disease is eliminated from those vaccinated in the population.

5. Demand for YF vaccine

The annual demand for YF vaccine remains difficult to predict and does not always reflect the actual need for the vaccine (see Section 4.1.1).[6]

Predicting the demand for YF vaccine in a country depends on several factors:

- Assessment of risk of YF in a given country (and sub-regions), which relies on the availability of demographic information in that country. GAVI has funded a risk assessment tool to validate need for YF vaccine, which has been used in several GAVI-eligible at-risk countries in Africa and has also been used to plan future preventive campaigns and before a request for future investment (GAVI, 2008); new lower-risk countries will use this tool over the next few years.
- Trends in vaccine use, for routine immunization, preventive campaigns, outbreak control and in travelers.
- Capacity of the country or district to use the vaccine, which can be affected by other short- or longer-term health priorities and also "environmental, economic, social, and political factors" (Briand et al., 2009):
    - Short-term factors include competing public health responses to other infectious disease outbreaks, such as cholera, meningitis, and especially polio.
    - Longer-term competing public health priorities can include malaria and HIV control, or other vaccine introductions.
- Priority for use in a country: YF can be seen as having a relatively low burden of disease in a country (measured by mortality and morbidity), and therefore support for YF vaccination might be given a low priority (Tomori, 2004). It is difficult to gauge the impact of this perception on health prioritization using publicly available information. For example, in the recent round of applications submitted to GAVI for funding for the introduction of pneumococcal, rotavirus, pentavalent, meningitis A, measles (second-dose), or YF vaccine,[7] the majority of applications were for pneumococcal or rotavirus vaccines. However, this proportion reflects eligibility for applications and the existence of already-funded YF programs as well as the relative priority of YF vaccination.[8]

5.1. Recent demand for YF vaccine for routine immunization

The United Nations Children's Fund (UNICEF) and the WHO[9] list approximately 44 countries that report having YF vaccine in their routine immunization (UNICEF, 2011a; see Appendix Table 6 for details). This has increased from 33 in recent years (Briand et al., 2009; reviewed in Veras et al., 2010; WHO UNICEF, 2010).

UNICEF is a major purchaser of YF vaccine, mostly for use in routine childhood immunization. Tenders for YF vaccine are issued separately from other vaccines. The latest tender was for "2010 to 2012: routine, preventive campaign and stockpile;" vaccine delivery was from January 2010 onwards (UNICEF, 2008a). The amounts of vaccine required and purchased via the tendering process for routine immunization was relatively stable and predictable (Table 1).

[6] Lauren Franzel, PATH SVS, oral communication 28 March 2011

[7] http://www.gavialliance.org/library/news/press-releases/2011/developing-countries-make-record-demand-for-life-saving-vaccines/

[8] Ulla Griffiths, LSHTM, written communication, 3 October 2012

[9] http://apps.who.int/immunization_monitoring/en/globalsummary/ScheduleResult.cfm

Table 1. YF vaccine purchased (millions of doses) for routine vaccination via UNICEF tendering process

	2009	2010	2011	2012
YF 5	5	5.5	5.5	5.7
YF 10	14.2	17	17.2	17.2
Total	**19.2**	**22.5**	**22.7**	**22.9**

Notes: From UNICEF Yellow Fever Vaccine Tender 2010–2012 (UNICEF 2008b); YF 5 = 5-dose vials; YF 10 = 10-dose vials.

Inclusion of amounts of vaccine required for the emergency stockpile and 'possible' preventive campaigns, however, illustrates the high variability in the amounts of vaccine that might be needed year-on-year and the problems associated with predicting total demand (Table 2).

Table 2. Quantities of YF vaccine (millions of doses) in the total UNICEF tender 2010–2012 (for routine, emergency, and preventive campaigns)

	2010	2011	2012
Predictable demand [a]	47.5 [b]	22.7	22.9
Possible demand		56.0	96.0
Total demand	**47.5**	**78.7**	**118.9**

Notes: From UNICEF Yellow Fever Vaccine Tender 2010–2012 (UNICEF 2008b); a. Predictable demand is for routine immunization only, with the exception of 2010. b. includes 25 M doses for emergency stockpile and planned preventive campaigns.

5.2. Recent demand for YF vaccine for preventive campaigns

The YFI aimed to develop an "immunity barrier," especially in West Africa, by immunizing populations at high risk from YF by instigating routine childhood immunization and preventive campaigns.

The total population of the 12 countries in Africa initially targeted for vaccination via preventive campaigns in 2007 was 283 M, and the goal was to immunize 48 M people in these countries by the end of 2010 (WHO, 2007a).

Nine countries (Benin, Burkina Faso, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo) conducted preventive vaccination campaigns between January 2007 and June 2010, and vaccinated almost 48 M people. All campaigns exceeded their objective of vaccinating more than 90 percent of eligible children and adults.

Often, planned campaigns have been delayed or phased to match resources including the availability of YF vaccine and, in 2010, only one preventive campaign was carried out in West Africa "owing to problems with the availability of vaccine" (WHO, 2011c).

Preventive campaigns are planned (or underway) for other African countries and South American countries (Table 3). The total target population to be vaccinated in these campaigns is approximately 145 M, compared with the 47 M already vaccinated.

In addition to the planned campaigns included in Table 3, a new list of countries that could benefit from preventive campaigns is currently in preparation.[10]

[10] Oliver Ronveaux, WHO AFRO, oral communication, September 22, 2011.

Table 3. Some of the known target populations for preventive YF campaigns, by country

Country	Target population	Population vaccinated by ~2010; notes including on coverage	References
Benin	6.33 M	6.32 M	WHO UNICEF, 2010
Bolivia	4.8 M	2007: 5 M; 86% coverage at national level	WHO, 2009; Pezzoli et al., 2009
Brazil	Not known	2008: 7 M (response to outbreak)	WHO, 2008c
Burkina Faso	7.55 M	7.57 M [8.9 M from GAVI]	WHO UNICEF, 2010; GAVI, 2008
Cameroon	7.47 M	7.51 M [8.25 M from GAVI] 2007: ~129,000 (outbreak control) 2009: target of 90% of 7.5 M aged > 9 months (not pregnant) in 62 health districts	WHO UNICEF, 2010; GAVI, 2008; WHO, 2009; Wiysonge et al., 2008; Pezzoli et al., 2012
Central African Republic	~4 M	Campaign planned for 2010–2011	WHO UNICEF, 2010
Côte d'Ivoire	15.4 M	Campaign planned for 2011–2012	WHO UNICEF, 2010
Ghana	~22 M	Campaign planned for 2011–2012. Planned but 'threatened due to financial shortfall'	WHO UNICEF, 2010; UNICEF, 2010
Guinea	6.2 M	June 2010: 6.2 M (aged > 9 months)	WHO UNICEF, 2010; UNICEF, 2010; WHO, 2011c
Liberia	2.91 M	2.89 M	WHO UNICEF, 2010
Mali	5.94 M	2005 and 2008: 5.87 M	WHO UNICEF, 2010; GAVI, 2008
Nigeria	~104 M	Campaign planned for 2012–2014. Planned but 'threatened due to financial shortfall'	WHO UNICEF, 2010; UNICEF, 2010
Peru	Not known	2004 – 2007: 10 M	WHO, 2009
Senegal	3.13 M	2007: 3.11 M; ~94% coverage	WHO UNICEF, 2010; GAVI, 2008; WHO, 2009
Sierra Leone	4.11 M	3.98 M	WHO UNICEF, 2010
Togo	3.64 M	2007: 3.59 M; coverage rate 84–94% [2.3 from GAVI]	WHO UNICEF, 2010; GAVI, 2008; WHO, 2009
TOTAL (Africa)	192.68 M	47.04 M	WHO UNICEF, 2010

Notes: M = million. The table presents data that was in the public domain at the time of writing. Other countries or areas within countries at risk of YF infection have since been identified (for example, Sudan), or are likely to be identified in the future. The GAVI website has information on support for YF vaccination.[11]

5.3. Recent demand for YF vaccine for emergency campaigns

Demand for YF vaccine for emergency use is much more difficult to predict based on epidemiological data; theoretically, it should decline as preventive campaigns and routine immunization increase their coverage and reduce the immunity gaps in at-risk countries.

Much of the YF vaccine used for outbreak response is derived from, and/or initially funded via, the global YF vaccine stockpile, which is maintained at 6 M doses per year. The YF vaccine used in outbreak responses is financed by GAVI, the European Commission Humanitarian Office (ECHO),

[11] GAVI: countries approved for support: http://www.gavialliance.org/results/countries-approved-for-support Accessed October 8, 2012.

and the United Nations Central Emergency Response Fund (CERF) and rarely from the affected countries themselves.[12,13]

In general, the level of 6 M doses seems to be sufficient to meet demand, but does not have much excess capacity; for example, 5.5 M doses were used in 2010.[14] Any leftover vaccine can be used, before it expires, in preventive campaigns and replaced in the stockpile. GAVI support for the stockpile is guaranteed until 2013.[14]

By 2008, the stockpile mechanism had supported outbreak response campaigns in at least six countries in Africa and at least three in the Americas (Table 4 and Appendix Table 7 and Appendix Table 8).

Table 4. Use of YF vaccine emergency stockpile in outbreak control up to 2008

Country	Population vaccinated	Doses used from stockpile	References
Brazil	7.00 M	4.00 M	GAVI, 2008; WHO, 2008c
Cameroon	Not known	0.13 M (in 2007)	GAVI, 2008
	0.82 M (in 2006)	Not known	WHO WER, 2008b
Burkina Faso	0.64 M (in 2005)	0	WHO, 2006
Central African Republic	0.06 M	0.06 M	GAVI, 2008; WHO, 2008b
Colombia	1.00 M		
Côte d'Ivoire	Not known	2.30 M	GAVI, 2008
	0.29 M (in 2005)	0	WHO, 2006
	Not known	0.86 M (in 2006)	WHO, 2008b
Ghana	0.09 M	Not known	WHO, 2008b
Guinea	Not known	0.16 M	GAVI, 2008
	0.9 M (in 2005)	0.8 M (in 2005)	WHO, 2006
Liberia	Not known	0.33 M	GAVI, 2008
Mali	2.45 M (in 2005)	2.26 M	WHO, 2006
Paraguay	Not known	2.00 M	GAVI, 2008; WHO, 2008d
Senegal	0.15 M (in 2005)	0	WHO, 2006
Sudan	2.79 M (in 2005)	1.70 M	WHO, 2006
Togo	1.7 M		GAVI, 2008
	1.3 M (in 2007)	1.3 M	WHO, 2008b

Notes: M = millions. The dates in parentheses are where the YF vaccine use has been reported for a particular year. The figures are from information in the public domain (only published as a compilation up to 2008); there might be more up-to-date summaries available and broken down by year of use.

5.4. Forecasting future demand for YF vaccine; 2011–2022

From 2001 to 2009, total demand for vaccine increased from 34 M doses per year to 105 M doses per year (Ferguson et al., 2010), and demand for routine EPI use has increased from approximately 5 M doses to 23 M doses (UNICEF, 2008b).

The future demand for YF vaccine is, however, still hard to predict and will be determined by the following key factors:

[12] Alejandro Costa, WHO, written communication, March 5, 2012; http://www.who.int/mediacentre/factsheets/fs100/en/

[13] http://www.who.int/mediacentre/factsheets/fs100/en/

[14] Alejandro Costa, WHO, oral communication, January 31, 2011.

- The introduction and maintenance by countries of routine childhood YF vaccinations.
- The YFI maintaining the global YF vaccine stockpile at a sufficient level to control unpredictable outbreaks. This should be possible with the current 6 M dose stockpile; however, if several outbreaks occur at once, the stockpile might be insufficient to meet requirements.
- Providing the remaining doses for the planned, or already underway, preventive campaigns in Ghana and Cote d'Ivoire as well as implementing the planned preventive campaign in Nigeria could consume more than 140 M doses.
- The expansion or initiation of preventive campaigns in countries previously considered to be at low- or medium-risk, particularly in Africa:
    - Preventive campaigns in these countries (Angola, Chad, Congo, Democratic Republic of Congo, Ethiopia, Guinea Bissau, Kenya, Mauritania, Niger, Rwanda, North and South Sudan, Tanzania, and Uganda) described as "Group B" countries, would require approximately 110 M doses.[15]

Other factors will also have an impact on demand, such as:

- Improved ongoing risk assessment, based on improved YF case-based and enzootic surveillance and laboratory testing; this is likely to increase demand for the vaccine.
- Improved (more rapid) detection and responses to YF outbreaks, so that vaccine can be used to prevent disease rather than vaccinate those already exposed to YFV.
- Improved prioritisation of YF vaccine use during outbreaks, which could help avoid vaccine "wastage" on people who are already immune.
- Under- (and over-) reporting of YF cases, which could result in poor epidemiological datasets, especially for some medium-risk areas.
- Re-vaccination with YF vaccine. Some endemic countries choose to re-vaccinate their population every 10 years, which can contribute to increasing demand for YF vaccine. This practice will be reviewed by a YF working group of the WHO.[16]

5.4.1. A conservative global-demand scenario

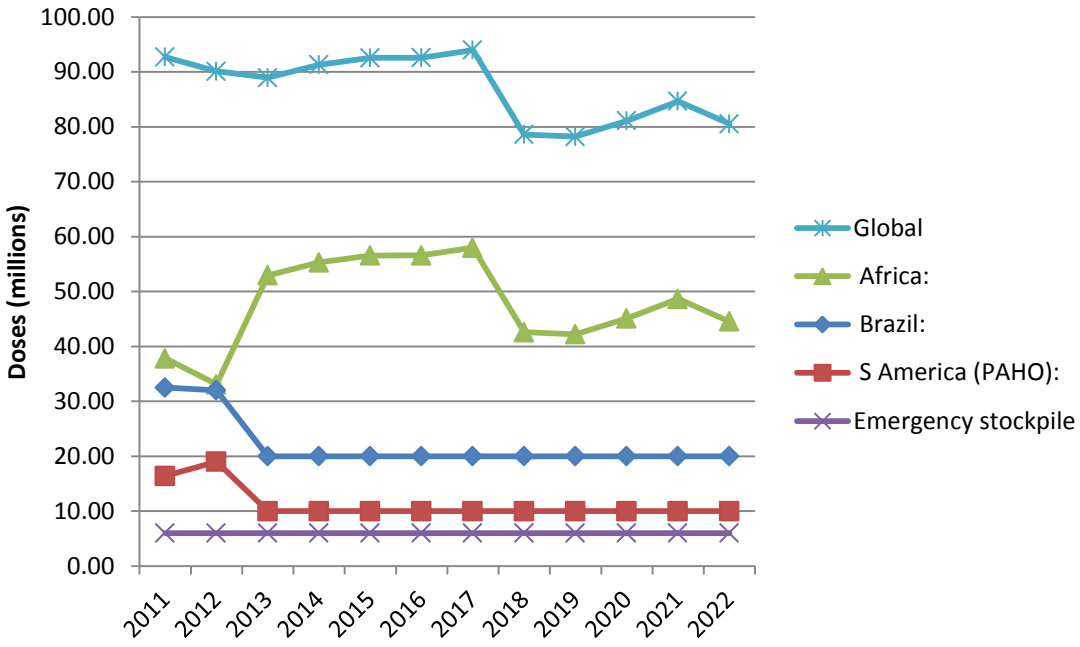
A forecast of a possible global demand for YF vaccine for the period 2011 to 2022 has been produced by the WHO, and was shared with the authors of this report.[17]

[15] Alejandro Costa, WHO, written communication, March 5, 2012.

[16] http://www.who.int/immunization/sage/SAGE_wg_call_yellow_fever.pdf

[17] Alejandro Costa, WHO, written communications, April 12, 2011 and March 5, 2012.

Figure 1. YF vaccine demand 2011–2022, according to a conservative global-demand forecast by WHO



Notes: "South America" excludes Brazil. The forecast and data for the figure were provided by Alejandro Costa, WHO.[17]

The aim of the forecast was to create a scenario:

- With relatively stable demand.
- That is consistent with the limitations in YF vaccine supply (see Section 7).
- That still meets preventive and reactive needs for YF vaccine.[18]

For these reasons, the term "conservative" demand forecast has been used in this report.

The forecast assumes:

- An increasing annual demand for vaccine for routine childhood use in Africa, from approximately 23 M doses in 2011 rising to 37 M doses in 2022.
- Approximately 10 to 15 M doses per year for use in preventive campaigns in Africa, except during 2013 to 2017 when approximately 30 M doses per year will be needed for preventive campaigns in Nigeria.
- An average of 10 M doses per year for routine immunization and preventive campaigns (combined) in South America (excluding Brazil).
- An average of 20 M doses per year for use in Brazil (which does not procure YF vaccine via PAHO), for routine and preventive campaign use combined.
- 6 M doses per year for the global emergency YF vaccine stockpile.

Using this approach, and spreading future demand where possible, the overall demand for YF vaccine should be within current global manufacturing capacity, assuming that the unpredictable aspects of the model do not exceed the assumptions stated above and that manufacturing capacity for YF vaccine does not fall below the current levels.

[18] Alejandro Costa, WHO, oral communication, January 31, 2011; written communication, April 12, 2011; and oral communication, April 14, 2011.

This model will be used in Section 12 when considering strategies to ease supply constraints for YF vaccine. The assumptions underlying the model are also described in more detail in Section 12.

5.5. Summary

- Between 2001 and 2009, the total demand for YF vaccine increased three-fold from 34 M to 105 M doses per year (Ferguson et al., 2010).
- In the short to medium term, the overall trend is for demand for YF vaccine to increase, assuming funding for vaccine procurement continues.
- It is possible to construct a demand scenario, as WHO has done, that meets anticipated need for the vaccine and that can be met with current manufacturing capacity for the vaccine; however, this assumes:
    - The manufacture of YF vaccine remains at, or above, current levels of demand. This cannot be guaranteed, however; manufacturers might choose to reduce their level of YF vaccine production and/or encounter short-term production problems that will reduce the amount of vaccine produced.
    - Unpredictable surges in demand for YF vaccine, which are likely to occur, do not exceed emergency stockpiles of the vaccine, including the global 6 M-dose stockpile. Some countries, such as Brazil, are assembling their own stockpiles for emergency use.
- New approaches to improve the availability of YF vaccine could play an important role in meeting the increasing global demand and address unpredictable surges in demand for the vaccine.

6. Financing the purchase of YF vaccine

The public-sector purchase of YF vaccine, for any of the three main uses, can be funded and/or procured:

- By the countries using the vaccine, especially if they are not eligible for GAVI support. Approximately 40 percent of routine YF vaccination is government funded or co-financed (UNICEF 2008b).
- By/via GAVI. Up to 60 percent of YF vaccine used for routine immunization is funded by GAVI (UNICEF 2008b); although, increasingly, countries are co-funding purchase or resources.
- Via the global stockpile for outbreak response.
- Via the PAHO Revolving Fund (a procurement rather than a funding mechanism), for Central and South America (excluding Brazil).
- By other non-governmental funding, such as ECHO and CERF.

6.1. Role of GAVI in funding YF vaccination

YF and pentavalent (DTP-HepB-Hib) vaccines are considered "the two primary underused vaccines used by GAVI-eligible countries" (CEPA, 2010).

In the past few years, GAVI and its partners have funded, in some African countries, routine childhood YF immunization and some preventive campaigns.

From publicly available information, routine childhood immunization in around six GAVI-eligible countries is not funded by GAVI and is presumably funded by the countries themselves (Table 5). "In 2011, 17 of the 26 GAVI-eligible countries are receiving support for routine yellow fever immunization" according to information from GAVI.[19]

Table 5. "GAVI-eligible" countries in Africa and whether they reported GAVI-support for YF vaccine in 2010 Annual Reports to GAVI

Country	YF vaccine in EPI [a]	Reported GAVI-support [b]	Notes [b]
Angola	Yes	No	Presume YF in EPI is funded by government; in 2010, failed to reach YF coverage target (40%) due to reduced vaccine production; last report of outbreak in 1971
Benin	Yes	Yes	Preventive campaign planned to end 2010; Global YF stockpile used
Burkina Faso	Yes	No	YF in EPI is funded by government; preventive campaigns planned from 2008; outbreak in 2010 (and earlier years); Global YF stockpile used
Burundi	No	No	No reports of outbreaks
Cameroon	Yes	Yes	Recent outbreak response campaigns; planned start of preventive campaigns from 2008; outbreak in 2011 and earlier years; Global YF stockpile used
CAR	Yes	Yes	Outbreak in 2010 and previous years
Chad	Yes	Yes	Suspected cases in 2009
Congo	Yes	Yes	

[19] http://www.gavialliance.org/support/nvs/yellow-fever/

Country	YF vaccine in EPI [a]	Reported GAVI-support [b]	Notes [b]
Congo DR	Yes	Yes	Outbreak in 2011 and previous years
Cote d'Ivoire	Yes	No	Presume YF in EPI funded by government; preventive campaign planned to end in 2011
Equatorial Guinea	No	No, not eligible for support?	No outbreaks reported
Ethiopia	No	No	No outbreaks since 1960s
Gabon	Yes	No, not eligible for support?	Presume YF in EPI funded by government; outbreak in 2011 and 1994
Gambia	Yes	No	Presume YF in EPI funded by government; good coverage in population since outbreak in 1978
Ghana	Yes	Yes	Outbreak in 2011 and previous years; Planned preventive campaign 2009–2012
Guinea	Yes	Yes	Outbreak in 2010 and previous years; Preventive campaign planned from 2009
Guinea Bissau	Yes	Yes	No outbreaks reported
Kenya	Yes (sub-national)	Yes	Outbreak in 1992–1993
Liberia	Yes	Yes	Outbreak in 2010 and previous years; planned start of preventive campaign in 2009; Global YF stockpile used
Mali	Yes	Yes	Outbreak in 2010; preventive campaign completed 2008; Global YF stockpile used
Mauritania	No	No	No outbreaks reported in recent years
Niger	Yes	Yes	No outbreaks reported?
Nigeria	Yes	Yes	Preventive campaign planned 2012
Rwanda	No	No	No outbreaks reported in recent years
Sao Tome & Principe	Yes	Yes	No outbreaks reported in recent years
Senegal	Yes	No	Outbreak in 2005; imported cases in 2010; presume YF in EPI funded by government; preventive campaign completed 2008; Global YF stockpile used
Sierra Leone	Yes	Yes	Preventive campaign in 11/12 districts in 2009; outbreak response in 2011; Global YF stockpile used
Somalia	No	No	No outbreaks reported recently
Sudan - North	No	No	No outbreaks reported recently
Sudan - South	No	No	No outbreaks reported recently
Tanzania	No	No	No outbreaks reported recently
Togo	Yes	Yes	Outbreak in 2007 and previous years; preventive campaign completed 2008; Global YF stockpile used
Uganda	No	No	Outbreak response in 2010–2011

Notes: EPI = Expanded Programme on Immunization, YF vaccine in routine childhood immunization; a. Schedule correct as of 20 September 2011, from WHO Vaccine Preventable Diseases Monitoring System (WHO website); countries have not been included if

they vaccinate only travellers to other countries; [20] b. Information from most recent Annual Report (2010) by country to GAVI , [21] South America: only Bolivia and Guyana are "at risk" and also listed by GAVI as eligible for support; Argentina, Brazil, Colombia, Ecuador, French Guiana, Panama, Paraguay, Peru, Suriname, Trinidad and Tobago, Venezuela: all have some areas of their countries at risk but are not eligible for GAVI support.

Since 2002, GAVI and its partners funded the establishment of the global YF vaccine stockpile (for outbreak response), which is used by countries in Africa and Central and South America. Countries are expected to reimburse the managers of the stockpile for vaccine use where possible.[22]

6.2. Impact of GAVI on YF vaccination

In the second GAVI evaluation (CEPA, 2010), it was concluded that:

- GAVI had added value by accelerating the introduction of YF vaccine as an underused vaccine: "2 to 6 countries had adopted YF vaccine into their EPI earlier than would have been expected in the absence of GAVI."
- "GAVI has significantly advanced the evidence base for YF vaccine introduction... supporting studies to collect disease burden data needed to identify high-risk groups for vaccination in target countries as well as funded monitoring of vaccine quality and safety and support of operational research."
- GAVI had "played a major role in improving vaccine coverage rates and sustainability by financing routine infant immunization and a vaccine stockpile."
- GAVI, however, "had not improved the affordability of YF vaccine;" indeed "the average price for 5- and 10-dose presentations has increased by 19 and 13 percent respectively from 2004 to 2010." This occurred "despite an improvement in YF vaccine supply through the addition of two prequalified (PQ) suppliers and based on UNICEF's product availability assessment." The price increased "even though UNICEF reported supply excess of the 10-dose presentations from 2004 to 2008, which represented the majority (66–77 percent) of shipped doses." "GAVI has not actively addressed strategies for reducing vaccine prices and has relied on natural market forces." "If there is continued 'unstable supply'... vaccine prices will remain high." The issues regarding affordability are not thought to be specific to YF vaccine, however, but reflect global increases in the price of vaccines, particularly older, "established" vaccines.[23]
- During the period of GAVI support, "the number of PQ products increased from two to four; however, only two suppliers received UNICEF awards."
- YF supply stability "was improved from 2004 to 2008 but was not sustained beyond 2008 and UNICEF and others continue to project YF vaccine supply limitations from 2010 onwards, at least in part due to production issues."

6.3. GAVI support for YF vaccine after 2011

GAVI's Strategy and Business Plan 2011–2015 (GAVI, 2011) states:

- In its Vaccine Goal, "The Alliance will maintain momentum on yellow fever, hepatitis B, and Hib vaccines while also supporting campaigns against yellow fever and meningitis A

[20] http://apps.who.int/immunization_monitoring/en/globalsummary/ScheduleResult.cfm

[21] 2010 Annual reports to GAVI, downloaded from links on http://www.gavialliance.org/country

[22] Alejandro Costa, WHO, oral communication, January 31, 2011.

[23] Alejandro Costa, WHO, written communication, March 5, 2012.

and additional vaccines including against human papillomavirus (HPV), which causes cervical cancer."
YF is not, however, included in any of the goal-level indicators.

- There are also "more general" goals for Financing, Health Systems, and Market Shaping, but YF is not included in the indicators for these either.

In the future, GAVI states on its website:

- It "...will maintain momentum on these antigens [including YF] but also target new vaccines, which hold the greatest potential to achieve progress on the Millennium Development Goals (MDGs), in particular MDG 4—the reduction of child mortality."
- Its "ambition is to accelerate the introduction of routine meningitis, pneumococcal, and rotavirus vaccines and support campaigns against yellow fever and meningitis."[24]

6.4. Summary

- There are several routes for the financing of YF vaccine purchase and delivery including public health funds in the country in question, GAVI, NGOs, and purchasing mechanisms such as the global stockpile and PAHO Revolving Fund. The proportion and importance of these varies between countries and over time.
- GAVI is an important source of funding for YF vaccine for routine and campaign use in the majority of GAVI-eligible African countries.
- GAVI has also played a significant role in accelerating the introduction of YF vaccination and increasing routine immunization coverage rates. It has not**,** however, improved the affordability of YF vaccine; this might be expected with an "established vaccine" with little new competition.
- The level of future funding from GAVI will depend on GAVI's prioritization of YF vaccine compared with other vaccines and levels of total funding for vaccination activities.

[24] http://www.gavialliance.org/about/strategy/phase-iii-%282011-15%29/vaccine-goal/

7. Supply of YF vaccine

YF vaccine is a live-attenuated vaccine. Since 1982, all YF vaccines have been manufactured from strains based on the attenuated 17D strain of YF vaccine, which was originally derived from the Asibi strain of wild-type YF virus in the 1930s (reviewed in Roukens and Visser, 2008).

Two sub-strains of the 17D strain, 17DD and 17D-204, are the main strains that are currently used in vaccines. Phylogenies of the different vaccine strains, based on sequencing or passage history are available (Stock et al., 2012). Although the sequence analysis confirms that the 17DD sub-strain is clearly separated from the 17D group of strains used in other parts of the world, the strains are 99.9 percent homologous (Stock et al., 2012). The two strains are believed to have similar (but not necessarily identical) immune and safety profiles (de Melo et al., 2011).

The 17D-204 sub-strain has been used (or is still being used) by various manufacturers in China, France (Sanofi Pasteur), Germany, India, the Netherlands, Senegal (Institut Pasteur), South Africa, the United Kingdom, and the United States (Sanofi Pasteur). The 17DD sub-strain has been used (or is still being used) by manufacturers in Brazil (Bio-Manguinhos) and Colombia (see Table 6) (Stock et al., 2012).[25]

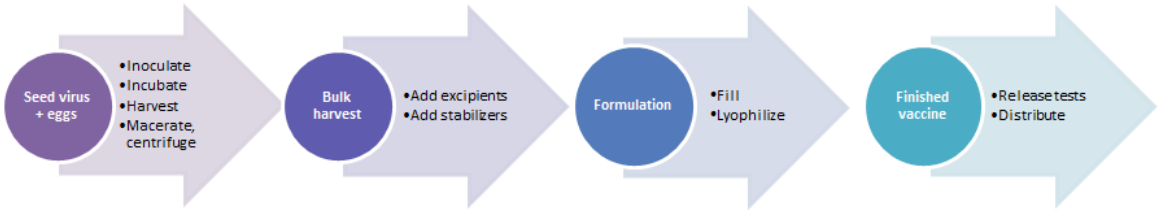
An additional "sub-sub-strain" designated 17D-213/77 has been derived from the 17D-204 strain, and is used by manufacturers in Russia (Chumakov Institute) and Switzerland (Crucell). This is currently the only strain that is available from WHO as a production master seed lot for YF vaccine production.[25]

In 2012, only six manufacturers are still producing YF vaccine (see Section 7.3 and Table 6).

7.1. Manufacturing process

The production process for YF vaccine has not changed significantly for several decades. The vaccine is produced in embryonated, specific-pathogen-free (SPF) eggs. The yield per egg is typically 100 to 300 doses (Monath, 2005). The main steps in the process are shown in Figure 2.

Figure 2. Main stages in the production of YF vaccine



Notes: Adapted from Monath 2005.

7.2. WHO requirements for YF vaccines

The current WHO "Recommendations for YF vaccine" were published in 1998 (WHO, 1998). A revised set of recommendations has been published in draft form (WHO, 2010a). These include

[25] Alexandra Sinyugina and Andrew Malkin, Chumakov Institute, written communication, April 11, 2012.

recommendations for the potency of YF vaccines, which is the number of live virus particles per dose. This is an issue of particular relevance to the question of YF vaccine supply because it determines the minimum amount of virus that must be delivered per dose.

7.2.1. Minimum potency

The minimum potency per dose for YF vaccines was first defined in 1957 (WHO, 1957) as "not be less than 1000 50-percent mouse lethal dose (MLD_{50}) or its equivalent in plaque-forming units (PFU), in the dose recommended by the manufacturer for use in humans."

In 2003, the first international standard for YF vaccines was assigned to improve comparisons between laboratories. The minimum potency currently recommended for use in humans should not be less than 3.0 $\log_{10}$ international units (IUs) per dose. Publicly available information on the relationship between MLD_{50}, PFU, and IUs from different manufacturers and national control laboratories is presented in Appendix Table 2.

7.2.2. Maximum potency

Release specifications (in terms of potency) vary between manufacturers, and between lots from the same manufacturer (Appendix Table 3).

Most manufacturers release vaccine with potency per dose that is approximately 2- to 100-fold greater than the WHO recommended minimum dose; this is at least in part to allow for a drop in titer during the shelf life of the vaccine.

At present, there is no defined upper potency limit for YF vaccines. It has been noted that the amount of virus per dose of vaccine has increased over the past 25 years (Ferguson et al., 2010), although it is not clear why this has happened.

If, in the future, a maximum potency for YF vaccines is established, this could have an impact on the total number of doses available globally, as it might be possible to fill more doses from each bulk harvest.[26] This could also have an impact on the feasibility of administering reduced-dose YF vaccine, by either SC or ID routes.

7.3. Global YF vaccine production capacity

Presently, there are only four manufacturers offering WHO PQ vaccine (Table 6): Bio-Manguinhos, Chumakov Institute, Institute Pasteur Dakar, and Sanofi Pasteur (France). Other manufacturers, including the China National Biotech Group and Sanofi Pasteur (US), produce vaccine for in-country travel markets only and are unlikely to play a role in addressing the need for vaccine in the major endemic areas.

In the second evaluation of GAVI (CEPA, 2010), "UNICEF product availability assessment indicates 'limited' to 'very limited' supply [of YF vaccine] in 2009 and 'still fragile' supply from 2010 to 2012." The authors of that report gave this assessment a low rating for robustness, however, because data "was missing," and there was the "use of proxies" and "qualitative supply assessments only."

From information available in the public domain,[27] there are no known plans by existing YF vaccine manufacturers for a rapid expansion of YF production capacity in the immediate future:

[26] Joachim Hombach, IVR WHO, written communication, August 23, 2012.

[27] In May 2012, Sanofi Pasteur provided an update, and statement for use in this report "In the 2011 context of a confirmed increased demand and market predictability, Sanofi Pasteur has made the decision to invest to significantly increase its YF vaccine production

- Crucell's plans for Flavimun®, which has been in the registration process for several years, are not known.
- It has been reported that the Instituto Nacional Salud (Colombia) is considering recommencing YF vaccine manufacture and that the National Administration of Laboratories and Institutes of Health (ANLIS, Argentina) is undertaking technology transfer related to YF vaccine production (Cortes et al., 2012); however, the current status and scale of both sets of plans are not known.
- Because of the high start-up and ongoing costs involved in YF vaccine manufacture and the unstable market for YF vaccine, it is generally considered unlikely that new manufacturers will enter the YF vaccine market, or that previous manufacturers such as Instituto Nacional Salud (Colombia) will restart production.[28]
- Because YF is not endemic in Asia, there is no obvious motivation for vaccine manufacturers in this region to initiate or expand production of YF vaccine for public sector use.
- In general, production of YF vaccine appears to be regarded as a lower priority than production of other more commercially successful vaccines; for example, Crucell's Flavimun® program was "de-prioritized" in favour of the company's measles and rubella vaccine (MoRuViraten®), which shared the same production facility.[29]

Given the right incentives, new manufacturers might start YF vaccine production (the Serum Institute of India was successfully incentivised to produce MenAfriVac [meningitis A vaccine]), but none are known to be doing this at present. It should be noted, however, that the Chumakov Institute has recently significantly expanded its YF production capacity to 10 to 12 M doses per year.[30]

If one or more of the main YF vaccine manufacturers were to increase their production capacity (or change production processes) in the medium to long term, this could potentially ease some of the supply issues for YF vaccine, assuming that the remaining manufacturers maintain production at current levels.

However, in any given year, global production of YF vaccine can (and does) fall short of expected supply due to unforeseen problems in the manufacturing process, such as a shortage of embryonated SPF eggs, low yield, or contamination problems. For example:

- The total global production capacity for YF vaccine in 2009 was estimated to be 90 to 115 M doses; however, actual production in 2009 was probably only 75 M doses because fewer than expected 50-dose vial presentations (by Bio-Manguinhos) were produced (Ferguson et al., 2010).
- In 2012, UNICEF reported that of the four manufacturers producing PQ YF vaccine, one was "under suspension" and one had only "limited availability" (UNICEF, 2012).

Supply of YF vaccine might also be restricted in the longer term by depletion of seed virus stocks:

capacity in the short to mid-term in order to match evolving country demand."
Michael Attlan, Isabelle Deschamps, Cecile Tricoire, Sanofi Pasteur, oral communication, May 9, 2012.
Isabelle Deschamps, Sanofi Pasteur, written communication, June 6, 2012.

[28] Alba Maria Ropero, PAHO, oral communication, February 16, 2011.

[29] http://www.crucell.com/page/downloads/8_John_Lewis_-_Technologies_Analyst_Day_London_12_March_2008.pdf

[30] Alexandra Sinyugina and Andrew Malkin, Chumakov Institute, oral communication, January 26, 2011, and written communication, April 11, 2012.

- In 2010, Bio-Manguinhos reported at a WHO meeting that, having prepared a new master seed, it had sufficient working seed vaccine virus for 19 years at 50 M doses per year (Ferguson et al., 2010).
- At the same meeting, issues of "limited seed stock availability" were reported by Institut-Pasteur Dakar, Senegal. Only one vial of master seed (passage 233) produced in 1974 remains and there is a limited stock of the working seed lot produced in 1985. An increase in production capacity would require a new working seed (Ferguson et al., 2010).

It is likely, therefore, that over the next few years, one or more vaccine manufacturers will need to produce and use new seed stocks for their production of YF vaccine.[31]

Vaccine derived from the new seed stocks will require preclinical and clinical testing. Changes in excipients or PFU per dose might be made and tested at the same time. Plans for these changes are not publicly available, but they are likely to take several years to complete. The clinical trials that will be needed might offer an opportunity to investigate dose-spared ID or other reduced-dose regimens.

A list of YF vaccine manufacturers and the presentations of YF vaccine produced are shown in Table 6. Detailed data on YF vaccine supply and actual production from each manufacturer are likely to be available only under confidentiality agreements.

[31] Alan Barrett, University of Texas Medical Branch at Galveston, oral communication, September 4, 2012.

Table 6. Manufacturers of YF vaccines and the presentations produced

Manufacturer (country); Trade name.	YF vaccine strain	Presentations	WHO PQ	Notes
Bio-Manguinhos (Brazil); Yellow fever vaccine	17DD	5-dose vial	Yes[a]	Bio-Manguinhos is parastatal (owned by the government) and focuses on supply for Brazil, with some sales to PAHO and Africa in some years. The company is conducting a dose-dilution study with the aim of producing a new formulation of the vaccine with a lower titer (potency) per dose (Ferguson et al., 2010). The results of the study in adults are not yet published.
		10-dose vial	Yes	
		50-dose vial	Yes[a]	
Institute Pasteur Dakar (Senegal); Stabilized YF vaccine	17D-204	5-dose vial	Yes	Has produced YF vaccine since 1966. The vaccine is used predominantly in African countries. The Agence Francaise de Developpement recently approved €8M for the construction and equipment of a new YF vaccine production unit. [32]
		10-dose vial	Yes	
		20-dose vial	Yes	
Chumakov Institute (Russian Federation); YF vaccine live freeze-dried	17D-213/77	2-dose ampoule	Yes	Has manufactured YF vaccine in Russia since the 1970s; until recently, for the travellers' market only (50,000–70,000 doses per year). Production has been scaled-up to 10–12 M doses per year (based on a 5-dose presentation), and is changing from ampoules to vials. A 10-dose presentation is expected at Q4 2012.[33]
		5-dose ampoule	Yes	
		10-dose ampoule	Yes	
Sanofi Pasteur (France); Stamaril	17D-204	1-dose vial	No	One of the leading producers of YF vaccine. Vaccine is produced in the USA and France using the same strain of YF, but at a different passage number. Only the vaccine manufactured in France is WHO PQ and purchased by UNICEF (10-dose presentation only). Sanofi Pasteur's YF vaccines are the only ones marketed and registered in Europe, Japan, and the US.[34]
		10-dose vial	Yes	
Sanofi Pasteur (USA); YF-Vax	17D-204	1-dose vial	No[b]	
		5-dose vial	No	
Crucell (Switzerland); Flavimun	17D-213/77	Not known	No[c]	NOT YET AVAILABLE. Crucell filed for registration in 2009. Vaccine uses the strain formerly produced by the Robert Koch Institute, of which 2.5 M doses were produced between 1963 and 2001 (Ferguson et al., 2010).
China National Biotech Group (China)	17D 204	Not known	No[b]	The vaccine is only used for travel market within China. The vaccine is not PQ because the Chinese national regulatory authority had not, until recently, been approved by the WHO (Ferguson et al., 2010). In March 2011, the WHO announced that "vaccine manufacturers in China are now eligible to apply for prequalification of specific products".[35]

Notes: M = millions; YFV = yellow fever virus; PQ = prequalified; a. these presentations might not currently be available for export; b. used in-country for vaccination of travelers only; c. likely to be used in-country for vaccination of travelers only.

[32] http://www.proparco.fr/jahia/Jahia/lang/en/home/presse-afd/communiques?cache=bypass&actuCtnId=44353

[33] Alexandra Sinyugina and Andrew Malkin, Chumakov Institute, oral communication, January 26, 2011, and written communication, April 11, 2012.

[34] Isabelle Delannoy, Sanofi Pasteur, written communication, April 16, 2012.

[35] http://www.who.int/immunization_standards/vaccine_regulation/nra_china_functional/en/index.html

7.4. Factors limiting global YF vaccine production

In 2012, the main factors limiting global production of YF vaccine are commercial, and also technical issues associated with the production process. These are summarized in Table 7.

Table 7. Factors that do or have previously limited production of YF vaccine

Limiting factor	Cause	Consequences	Remedy
Small number of YF vaccine manufacturers.	Absence of stable demand or market for YF vaccine. Lack of certainty of funding for YF vaccine purchasing. Short-term demand forecasting.	Concern from producers that they will produce more YF vaccine than will be purchased, leading to reluctance to commit to a given level of production and unwillingness to invest in YF vaccine production.	Increase funding for YF vaccine procurement and/or introduce longer term funding commitments or incentive.
Competition for production capacity by other vaccines.	Facilities for vaccine production are limited, so vaccines 'compete' for production capacity.	The most economically attractive vaccine is likely to be favoured, which is rarely YF vaccine.	Increase funding for YF vaccine procurement and/or ensure longer term funding commitments.
Supply of SPF eggs.	There are a limited number of SPF egg suppliers. SPF eggs are also used for production of live-attenuated influenza vaccines.	Long lead times are required for SPF egg ordering and supply. Manufacturers are unable to respond rapidly to acute vaccine shortages caused by unexpected surge in demand.	Increase the number of SPF egg suppliers.
Availability of vaccine seed stocks.	Gradual depletion of existing seed stocks over time.	Finite capacity for YF production until new seed stocks are produced and characterized.	One or more manufacturers will need to establish and characterize new master or seed virus stocks.
Lyophilization and fill/finish capacity.	Lyophilization is a batch process that can take several days per cycle.	The lyophilization step limits the number of YF vaccine 'vials' that can be produced.	Increase the number of doses per vial, and/or invest in more lyophilizers and filling lines.

Notes: information from public-domain literature (including Ferguson et al., 2010) and key opinion leaders (KOLs).

7.5. Summary

- YF vaccine is manufactured using a process that has not changed significantly for decades.
- The vaccine released by manufacturers typically has a potency 2- to 100-fold higher than required by the WHO recommendations. For most YF vaccines, the average PFU per dose has increased over the past few decades.
- The global production capacity for YF vaccine is limited by a combination of commercial and technical factors, including:
    - The uncertainty and commercial unattractiveness of the YF vaccine market limits the number of manufacturers and the amount of vaccine produced by each manufacturer.
    - Bottlenecks in the production process; in particular, the need to lyophilize the vaccine and the availability of SPF eggs.
    - Limited availability of seed virus for some manufacturers.
    - Acute or short-term production problems such as low yield or contamination.
- Taken together, these factors result in a limited supply chain that often fails to meet demand and that is relatively inflexible and unable to respond to unexpected surges in demand for YF vaccine.

8. YF vaccine: summary of supply–demand issues

In the past 15 years, there have been examples of great successes in controlling YF in several countries in South America and Africa, due to:

- Completion of national or subnational preventive mass campaigns in some countries, which have protected the populations of whole countries from YF.
- Effective responses to most YF outbreaks, which have prevented many thousands of deaths in those geographic areas.
- Successful introduction of YF vaccine into routine childhood immunization in many countries; some of these have achieved very high rates of coverage and protect all their infant populations from YF infection.

These successes have been largely due to the interventions of the WHO, GAVI, UNICEF, and the PAHO Revolving Fund working with countries to ease many of the supply–demand imbalances:

- The establishment of a (rolling) global stockpile of YF vaccine has satisfied the needs for most outbreak responses in both Africa and South America. It is considered to be "relatively easy" to fundraise to support outbreak campaigns, even if funding is obtained retrospectively.[36]
- Longer-term forecasting and procurement has helped some purchasers and manufacturers predict the supply needs and increase the attractiveness of the market to manufacturers.
- Better risk assessment for YF infection has reduced some of the "wastage" of vaccine on individuals who are not at sufficiently high risk of YF infection to benefit from vaccination in the short term.

Despite these successes, there have also been:

- Acute shortages of YF vaccine in some countries at some times, which have delayed or prevented routine immunization or effective outbreak responses (Appendix Table 7):
    - In 2009, the demand for YF vaccine was 105 M, but only 75 M doses were produced.
- Chronic undersupply of YF vaccine for some areas of demand, which has delayed preventive mass campaigns and routine immunization (Appendix Table 6):
    - In 2010, only one preventive campaign was carried out in West Africa "owing to problems with the availability of vaccine"(WHO 2011c).
- Chronic problems of undertendering and undersupply for some markets that have financing available for procurement of YF vaccine:
    - This has been a problem in PAHO-supported countries. In 2009 the amount of YF vaccine provided by manufacturers was approximately 7.5 M doses compared with the 15 M doses offered by the manufacturers and the 20 M doses requested by PAHO.[37]

The current position was summarized at a recent UNICEF "Consultation with Industry" meeting (UNICEF, 2012). The key points were that:

- There was sufficient YF vaccine available for the emergency outbreak stockpile and for routine immunization.
- There was not sufficient vaccine to cover all planned preventive campaigns, resulting in campaigns being delayed.

[36] Alejandro Costa, WHO, oral communication, January 31, 2011.

[37] Alba Maria Ropero, PAHO, oral communication February 16, 2011.

- There were concerns regarding the manufacture of YF vaccine:
    - Of the four manufacturers producing PQ YF vaccine, one was currently "under suspension" and one could only produce limited amounts of vaccine.
    - The emergency stockpile was with one supplier only.
- Overall, demand for YF vaccine continued to exceed available supplies.

Strategies that could be employed to improve the availability of YF vaccine to prevent or mitigate supply shortages are discussed in Section 9.

9. Short- to medium-term strategies to improve supply of YF vaccine

Improving the availability of YF vaccine to address imbalances between the supply and demand could be achieved in the short to medium term by intervening at several levels in the overall process of planning, manufacturing, procuring, and use of YF vaccine:

- Public health and procurement:
  - The overall demand for vaccine could be reduced by an actual change in need for vaccine or a reduction in the unnecessary use (or wastage) of vaccine.
  - Procurement processes could be improved to incentivise YF vaccine producers.
- Manufacturing:
  - Changes in the YF vaccine manufacturing process could be made to increase the number of doses available; this might be achievable by reformulation to change potency or by changing the presentation of vaccine to give more flexibility of use within different-sized sessions.
  - Manufacturers could increase their capacity for production of bulk vaccine and/or lyophilization.
- Use of vaccine: the way the vaccine is used in the clinic could be changed, for example:
  - By better matching of session sizes to vaccine presentation (number of doses in a vial).
  - By the introduction of dose-sparing.

These factors are discussed in more detail below.

9.1. Public health and procurement factors

Various strategies can be applied by public health organizations and public-sector vaccine purchasers to decrease or smooth the demand for number of YF vaccine doses required. Detailed discussion of these approaches is outside the scope of this report, but they include:

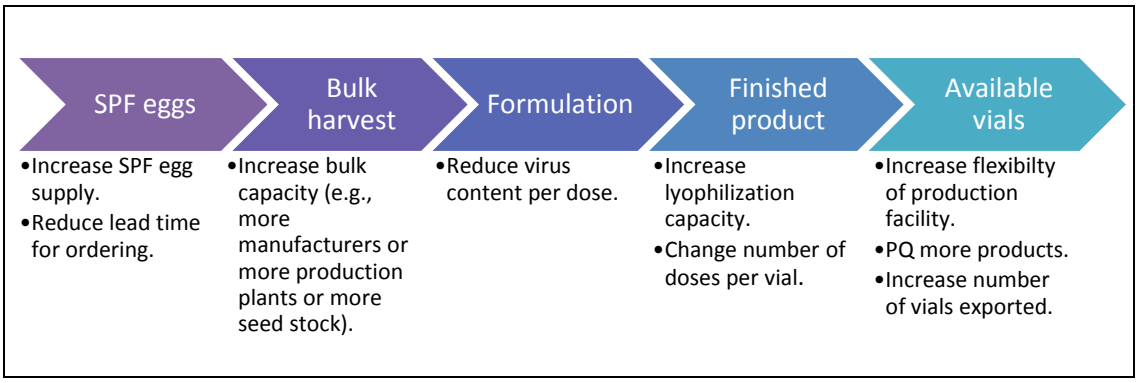
- Vector control can affect need for vaccine, although this is not easy to achieve in nonurban areas and even in urban areas (as seen with the lack of successful dengue control in many urban areas).
- Surveillance for cases of YF disease and for YF virus in NHPs and vectors and levels of immunity in a population; this can also ensure that outbreaks are detected early so that the outbreak response can be smaller.
- Risk assessment, based on surveillance and knowledge of human behaviours.
- Travel vaccination, which can prevent the ingress of virus into susceptible populations.
- Stockpiling of vaccine, which can improve the speed of access to vaccine, might also increase wastage of vaccine, if it is not cycled into use before its shelf life is exceeded.
- Reducing wastage of vaccine caused, for example, by not matching doses per vial with session size, by over-ordering vaccine and having policies of booster doses that aren't necessary and also from damage to vaccine due to problems with the cold chain.
- Forecasting of vaccine need, which relies on good risk assessment and demographic data and can be shared with manufacturers to plan for capacity changes.
- Advocacy for increased prioritization of YF control, within countries and at the international level, can increase the financial and human resources for YF vaccination.
- Procurement initiatives for vaccine longer-term planning and commitment for YF vaccine purchase increases the attractiveness of the YF vaccine market for manufacturers and decreases risk of supply shortages.

- Increasing the amount of YF vaccine made available for an international public-sector market, including by parastatal manufacturers (such as Bio-Manguinhos) that primarily supply their own country's needs.
    - Parastatal manufacturers can have their own reasons for increasing YF vaccine production without being able to increase the doses available to an international public health market, such as a requirement to build a larger in-country stockpile in case of large outbreaks within the country of interest.
- Targeting of YF vaccine, which can ensure that those most likely to benefit from YF vaccination gain access to it.

9.2. Manufacturing strategies to increase production of YF vaccine

Several changes could be made to the YF vaccine manufacturing process to increase the amount of vaccine produced (Figure 3).

Figure 3. Possible changes in the manufacturing process to improve the supply of YF vaccine



Notes: PQ = prequalify (WHO); SPF = specific-pathogen-free.

Three steps in the manufacturing process were reported by key opinion leaders (KOLs) to be significant bottlenecks in the current production of YF vaccine (Section 7.4):

- *Supply of SPF eggs*.[38] The global supply of embryonated SPF eggs required for YF vaccine production is limited. Securing access to sufficient numbers of eggs requires advance ordering and long lead times. In addition, SPF eggs are also used for the production of live attenuated influenza vaccines and in the early stages of the production of split and inactivated influenza vaccines, placing additional demands on the limited supply.
- *Lyophilization capacity*.[38,39,40]. Lyophilization is a time-consuming "batch," rather than continuous, process, which can take 36 to 48 hours per cycle. In cases where lyophilization is the bottleneck, throughput could be increased by installing more lyophilization equipment.
- *Supplies of seed stocks*. YF vaccines are produced using a seed-lot system. A seed stock of virus (the working seed or secondary seed) is produced and extensively characterized. Vials from this stock are used to inoculate eggs to produce vaccine batches that are all at the same passage level and "standardized," even though they are produced over a period of years.

[38] Dr Reinaldo de Menezes Martins, Bio-Manguinhos, written communication, February 7, 2011.

[39] Alejandro Costa, WHO, oral communication, January 31, 2011.

[40] Brendan Flannery, PAHO, oral communication, January 25, 2011.

Gradual depletion of the secondary seed stocks limits the amount of vaccine that can be produced by a manufacturer, until eventually a new seed stock has to be produced, which then has to undergo full characterization and testing including the monkey neurovirulence test as described by Marchevsky et al. (2006).

- At least one manufacturer has plans to address limitations in seed stock availability during the next few years. [41]
- The Institut Pasteur Dakar has reported limited supplies of working seed stock (Ferguson et al., 2010), and relatively recently Bio-Manguinhos needed to produce a new working seed lot (Marchevsky et al., 2006; Ferguson et al., 2010).

Other approaches shown in Figure 3 that could be taken in the short to medium term include

- Reducing the titer of YF vaccine per dose, thereby stretching the amount of bulk product. All manufacturers currently release vaccine with a higher virus content per dose than the WHO recommended minimum potency, typically by 2 to 100 times (see Section 7.2 and Appendix Table 3). There could, therefore, be scope for reducing the potency of vaccine filled per vial but this would probably require reformulation and retesting for stability and in clinical trials for non-inferior immunogenicity and adverse events.
  - Bio-Manguinhos (in Brazil) is currently developing and undertaking clinical testing of a new, lower-potency formulation.[42] The results of a clinical trial testing lower potency doses of YF vaccine in adults have been published (Martins et al., 2013). The data show that doses of vaccine of 27,476 IU to 587 IU (an approximately 45-fold dilution) induced similar seroconversion rates and neutralizing antibody titers.
  - If the supply bottlenecks are at the lyophilization or filling stage (as suggested above), however, simply reducing the potency of vaccine is unlikely to increase supply because the same number of vials will be produced and released.
- Increasing the number of doses of vaccine filled per vial. The total number of vials produced would remain the same, although the number of doses released for a given lyophilization capacity could be increased. If the number of doses per vial does not match the immunization session size, this strategy is likely to result in an increase in vaccine wastage, which would increase price per dose delivered.
- Increasing the number of PQ YF vaccine products. Currently, there are only two manufacturers of licensed YF vaccines that are not PQ (Sanofi Pasteur, US, and the China National Biotech Group [CNBG]):
  - The annual production capacity of Sanofi Pasteur (USA) is not known, but there have been several times when Sanofi Pasteur (USA) was unable to keep up with the demand in the travel vaccine market.[43]
  - The capacity of CNBG is relatively small; actual production had been reported to be 200,000 to 300,000 doses per year, although this was expected to increase toward 2 M doses per year by 2010 (Ferguson et al., 2010).

  Therefore, increasing the number of PQ manufacturers might not have much impact in the short to medium term.

[41] Alan Barrett, University of Texas Medical Branch at Galveston, oral communication, September 4, 2012.

[42] Reinaldo de Menezes Martins, Bio-Manguinhos, written communication, February 7, 2011.

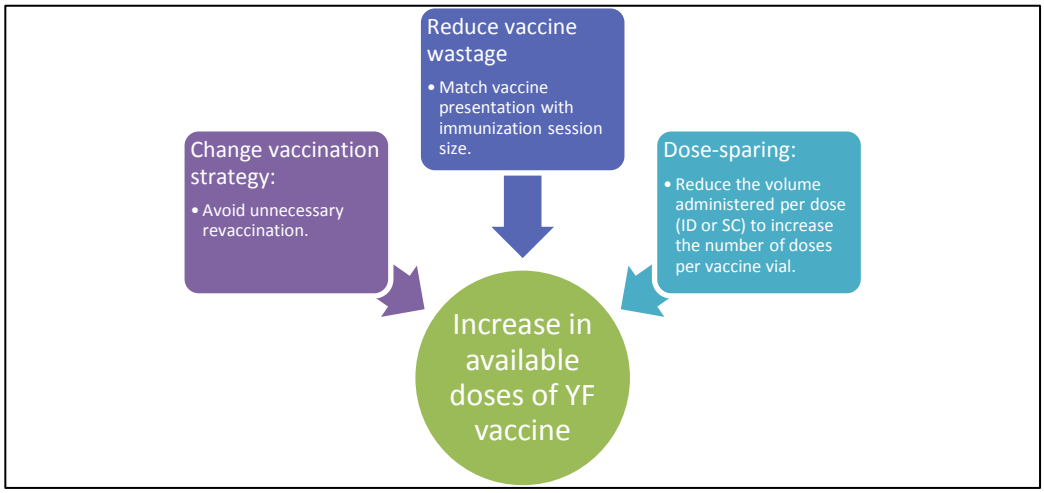
[43] Erin Staples, Centers for Disease Control (CDC), USA, written communication, October 5, 2012.

From information in the public domain, it is not known if manufacturers of PQ YF vaccine will opt to make changes in production (beyond the examples listed above) that require significant investment in facilities or equipment (for example, new bulk production, fill/finish lines and lyophilizers, or changes that involve reformulation). Therefore it is difficult to predict whether the supply of YF vaccine is likely to increase (or decrease) beyond the next 2 to 5 years due to changes in manufacturing process or capacity.

9.3. Strategies to optimize vaccine use in the clinic

Modifications to the way that the vaccine is used could also "stretch" supplies of YF vaccine. These factors are largely under the policy-level control of purchasers of vaccine, ministries of health, public health advisory and regulatory bodies, but the actions are taken at the time of vaccination (Figure 4 and sections below).

Figure 4. Strategies implemented at the point of use of YF vaccine to increase availability



Notes: ID = intradermal; SC = subcutaneous; YF = yellow fever.

9.3.1. Change in revaccination strategy

The way YF vaccine is used in outbreak and preventive campaigns will affect the number of doses of vaccine available to YF-susceptible individuals.

Reducing the number of individuals that are unnecessarily revaccinated, either during campaigns or by routine boosting every ten years, will reduce demand for doses. This can be difficult to implement if documentation or recall of prior vaccination is poor or if there is concern that prior vaccination might have been suboptimal. Policy to support this change will be easier to develop if there is stronger evidence for the long-lasting immunity after one dose of live attenuated vaccine; this is on the agenda of the YF vaccine working group of WHO SAGE.[44]

9.3.2. Reduction in vaccine wastage

Vaccine wastage can occur with any vaccine, for several reasons:

[44] http://www.who.int/immunization/sage/working_mechanisms/en/index.html; http://www.who.int/immunization/sage/SAGE_wg_call_yellow_fever.pdf

- Mismatch in ordering or stock levels and local demand for vaccine, which can mean that vaccine exceeds its shelf life before it can be used. This has been a localized problem for some countries with YF vaccine.
- Damage to vaccine (usually cold chain infringements), which require disposal of the vaccine vial without use. The extent of this type of wastage is not known for YF vaccine.
- Mismatch of vaccine presentation to session size, which results in unused, reconstituted doses being discarded at the end of the immunization session or within six hours of reconstitution (WHO, 2000). This is more likely in routine childhood immunization with YF vaccine because the session sizes are smaller than in campaign use. One KOL stated there fewer than five YF vaccinations are administered per session in some routine settings in South America.[45]

In routine immunization clinics, reported wastage for YF vaccine can be much higher than for other vaccines:

- In Cameroon, 27.2 percent wastage of YF vaccine was detected at fixed sites and 38.8 percent in outreach (Ebong et al., 2011).
- In a survey in The Gambia in 2004, 49.86 percent wastage of YF vaccine was found in public health settings. This was the highest level of vaccine wastage. Bacille Calmette Guerin (BCG), which was in 20-dose vials and, like YF vaccine, needed to be discarded within six hours of reconstitution, was also high at 44.08 percent, but wastage of Hib (supplied at fewer doses per vial) was only 5.4 percent (Johnson, 2004). Thus, the number of doses per vial seems to have been inappropriately high for the immunization setting, resulting in vaccine being discarded and wasted.
- In Ghana in 2005, the "national wastage rate" for YF vaccines was 20 percent; the authors found underreporting on wastage "due to fear;" stocks of expired YF vaccine and overstocking (Ghana Health Service, 2008).

The cause of wastage in routine clinics is not reported, however, which makes planning to address it much more difficult.

In some countries, to help increase session size to better match vial presentation, the policy is to request parents to return on specific days for YF vaccination.[46] This reduces the wastage of vaccine, but can result in missed opportunities to vaccinate susceptible infants, as well as lead to additional costs to parents.

YF vaccine wastage rates used for planning purposes vary widely between countries and over time; in their 2010 Annual Reports to GAVI[47] there does not seem to be an obvious association with vaccine wastage rates and doses per vial (it is presumed that these rates are for routine childhood vaccination):

- 17 African countries listed wastage rates for YF vaccine, which varied from 5 percent (Guinea, 5-dose vials; Sierra Leone, 10-dose vials) to 55 percent (Guinea Bissau, 10-dose vials).
- Two countries anticipated their rates increasing (Benin from 30 to 45 percent; and Congo 20 to 25 percent) and five anticipated a decrease in rates (Central African Republic [CAR], Congo DR, Guinea Bissau, Kenya) with the final rate ranging from 10 to 30 percent.

[45] Brendan Flannery, PAHO, oral communication, January 25, 2011.

[46] Alba Maria Ropero, PAHO, oral communication, February 16, 2011.

[47] 2010 Annual reports to GAVI, downloaded from links on http://www.gavialliance.org/country

In campaign settings, wastage of YF vaccine is reported to be much lower than for routine childhood immunization, which is probably due to the higher session sizes but might also be due to intensive supervision over short durations of activity:

- In a mass campaign, in Cameroon in 2004, the wastage rate was 4.6 percent (Wiysonge et al., 2008).
- Two KOLs estimated that vaccine wastage in campaign settings ranges from 2 to 10 percent, which is considered very low.[48,49]

9.3.3. Preferred presentations of YF vaccines

The presentations of YF vaccine produced by the different manufacturers are shown in Table 6. Country preference (reflected in UNICEF procurement) is for 10- and 20-dose presentations for preventive and outbreak campaigns; 50-dose vials are acceptable "to an extent."[46]

For routine immunization, 5- and 10-dose presentations are preferred (UNICEF, 2008c). Other users of YF vaccine have stated that the ideal presentation would be single-dose vials,[46,50] with the recognition that this would likely be more expensive per dose. Also single-dose presentation is currently unavailable outside the travel market in Canada, Japan, and the US and so is likely to require additional investment in manufacturing facilities by some manufacturers. If lyophilization capacity is a limiting factor in the production of YF vaccine, changing to single-dose vials would, most likely, reduce further the number of doses of YF vaccine available per year.

Computational modeling has been used by Lee and colleagues (Lee et al., 2010) to determine the optimal number of doses per vial in terms of cost per dose of vaccine for a number of different vaccine types; inputs include the cost of vaccine storage and disposal. The relationship between optimal presentation and number of patients to be vaccinated per day is complex:

- For YF vaccine, for 1 to 13 and 22 to 25 patients per day, 5-dose vials are usually optimal; for 14 to 21 and 26 to 27 patients per day, 20-dose vials are most cost effective.
- For daily patient rates of 28 to 50 patients per day, 50-dose vials are most cost effective.

In campaign settings, the number of individuals immunized per session is much higher:

- One KOL based in Africa stated that approximately 400 to 600 individuals per day can be vaccinated at a single immunization post.[51] International Finance Facility for Immunisation (IFFIm) state "a vaccination team can immunise up to 1,200 people per day."[52]
- In a mass campaign in an urban setting in Cote d'Ivoire in 2001, 1,325 persons per day per team were immunized, using approximately 66 vials of vaccine of 20-doses of Aventis (Sanofi) Pasteur vaccine per vial (Fitzner et al., 2004).
- In Sudan in 2005, Médicins Sans Frontières (MSF) estimated that "each vaccinator immunized 1,200 people per day; later, between 100 and 200 people were immunized per vaccinator in an effort to catch up with people who could not get there during the major vaccination days."[53]

[48] Alejandro Costa, WHO, oral communication, January 31, 2011.

[49] Alba Maria Ropero, PAHO, oral communication, February 15, 2011.

[50] Brendan Flannery, PAHO, oral communication, January 25, 2011.

[51] Olivier Ronveaux, WHO AFRO, oral communication, January 21, 2011.

[52] http://www.iffim.org/funding-gavi/results/yellow-fever-campaign/

[53] http://www.doctorswithoutborders.org/news/article.cfm?id=1649&cat=field-news

For these reasons, in campaign settings, 20-dose and 50-dose presentations can be used without excessive vaccine wastage.

9.3.4. Dose-sparing at the point of vaccination

Another strategy that could be implemented "downstream" by vaccine purchasers and users of YF vaccine is the administration of a reduced volume of the existing formulations of YF vaccine. This strategy is based on the fact that the potency of YF vaccines greatly exceeds the required minimum level, at least when they are first released (see Appendix Table 3):

- This suggests a lower dose (by volume) could possibly be given by the standard SC route, or by a change of route to ID (see next bullet point), although the impact of this on immunogenicity and safety would need to be carefully demonstrated".
  Results published by Martins et al. (2013) suggest that, in young healthy adults, it might be possible to administer a lower dose of YF vaccine by the standard SC route, without having a negative impact on immunogenicity (see Section 9.2).
- The supposed immunological efficiency, and probable superiority, of the ID route means that a change to this route of administration might allow an even lower dose to be used than is necessary by the SC route. This also needs to be confirmed in clinical studies, although initial studies in a HIC suggest that ID delivery of a 20 percent dose (by volume) induces immune responses equivalent to the standard dose (by volume) delivered SC (Roukens et al., 2008; Roukens et al., 2009). These investigators did not test a reduced volume delivered by SC route and only looked at immunogenicity up to 12 months after vaccination.

Delivery of fractional doses (by volume) of YF vaccine could be relatively easy to test and to implement compared with some other approaches to improve availability of the vaccine. It is possible that:

- No modification of current manufacturing processes, or reformulation or change of presentation, would be required; this assumes that there are no safety issues arising from changing route of delivery from SC to ID (for example, due to potentially reactogenic stabilizers in the vaccine).[54]
- No capital investment would be needed.
- "Only" clinical testing (of each vaccine strain in the appropriate populations and setting) would be required to give confidence of non-inferior immunogenicity and safety. This would likely precede, if desirable, a label change by the manufacturer to support a policy of delivery of a reduced volume, possibly by a different route. This might be for "general use"' or just in times of acute shortage of vaccine.

The potential benefits and possible drawbacks associated with this approach, and the issues involved in demonstrating feasibility and implementation, are discussed in more detail in Sections 12 and 13.

9.4. Comparison of strategies to increase availability of YF vaccine in the short to medium term

For the purposes of this analysis, four different market clusters were identified: Africa, (Central and South) Americas (excluding Brazil), Brazil, and Global. The classifications were based on the geographic regions having different:

[54] Erin Staples, CDC, written communication, October 5, 2012.

- Patterns of recent demand.
- Supply issues for YF vaccine.
- Processes in the future for production, procurement, and use of YF vaccine.

The regions used are the same as those used in the WHO's conservative YF vaccine demand forecast model (Section 5.4 and Section 12) and in the preliminary modeling used in this report (Section 12.3).

Using input from KOLs, an attempt was made to estimate the probability (based on likelihood and ease) of implementation of the "manufacturing" and "point-of-use" strategies to improve YF vaccine supply and their likely impact on the availability of the vaccine if successful (summarized in Table 8). "Public health strategies" have not been included in the table to improve clarity.

The predictions should be tested further with key stakeholders, but could have utility to compare a reduced-volume dose-sparing strategy with manufacturing-based strategies.

Table 8. Manufacturing and point of use strategies to ease YF vaccine supply–demand issues

	Africa		**Americas (excluding Brazil)**		**Brazil**		**Global**	
	p [a]	Impact [b]	*p*	Impact	*p*	Impact	*p*	Impact
Manufacturing strategies								
Increase supply of SPF eggs	Not known	Low	Not known	Low	Not known	Low	Not known	Low
Increase capacity for lyophilization	Low	High	Low	High	Low	High	Low	High
Increase overall capacity for bulk YF vaccine production	Not known	Med	Not known	Med	Not known	Med	Not known	Med
Increase number of doses per vial	Low	Low	Low	Low	Low	Low	Low	Low
Reduce potency per dose	Low	Low	Low	Low	Med	Med	Low	Low
Increase number of PQ manufacturers	Low	Med	Low	Med	Low	Med	Low	Med
Point-of-use strategies								
Change vaccination strategy (e.g., reduction in re-vaccination)	Low	Low	Low	Med	Low	Med	Low	Med
Match vial size to session (reduce waste)	Med	Med	Med	Med	Med	Med	Med	Med
Dose-sparing (reduced volume per dose)	Med	High	Med	High	High	High	Med	High

Notes: *p* = probability; SPF = specific pathogen free; a: likelihood of implementation; b: likely impact if successfully implemented; predictions are based on gray and peer-reviewed literature and KOL interviews and comments. There might be information that is not in the public domain that could better inform these predictions.

From Table 8, it can be seen (based on information in the public domain) that many manufacturing strategies were considered to have a low likelihood of being implemented. The exceptions to this were the activities known to be underway at Bio-Manguinhos in Brazil to evaluate reduced potency YF vaccine and to increase YF vaccine production capacity; the likely impact of these initiatives on global YF vaccine supply was, however, thought to be only moderate.

The “point-of-use” approaches of better matching of existing “vial size” (doses per vial) to immunization setting and also delivery of reduced-volume doses were considered to have a higher likelihood of being implemented (if clinical and programmatic data supported their use) and could have a significant impact on vaccine availability.

9.5. Summary

- A range of strategies to ease supply–demand issues for YF vaccine, which could possibly be implemented in the short to medium term, have been described. These include changes to the vaccine-manufacturing process or capacity, or involve changes to the way the vaccine is administered.
- From public domain information only, some changes in manufacturing process or capacity have a low likelihood of being implemented due to the investment required by vaccine producers. It is possible, however, that some YF vaccine manufacturers already have plans to change or increase production capacity that are only available under a confidentiality agreement.
- Strategies implemented at the point of use of vaccine, in particular, the delivery of reduced-volume doses, were considered by KOLs to be relatively easy to trial and use and, if successful, were more likely to be implemented.

10. Long-term strategies to increase availability of YF vaccine

In the longer term (the year 2022 and beyond), changes in vaccine manufacturing processes or capacity, and changing the nature of YF vaccine, could facilitate improved supply of YF vaccine.

10.1. Changing the vaccine manufacturing process for live attenuated YF vaccine

Changing production of YF 17D vaccines from egg-based to cell-culture-based systems could have several advantages, including:

- Reduced dependence on SPF eggs, thereby reducing lead-time for vaccine production (Figure 3).
- Vaccines that could be used safely in egg-allergic individuals.

Recent data (Freire et al., 2005) obtained with chicken-egg fibroblasts suggest that, in contrast to earlier attempts, high yields can now be obtained in cell culture, indicating that this approach could be less costly than earlier attempts at cell-based production of YF vaccine. From information in the public domain, none of the current YF vaccine manufacturers appear to be pursuing cell-based production of live attenuated YF vaccine, possibly because of the problems of maintaining both genetic stability and the attenuated phenotype when the vaccine is grown in cell culture. They would also need to conduct (expensive) clinical trials and carry out the full vaccine relicensure process.

10.2. Development of novel inactivated YF vaccines

The development of inactivated YF vaccines is being considered primarily for reasons of safety, rather than cost (reviewed in Hayes, 2010), in particular:

- To reduce risk of live-vaccine-associated SAEs, notably yellow fever vaccine-associated viscerotropic disease, and especially in those considered to be at higher risk (aged greater than 60 years, aged less than six months, and in some immunocompromised people).
- To reduce the risk of inadvertent transmission of vaccine virus to people other than the vaccinee, either by blood transfusion (Lederman et al., 2010) or breastfeeding (Couto et al., 2010; Kuhn et al., 2011; Traiber et al., 2011).

Other potential advantages and indications for an inactivated YF vaccine include:

- Use in a prime-boost regimen, administered before the live attenuated vaccine, to reduce the risk of SAEs after the live vaccine (Hayes, 2010).
- Use in those people for whom a live attenuated YF vaccine is contraindicated or precautionary for safety reasons, including infants aged less than six months, some pregnant women, some immunocompromised, and some older people.
- Potentially, inactivated YF vaccines could be included in routine childhood immunization; for example, alongside DTP-HepB-Hib-IPV, including as a combination vaccine with one or more of these antigens, avoiding the scheduling disadvantages of a live vaccine.
- Inactivated YF vaccines might be suitable for delivery by novel technologies, such as microneedle patches.

10.2.1. Status of development of inactivated YF vaccines

Two companies are known to be developing inactivated YF vaccines:

- Xcellerex Inc (Malborough, MA) is developing an inactivated, whole virion YF vaccine, which is adsorbed onto aluminium hydroxide (XRX-001; Monath et al., 2010; Monath et al., 2011). The vaccine is derived from the attenuated YF-Vax (Sanofi, see Table 6), adapted for growth, produced in Vero cells and inactivated with β-propriolactone.

  Preclinical experiments, in a hamster challenge model of passively acquired immunity to derive serological (neutralizing antibody), were used to derive serological correlates of protection for the XRX-001 and YF-17D vaccines (Julander et al., 2011).

  In a phase I trial, XRX-001 induced the development of neutralizing antibodies in 100 percent of subjects receiving 4.8 µg of antigen in each injection (after two doses). This dose level is similar to that of two other inactivated vaccines against flaviviruses: Japanese encephalitis (JE; IXIARO®, Intercell, Austria), used at 6 µg per ml per dose in a two-dose regimen (Schuller et al., 2009), and tick borne encephalitis (Encepur™, Novartis Vaccines, Germany) (Schondorf et al., 2007), used at 2.4 µg per dose (Monath et al., 2010).

  XRX-001 is currently in a liquid formulation and has been shown to be stable at 2 to 8°C for at least six months and for at least eight weeks at 25°C. At this point, it is too early to estimate the likely cost of the vaccine.

- Bio-Manguinhos/Fundacio Oswaldo Cruz is developing an inactivated YF vaccine based on 17-DD cultured in Vero cells, and then inactivated by high hydrostatic pressure, an approach that avoids introduction of additional toxic agents and has been shown to preserve immunogenicity with other viruses (Gaspar et al., 2005). In mice, the inactivated YF vaccine was less immunogenic than live YF vaccine; the current development status of this vaccine is not known.

In general, the fact that inactivated vaccines have been developed against other flaviviruses suggests that it might be possible to develop a similar, inactivated whole-virion (or subunit) vaccine against YF; however, it is likely that an inactivated YF vaccine will be more expensive per dose than the current live vaccine, and will require more than one dose to induce protective immunity, that may lead to suboptimal coverage rates in some areas.

10.3. Development of novel live YF vaccines

Live attenuated YF vaccine strains are being used as vectors for vaccines against other pathogens (including JE, dengue, and West Nile), the most notable example being the Chimerivax™ family of vaccines being developed by Sanofi Pasteur (reviewed by Guy et al., 2010); however, these vaccines are not expected to induce protective immunity to YFV because the key structural proteins that are targets for neutralizing antibodies against YFV are replaced with sequences from the pathogens of interest.

Themis Bio (Austria)[55] is developing several vaccines, including YF, Dengue, and Chikunyunga virus vaccines, using a live attenuated Schwarz vaccine strain of measles virus as a vector. The company's timelines suggest that the YF vaccine will not enter phase I clinical trials until 2012 or

[55] www.themisbio.com

later,[56] and given that this is a relatively untested vector system, it is uncertain whether this will be a successful approach to developing a YF vaccine.

Baxter Biosciences (Austria) have published a report describing the preclinical development of novel YF vaccine(s) using the prME protein gene from YF vaccine (Stamaril) inserted into modified vaccinia virus Ankara (MVA) or D4R-defective vaccinia virus (dVV). Experiments in a mouse model demonstrated T-cell responses ($CD4^+$ and $CD8^+$) and antibody-mediated protection against challenge, even in mice with past vaccination with vaccinia virus (Schäfer et al., 2011). The two recombinant vaccines had a better safety profile than YF-17D, following intracerebral administration in the mouse model.

10.4. Alternatives to the use of YF vaccine in the control of YF

Nonvaccine approaches to the control of YF, used either in conjunction with, or instead of, vaccination could increase vaccine availability.

10.4.1. Anti-viral therapies

If an effective antiviral therapy for symptomatic YF disease was developed, this could reduce the rates of mortality and morbidity with symptomatic YF disease and might lead to an overall reduced use of vaccine. Vaccination would still be required to prevent spread because most people infected with YF are asymptomatic.[57]

Flaviviruses such as YFV present a range of possible targets for antiviral compounds and, because members of the flavivirus family share replication strategies, it is possible, even likely, that compounds with activity across a range of viruses in the family will be identified (Sampath and Padmanabhan, 2009; McDowell et al., 2010).

Despite this, there are no licensed antiviral compounds against YF or any of the flaviviruses, and the development of these compounds faces several hurdles:

- Preclinical studies: ribavirin (RBV) inhibits replication of all flaviviruses *in vitro*, but its *in vivo* efficacy in animal models is poor (McDowell et al., 2010). There is an active program of research into antiviral compounds that are active against flaviviruses (reviewed by Sampath and Padmanabhan, 2009), particularly for viruses such as West Nile Virus, for which there is no effective vaccine. Although promising candidates have been identified from *in vitro* studies, none have had sufficient efficacy or low toxicity in *in vivo* models to have progressed to clinical trials.[58]
- Programmatic issues: most cases of YF in endemic areas tend to occur in remote areas with poor infrastructure for clinical research, which implies that clinical testing of antiviral compounds in the field will be more difficult than in HICs or urban areas of LMICs (Monath, 2008). The drugs might also be too expensive for routine use in LMICs.

Recently, YF vaccine strains have been shown to be lethal following intra-peritoneal (IP) inoculation of mice deficient in receptors for IFN-α, β, and γ (strain AG129; Thibodeaux et al., 2012a); the AG129 mice showed neurotropic and viscerotropic disease. The authors consider that this model offers a lower-biosecurity strategy for anti-YF therapeutic development and the model has already been

[56] Themis Bio, company presentation http://www.themisbio.com/downloads/Themis_presentation.pdf?f=141630b26ef18cf10a187145a13f6226_VGhlbWlzX3ByZXNlbnRhdGlvbi5wZGY%3D.pdf

[57] Erin Staples, CDC, written communication, October 5, 2012.

[58] Alan Barrett, University of Texas Medical Branch at Galveston, oral communication, September 4, 2012.

used to test the efficacy of monoclonal antibodies in preclinical models of YF-like disease (Thibodeaux et al., 2012b).

10.4.2. Vector control to reduce risk of YF

DDT was used to eradicate *Aedes aegytpi* from 22 countries in the Americas after the Second World War; however, alternative insecticides and spraying strategies are not effective against the mosquito for vector-behavioural reasons. The WHO recommendation is for community-based elimination of breeding sites, but there is no evidence that this approach has ever been successful (Reiter, 2010).

10.5. Summary

- New types of YF vaccine might become available in the long term. These might be safer than the current live attenuated vaccine, but are likely to be more expensive to produce so might not improve vaccine availability or affordability in LMICs.
- Antiviral therapies to treat YF are technically feasible, but are likely to be difficult to develop and test.
- An inexpensive, widely available alternative to the current live attenuated vaccine does not appear to be very likely, even in the long term.

11. Delivery of reduced doses of YF vaccine: introduction

Delivery of reduced volumes of YF vaccine per dose (dose-sparing) was identified in Section 9.3 as being a potentially promising strategy for increasing the availability of YF vaccine. In addition, this approach could potentially reduce the total purchase cost of YF vaccine. This strategy will therefore be the focus of the remainder of the report.

This section provides a brief introduction to the concept of dose-sparing in the context of YF vaccine and raises some of the issues associated with its implementation. Subsequent sections deal in more detail with:

- Preliminary modeling of the potential impact of dose-sparing (Section 12).
- Programmatic issues involved with implementation of dose-sparing (Section 13).
- Clinical evaluation of dose-sparing strategy for YF vaccine (Section 14).

11.1. The dose-sparing concept

The dermis of the skin is rich in antigen-presenting cells, and it has been suggested that it is therefore a more immunologically efficient site for the delivery of vaccines. Delivery of vaccines by the ID route, therefore, has been used as a way to achieve dose-sparing without the need for additional adjuvants. Evidence for dose-sparing has been obtained with some, but not all vaccines tested; positive results have been obtained with inactivated poliovirus vaccine (IPV), influenza, rabies, and YF vaccine (reviewed by Lambert and Laurent, 2008; Hickling et al., 2011).

11.2. Evidence for utility of “reduced dose” YF vaccine

There are historical reports of YF vaccine being delivered by scarification, implying delivery of a low volume and dose of the vaccine; administration of the vaccine using this technique is assumed to have protected the populations in question (Frierson, 2010).

In 1943, Fox et al., observed, using outdated methodology, a “protective immune response” after ID administration of 17D vaccine to a small number of recipients (cited in Roukens and Visser, 2008).

There have been two recent clinical studies of ID delivery of YF vaccine (see Table 9 and Appendix Table 10 for details of design and conclusions):

- In a very small Netherlands-based retrospective study, Roukens et al. administered 0.1 ml of YF vaccine intradermally by needle and syringe (N&S), with a control of 0.1 ml saline intradermally in the contra-lateral arm. This was delivered as a “skin test” to seven egg-allergic people deemed to be too allergic to receive the full 0.5 ml subcutaneously. They concluded that the egg-allergic subjects made a potentially protective immune response (Roukens et al., 2009).
- In 2005 to 2007, the same investigators carried out a randomized controlled trial (RCT) in healthy adults in the Netherlands, comparing dose-sparing (by reduced volume) of 17D strain YF vaccine delivered intradermally versus full-dose, by volume, delivered subcuntaneously. They evaluated vaccine viremia at day 5 after vaccination (a marker of a change in vaccine virus behaviour), serology (as a correlate of protection), and adverse events. They concluded that the 0.1-ml ID dose was equivalent to a 100 percent SC dose and recommended larger trials in endemic countries (Roukens et al., 2008).

Table 9. Recent clinical studies of ID administration of YF vaccine

Reference	Intervention	Population, setting	Design and outcomes	Results; notes
Roukens et al., 2009	**Vaccine**: 17D Arilvax (Medeva) or Stamaril (Sanofi Pasteur). **Volume**: 0.1 ml. **Route**: ID. **Device**: N&S. **Comparator**: historical controls.	**Population**: aged 1–53 years (1, 2, 17, 20, 26, 28, 53) who were egg allergic. n = 7 (4 males, 3 females). **Setting**: travel clinic, Leiden, Netherlands.	**Design**: retrospective. **Outcomes**: serology (titers and IU by PRNT assay) once, at 3–32 weeks.	**Results**: 7/7 had serology "above protective threshold." **Notes**: very small sample size. Authors concluded that would need to repeat study in more egg-allergic subjects for confidence that 0.1 ml given in medically controlled conditions is safe and "protective."
Roukens et al., 2008	**Vaccine**: 17D (Stamaril): 3.5 x 10^4 PFU per 0.5 ml dose or 5 x 10^3 MLD_{50}. **Volume**: 0.1 ml (20% dose); potency in this ID dose was still above WHO minimum. **Route**: ID (dorsal forearm; > 6mm wheal). **Device**: N&S. **Comparator**: 0.5 ml (100% dose) SC (upper deltoid).	**Population**: healthy adult volunteers (aged over 18 years). n: 155 primary and n=20 booster. **Setting**: Leiden University, Netherlands.	**Design**: RCT (block randomisation), non-inferiority. No reduced dose SC arm. **Outcomes**: serology at 2, 4, 8 weeks and 1 year (by PRNT); AEs by 3-week diary; viremia at 5 days.	**Serology results**: no difference ID vs. SC (including kinetics); all above WHO protective level; similar in primary/booster doses. **Tolerability**: greater proportion of primary ID vaccinees had redness and itching and for longer vs. SC. Greater proportion of SC primaries had pain and myalgia. No difference in severity of AEs; No severe AEs. **Viremia**: detected in 50% of primary but not booster doses (both ID and SC), but some loss to follow-up. **Notes**: Stamaril is 5x "overfilled" compared with WHO minimum.

Notes: AEs = adverse events; ID = intradermal; MLD_{50} = 50-percent mouse-lethal dose; n = Sample size; N&S = needle and syringe; PRNT = plaque-reduction neutralization test; SC = subcutaneous.

The two clinical studies by Roukens et al. provide a precedent for safe use of ID delivery of YF vaccine, but clinical studies need to be repeated in larger and more representative populations, and with a wider range of YF vaccines. Suggestions for questions to be addressed in future clinical trials are discussed in detail in Section 14, and include:

- Testing vaccines with a lower PFU per dose.[59] The vaccine chosen for the Roukens et al. studies had a high titer per dose. Consequently, injection of a reduced volume still resulted in delivery of a dose above the WHO-recommended minimum potency.
- Modifications in trial design should be considered, including one or more lower-dose SC group(s).[59]
- A more detailed investigation of viremia (over a wider time period) in the low-dose and ID groups.[59]

11.3. Justification for changing the route of injection from SC to ID

Although delivering vaccines by the ID route is generally accepted to be more immunogenic than some other routes (reviewed by Lambert and Laurent, 2008; Hickling et al., 2011), for most vaccines there is little or no clinical evidence to show the ID route is truly more immunologically efficient than the SC or IM routes.

It is possible that reduced-volume doses of YF vaccines could be delivered subcutaneously and could be sufficiently immunogenic; therefore, data from clinical trials will be required to justify a change in route.

[59] Joachim Hombach, IVR, WHO, written communication, August 23, 2012.

Data from a recently-published clinical trial suggest that this approach might be feasible (Martins et al., 2013). In this study, reduced potency (rather than reduced volume) doses of YF vaccine were administered subcutaneously to healthy young adults. A dose of 587 IU (approximately 45-fold lower than the full dose of 27,476 IU) induced similar seroconversion rates and neutralizing antibody titers to the full dose.

It is therefore possible that a reduced volume (0.1 ml) of YF vaccine given subcutaneously would also be sufficiently immunogenic. The Martins et al. (2013) study needs to be repeated in infants and with different batches of YF vaccine to determine whether this approach will be widely applicable.

Finally, it should be noted that data from trials with other (inactivated) vaccines have shown that 20 percent of the standard dose is not always sufficient when delivered intradermally. Sometimes more vaccine antigen is required (reviewed by Hickling et al., 2011).

11.4. Summary

- Intradermal delivery of reduced volumes of some vaccines (notably inactivated influenza and rabies vaccines) has been shown to induce similar immune responses as the standard dose delivered by the standard route.
- Two small clinical trials in HICs suggest that dose-sparing of YF vaccine via ID delivery might be feasible, but much more evidence is required before public health purchasers in LMICs would be confident to change their strategy of use.
- Results from a dose-response study in healthy adults (Martins et al., 2013) suggest that reduced potency doses (up to 45-fold lower) of YF vaccine from one manufacturer, administered subcutaneously, induce similar immune responses to the full dose in healthy young adults.

12. Impact of dose-sparing by reduced volume on YF vaccine availability and cost

For this report, some preliminary modeling of the potential impact of delivering reduced-volume doses of YF vaccine on vaccine demand has been carried out using data from the WHO conservative demand forecasting model described below and in Section 5.4.[60]

The modeling is described as preliminary because:

- It uses only limited data and inputs that were either publicly available or were provided on a nonconfidential basis to the authors of the report.
- The impact of delivery of reduced doses of vaccine was considered for one type of immunization setting only (preventive campaigns).
- No sensitivity analyses have been carried out to date. These should be conducted once a more detailed set of inputs are available for the model.

12.1. Demand forecasting data used for this modeling

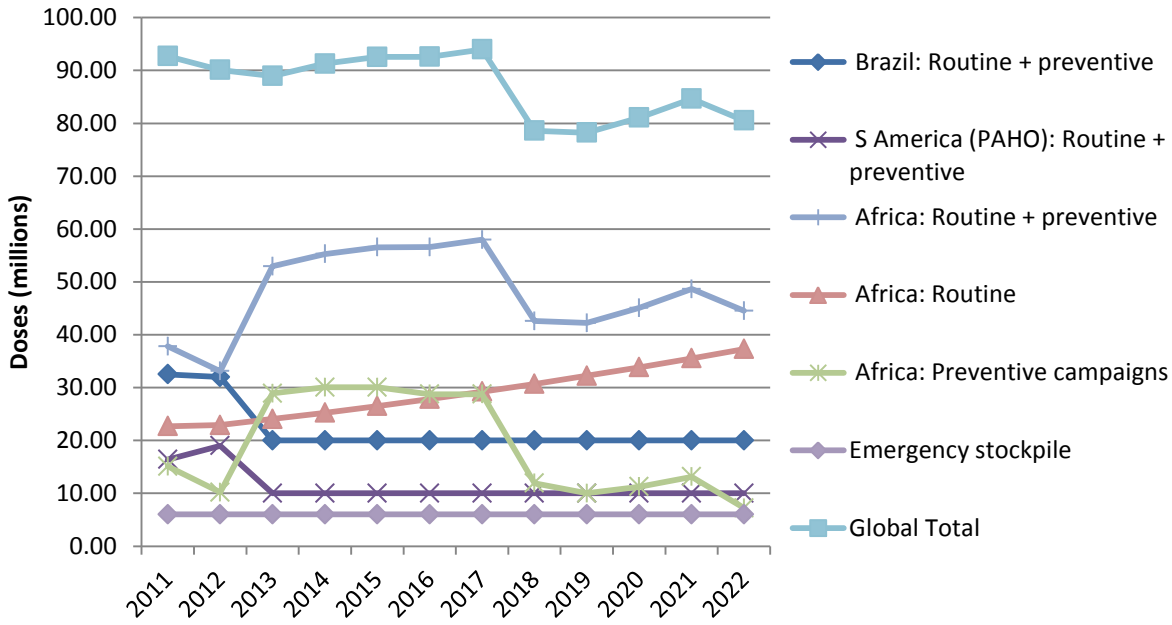
A conservative forecast for YF vaccine demand by geographic area has been produced by the Global Alert and Response Group of WHO (Figure 5). In this model:

- The forecasted demand has been divided into preventive campaigns and routine immunization for Africa, but only an overall demand (campaign and routine immunization combined) is presented for South America (excluding Brazil) and Brazil.
- The total global demand is the sum of the demand for Africa, South America, and Brazil (Figure 5).

This is the baseline WHO forecasting data which has been used for the preliminary modeling of the impact of implementation of dose-sparing in this report (see Sections 12.3.1 to 12.3.4).

[60] Demand forecast was provided by Alejandro Costa, WHO, written communication, April 12, 2011.

Figure 5. YF vaccine demand 2011–2022 according to WHO conservative global demand forecast



Notes: PAHO = Pan American Health Organization; The forecast and data for the figure were provided by Alejandro Costa, WHO.[61]

12.2. WHO's conservative demand forecast: assumptions

The assumptions underlying the WHO's forecasting model are explained below.[61]

African market cluster:

- The demand for routine immunization is modeled as steadily increasing, and assumes high coverage of the birth cohort with a single dose of YF vaccine per infant.
- The gradual increase in the demand each year for routine immunization reflects the increase in African birth cohort rather than any increase in YF endemicity or change of vaccine policy; however:
    - It is likely that endemicity and immunization policy will change over time.
    - High coverage might not be achievable in practice, but it is important to aim and plan for WHO-approved levels.
- Preventive campaigns are assumed to cover 60 percent of the population and these will be run in the remaining identified high-risk countries and Group B countries (Angola, Chad, Congo, Democratic Republic of Congo, Ethiopia, Guinea Bissau, Kenya, Mauritania, Niger, Rwanda, Tanzania, Uganda, and North and South Sudan).
- Campaigns in Nigeria will be spread over four years, probably starting from 2013.
- Excluded from the model is demand for YF vaccine due to any additional preventive campaigns not yet in the global planning process or any outbreak response campaigns.

South America ("PAHO") market cluster:

- Due to differences in procurement and use patterns, the South American market cluster excludes Brazil.

[61] Alejandro Costa, WHO, written communication, March 5, 2012.

- Excluded from the WHO forecast are detailed estimates of the amount of vaccine used for routine immunization and preventive campaigns for each country because there is less data on vaccine use for this region:
    - Up to 90 percent of YF vaccine used in this market cluster is for isolated preventive campaigns in areas around an outbreak but this is very unpredictable.[62]
    - Some countries and areas will have very little routine YF immunization and tend just to respond to outbreaks.
    - Other countries will have YF preventive campaigns in areas that had not previously been considered to be endemic.
    - To be conservative, it was assumed that 75 percent of the vaccine used in South America is used in preventive campaigns, and 25 percent is used for routine immunization.

Brazil market cluster:

- Excluded from the WHO forecast are detailed estimates of the amount of vaccine used for routine immunization and preventive campaigns in Brazil, due to the complexity and unpredictability of YF vaccine demand in this region.
    - For the modeling, it was assumed that 75 percent of the vaccine used in Brazil is used in preventive campaigns, and 25 percent is used for routine immunization.

  Published information on recent and current YF vaccination policy in Brazil states that, since 2009, all Brazilian children (birth cohort of approximately three million per year) have been eligible for routine YF vaccination (aged approximately nine months), although in practice only those in some states and sub-areas receive it:
    - In 13 out of 27 states, routine immunization of infants is recommended for all infants. In a further seven states, it is recommended just for infants in at-risk sub-areas (Veras et al., 2010).
    - This is equivalent to 1.3 M children per year, out of a birth cohort of 3 M and a population of 190 M. Usage of YF vaccine in infants is, therefore, a relatively small proportion of the total demand for YF vaccine.

  Booster vaccinations every 10 years are currently recommended in Brazil, which contributes to total demand, but is thought to be incompletely implemented.[63]

  Preventive campaigns are used in populations in geographic areas considered at risk of YF transmission. This can lead to large, unpredictable surges in demand; for example, there could be a surge of demand from 100,000 to 14 M doses for at-risk areas, including the Federal District.[63]

Emergency stockpile:

- In the WHO forecasting model, the stockpile will be maintained at six million doses.
- Excluded from the model: The stockpile level does not reflect the actual use of YF vaccine in emergency response, but just an additional "rapid response" funding and supply mechanism. A variable proportion of YF vaccine used in emergency outbreak responses worldwide is funded and supplied by the country in question (sometimes by diversion from routine/preventive use) and/or by agencies.

[62] Alejandro Costa, WHO, oral communication, April 12, 2011.

[63] Brendan Flannery, PAHO, oral communication, January 25, 2011.

12.3. Modeling of the impact of dose-sparing on vaccine availability: assumptions

For this report, some preliminary modeling of the potential impact of delivering reduced-volume doses of YF vaccine on vaccine demand in each of the geographic areas (or market clusters) has been carried out, using the demand data from the WHO forecasting model described above.[64]

The following additional assumptions and values have been made in this report:

- An average price per standard 0.5 ml dose of US$0.82 was used, which is based on a weighted average of UNICEF prices for YF vaccine in 2011,[65] which were:
    - 6.69 M 5-dose vials purchased at $0.660 per dose.
    - 25.2 M 10-dose vials purchased at $0.864 per dose.
    - 0.68 M 20-dose vials purchased at $0.605 per dose.

  These costs are assumed to include vaccine and diluent, but not the cost of the syringe.
- The dose-sparing would be achieved by using 0.1 ml per dose of vaccine that is currently administered at 0.5 ml per dose; therefore a 5-fold increase in number of doses available per vial of vaccine was assumed; however:
    - The actual volume required for a non-inferior immune response might be higher than 0.1 ml.
    - The actual increase in number of doses would be dependent on the volume of diluent used to reconstitute the lyophilized vaccine and the dead space within the reconstitution and vaccine "drawing up" system.
- Impact of dose-sparing is expressed as the total number of 0.5 ml standard doses used.
- The dose-sparing (by volume) strategy is applied only to preventive campaigns, and not to campaigns for immediate outbreak response or to catch up routine immunization. This is because:
    - KOLs thought this was the best or most likely setting for dose-sparing.[66-68]
    - Because preventive campaigns are preplanned settings of known size and based on knowledge of demography and epidemiology.
    - In preventive campaigns, there are usually sufficient vaccinees per session to avoid the wastage from unused reconstituted vaccine at the end of immunization sessions.
    - Preventive campaigns are likely to be situations where the number of YF vaccine vials and therefore number of doses of YF of vaccine available could be the limiting factor, and so could be more attractive for early implementation than routine or emergency response vaccine use.
- Dose-sparing would be implemented in 100 percent of preventive campaigns worldwide, starting at 2011 (to match up with the forecasting period):
    - This is for simplicity of the illustration of potential maximum impact.
    - At this point it is not possible to estimate what proportion of campaigns would or would not use the approach. However, preventive campaigns tend to be

[64] Demand forecast was provided by Alejandro Costa, WHO, written communication, April 12, 2011.

[65] http://www.unicef.org/supply/files/2011_Vaccine_Projection_final.pdf

[66] Olivier Ronveaux, WHO AFRO, oral communication, January 21, 2011.

[67] Alba Maria Ropero, PAHO, oral communication, February 15, 2011.

[68] Alejandro Costa, WHO, oral communication, January 31, 2011.

implemented by the public sector, based on well-described policy so implementation of dose-sparing might be more complete than for multi-agency or private-sector immunization settings; recent campaigns have been well executed and have achieved very high and validated coverage rates.

- Assumptions have been made for the proportion of YF vaccine used for preventive campaigns and routine immunization in Brazil and South America; the "WHO model" forecasts these two applications separately only for Africa:
    - In both Brazil and "South America excluding Brazil," it was assumed that 75 percent or the forecasted demand for YF vaccine would be used in preventive campaigns and 25 percent would be used for routine immunization. This split was assumed to be constant over the timescale in question.
    - This figure was chosen to be at the lower end of the probable true average value, which might be as high as 90 percent for some countries (but much lower in others).[69]

The following factors have been excluded from the model:

- The costs of changing the route of delivery from SC to ID (including training) and the incremental cost of devices, storage, and waste disposal.
    - The incremental costs of changing device to facilitate ID delivery are modeled separately (see Section 12.4).
    - Administration of vaccine by the ID route might also impact the number of doses a vaccinator can deliver per clinic hour. These are important costs to explore before considering introduction in an LMIC setting.[70]
- Upfront costs to demonstrate non-inferiority of reduced-volume dose-sparing and also securing regulatory approval for its use.
- Use of dose-sparing in outbreak response campaigns; vaccine supplies could be stretched in these scenarios, but the actual savings would be very dependent on session size and vaccine presentation.

For these reasons, the values calculated for "number of doses saved" by dose-sparing are probably more robust that the cost savings.

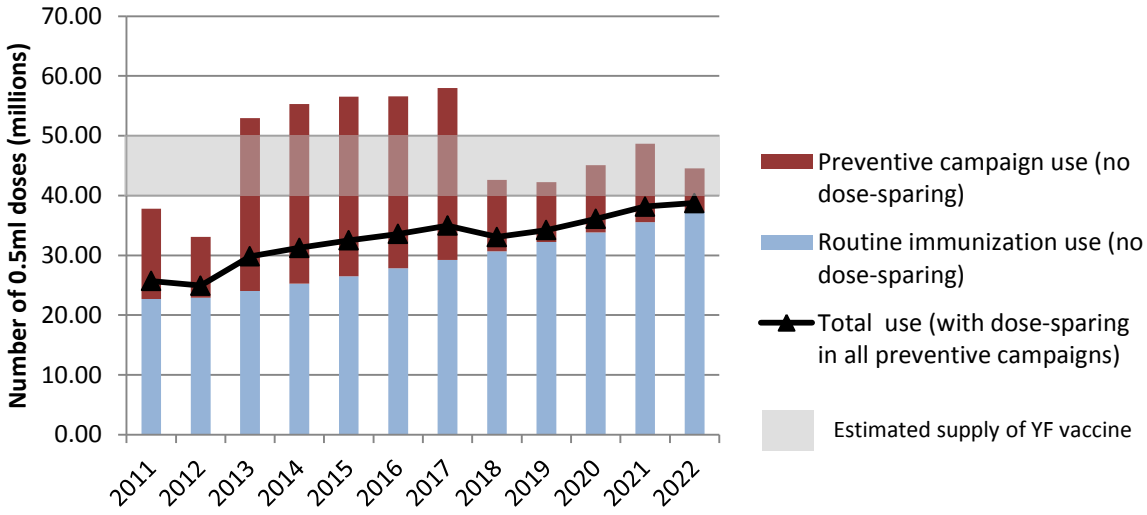
12.3.1. Impact of dose-sparing during preventive campaigns in Africa

Africa is the region with the highest forecasted demand for YF vaccine (Figure 5), and a significant proportion of this demand (36 to 63 percent in the WHO forecast) is for use in preventive campaigns (Figure 6). Implementation of a reduced-volume dose-sparing strategy in preventive campaigns in this region, therefore, has the potential to deliver the greatest savings in number of doses of vaccine that need to be procured (and vials used) and, consequently, in the cost of purchase of YF vaccine.

[69] Alejandro Costa, WHO, oral communication, April 12, 2011.

[70] Joachim Hombach, IVR WHO, written communication, August 23, 2012.

Figure 6. Impact on total use of YF vaccine doses in Africa from implementation of a dose-sparing strategy in all preventive campaigns



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[71] The estimated supply is based on 2012 levels and does not allow for possible future changes in manufacturing capacity that could increase or decrease future supply.

From the results of the simple modeling illustrated in Figure 6, it can be seen that in the conservative WHO demand forecast, the total amount of YF vaccine demand in Africa for routine and preventive campaign use (without any dose-sparing) is within the maximum forecasted supply for most of the period covered. For most years, however, the total demand is greater than the minimum forecasted supply of YF vaccine. Furthermore, the model assumes that there are no problems or unexpected restrictions in vaccine supply, which could reduce even further the amount of vaccine available in any given year. During 2013 to 2017, there is a predicted significant spike in demand in vaccine for the preventive campaign in Nigeria, which means that global demand could exceed supply (based on 2012 predictions) unless there are increases in production and there are no unforeseen problems with vaccine production and supply.

If a dose-sparing (20 percent by volume) strategy were to be implemented in 100 percent of African preventive campaigns, this could reduce the total demand for Africa (excluding emergency response) to less than 40 M 0.5-ml doses of YF vaccine per year, which is well within the minimum forecast for supply (using 2012 estimations). This could ensure that low vaccine supply would not limit planned activities, and it could also release vaccine vials for emergency outbreak responses or accelerate the completion of preventive YF vaccine campaigns or for use in other territories.

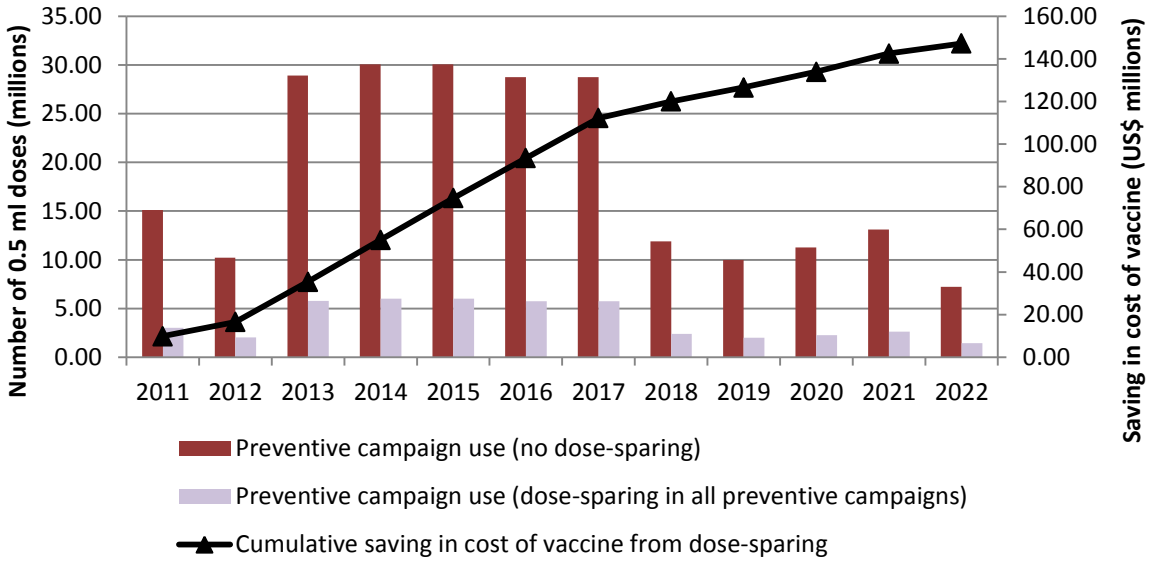
If the funding, supply and implementation of planned preventive campaigns is successful, the demand for YF vaccine for preventive campaigns should decrease after 2017. However, even if this is the case, from 2018 onwards the forecasted demand still exceeds the lower limit of the estimated supply of YF vaccine.

Assuming an average cost per dose of US$0.82 for a 0.5-ml dose (Section 12.3),[72] implementation of dose-sparing in all preventive campaigns in Africa could potentially save US$147 M in the purchase cost of vaccine during the period 2011 to 2022 (Figure 7).

[71] Alejandro Costa, WHO, written communication, March 5, 2012.

[72] http://www.unicef.org/supply/files/2011_Vaccine_Projection_final.pdf

Figure 7. Impact on total YF vaccine use and cumulative cost-saving from implementation of a dose-sparing strategy in all preventive YF vaccine campaigns in Africa



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[73] Incremental costs of change of delivery device have not been included.

12.3.2. Impact of dose-sparing during preventive campaigns in South America

YF demand for Brazil is considered in the WHO demand forecast separately from the rest of South America due to different patterns in procurement and use; therefore, the impact of dose-sparing in preventive campaigns has also been treated separately for this report.

There is less information publicly available on YF vaccine use in South America than for Africa. The WHO demand forecast assumes "steady-state" use of YF vaccine of 5 to 10 M doses per year, but doesn't separate this out into preventive campaign and routine use. For the purposes of the modeling of impact of dose-sparing for this report, it was assumed that 75 percent of YF vaccine demand was for preventive campaign use. This is a conservative estimate; it is possible that up to 90 percent of YF vaccine use in this region is in preventive campaigns.[74]

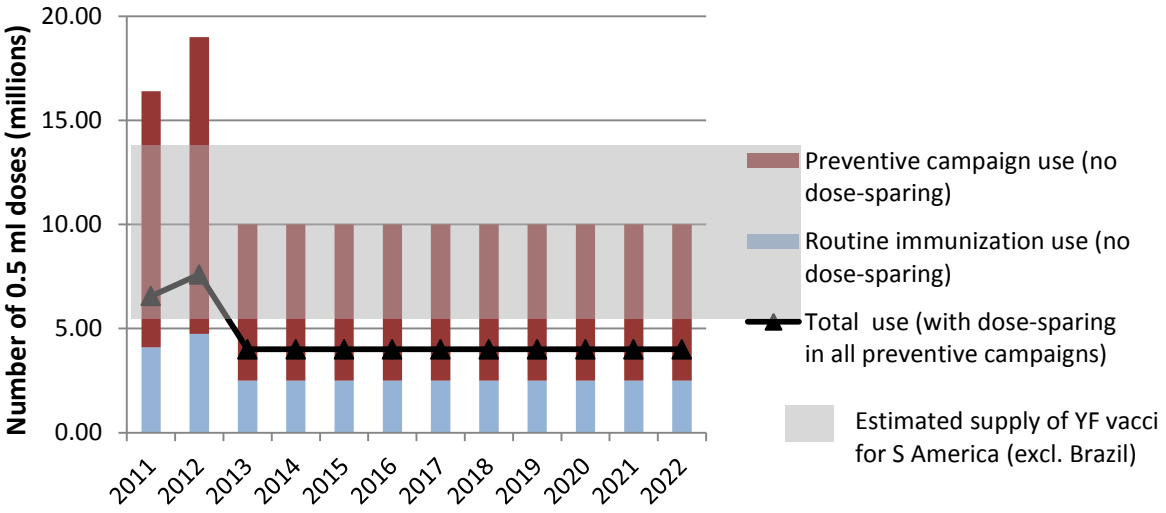
Assuming dose-sparing was applied to 100 percent of the preventive campaigns, this dose-sparing strategy could have a significant effect on the overall demand for vaccine, reducing demand from 10 M 0.5-ml doses per year to 4 M 0.5-ml doses per year (Figure 8). This could be a particularly valuable savings because, in recent years, South American countries have been offered only 40 to 50 percent of the YF vaccine requested during PAHO procurement.[75]

[73] Alejandro Costa, WHO, written communication, March 5, 2012.

[74] Alejandro Costa, WHO, oral communication, April 12, 2011.

[75] Alba Maria Ropero, PAHO, oral communication, February 16, 2011.

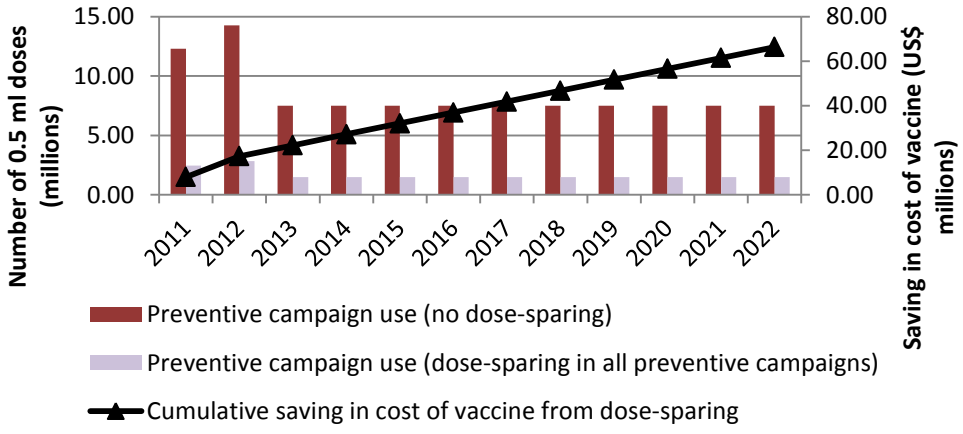
Figure 8. Impact on total YF vaccine use in South America (excluding Brazil) from implementation of a dose-sparing strategy in all preventive campaigns



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[76] The estimated supply is based on 2012 levels and does not allow for possible future changes in manufacturing capacity that could increase or decrease future supply.

Assuming an average cost per dose of US$0.82 for a 0.5-ml dose (Section 12.3)[77], implementation of 20 percent by volume dose-sparing in all preventive campaigns in South America could potentially save US$66 M in the purchase cost of vaccine during the period 2011 to 2022 (Figure 9).

Figure 9. Impact on total YF vaccine use and cumulative cost savings from implementation of a dose-sparing strategy in all preventive YF vaccine campaigns in South America (excluding Brazil)



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[78] Incremental costs of change of delivery device have not been included.

[76] Alejandro Costa, WHO, written communication, March 5, 2012.

[77] http://www.unicef.org/supply/files/2011_Vaccine_Projection_final.pdf

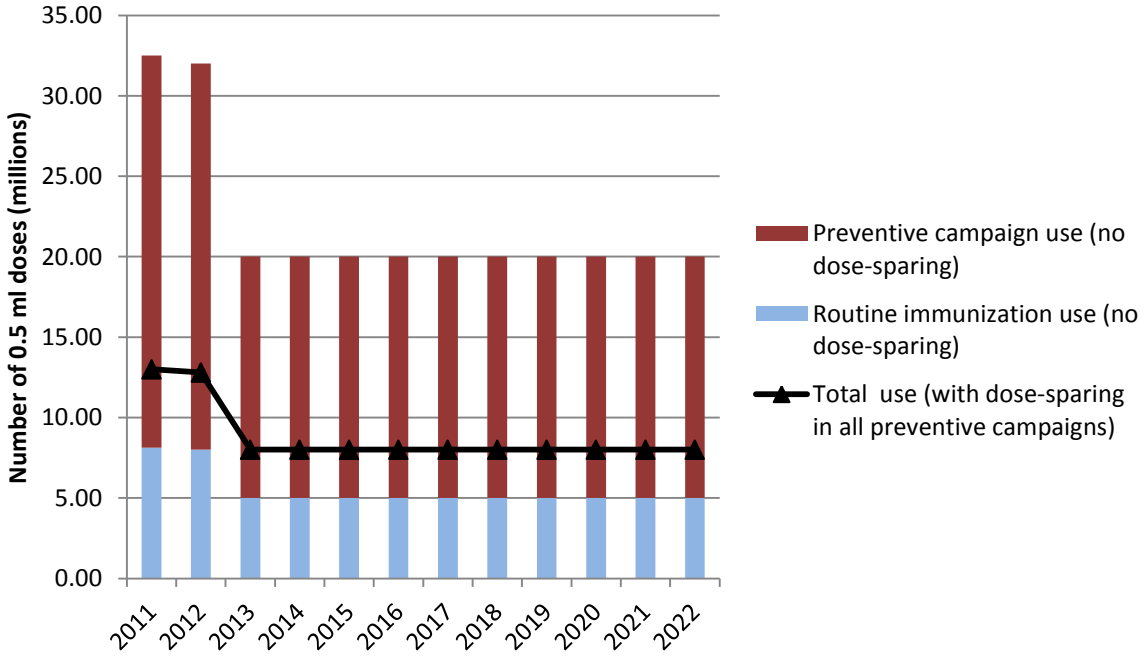
[78] Alejandro Costa, WHO, written communication, March 5, 2012.

12.3.3. Impact of implementation of dose-sparing during preventive campaigns in Brazil

There is little publicly available information on the relative proportions of YF vaccine used in preventive campaigns versus routine immunization in Brazil. For the purposes of modeling dose-sparing in this report, it was assumed that 75 percent of the vaccine is used in preventive campaigns and that this proportion remains stable across the timeline.[79]

Implementation of dose-sparing in preventive campaigns could have a significant impact on the total demand for YF vaccine in Brazil, reducing it from an estimated 20 M doses to less than 10 M 0.5-ml doses per year from 2013 to 2022 (Figure 10).

Figure 10. Impact on total YF vaccine use in Brazil from implementation of dose-sparing in all preventive campaigns



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[80]

The annual YF vaccine production capacity of Bio-Manguinhos is estimated to be 50 to 70 M 0.5-ml doses per year (depending on the proportions of the different presentations produced; see Table 6), which should exceed domestic demand for all years forecasted. Furthermore, Bio-Manguinhos is known to be exploring other strategies to "stretch" YF vaccine production capacity, namely evaluating whether a lower-potency formulation could be possible.[81] YF vaccine supply might, therefore, be less of an issue in Brazil compared with other market clusters. The predominant benefit of implementing dose-sparing of YF vaccine in Brazil could be to help smooth out demand surges caused by unpredictable outbreak response activities.

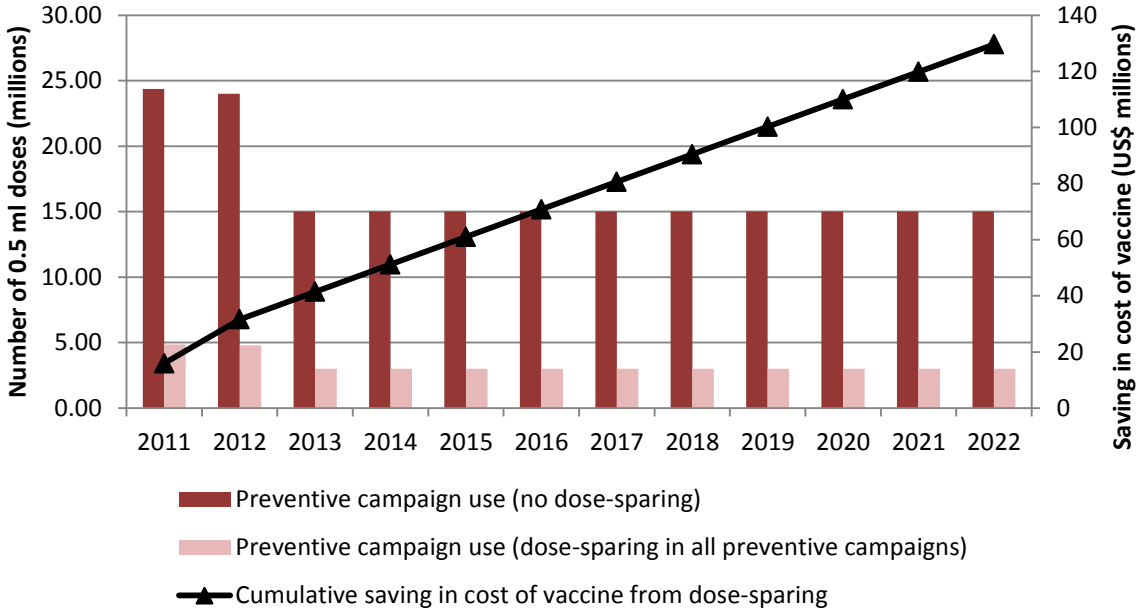
[79] No data was available on the proportion of YF vaccine that is used in preventive campaigns vs. routine immunization in Brazil, so a conservative estimate of 75 percent was used.

[80] Alejandro Costa, WHO, written communication, April 12, 2011.

[81] Dr Reinaldo de Menezes Martins, Bio-Manguinhos, written communication, February 7, 2011.

Assuming an average cost per dose of US$0.82 for a 0.5-ml dose (Section 12.3)[82], implementation of dose-sparing in all preventive campaigns in Brazil could potentially save US$130 M in the purchase cost of vaccine alone during the period 2011 to 2022 (Figure 11).

Figure 11. Impact on total YF vaccine use and cumulative cost savings from implementation of a dose-sparing strategy in all preventive YF vaccine campaigns in Brazil



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[83] Incremental costs of change of delivery device have not been included.

12.3.4. Potential global impact of implementation of dose-sparing in all preventive campaigns

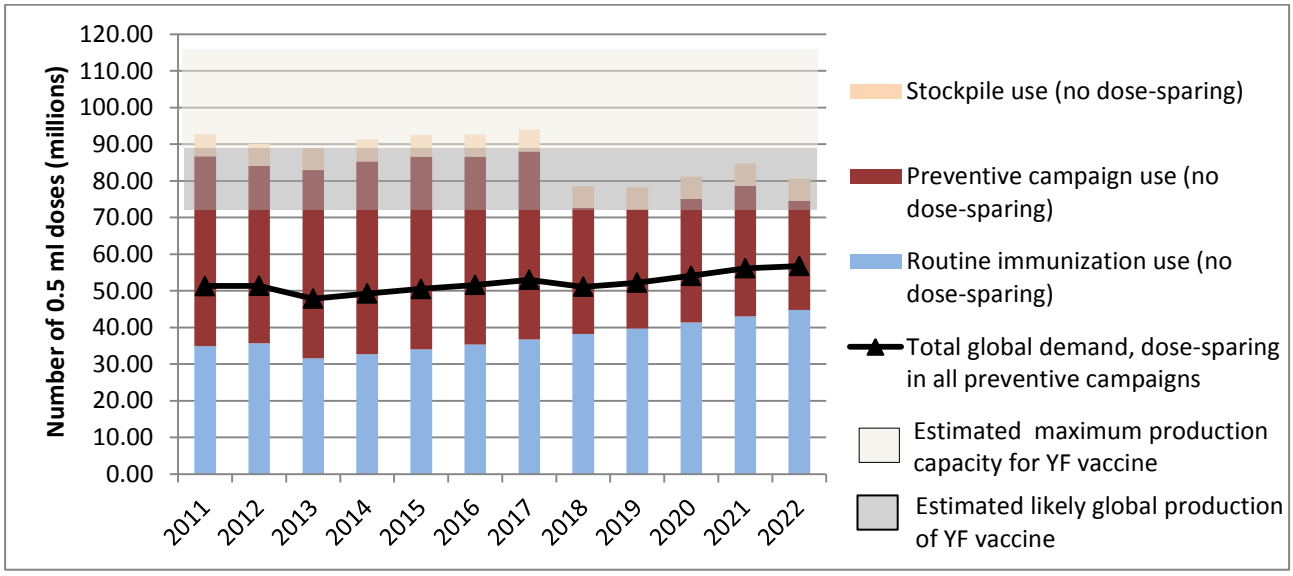
The global production capacity for YF vaccine in 2009 was estimated to be 90 to 115 M doses; however, the number of doses produced was estimated to be 75 M, only 65 percent of the estimated maximum level. This was due, at least in part, to a lower than expected number of 50-dose vials being produced (Ferguson et al., 2010).

From publicly available information, it is reasonable to assume that the overall production capacity for YF vaccine will not increase in the immediate term (see Section 7). This level would be sufficient to meet the estimated global demand for YF vaccine according to the WHO forecast. However, it is likely that in any given year, global production will be lower than the theoretical maximum due to variation in the proportions of the different presentations produced and/or unexpected problems that interrupt production. In this situation, global demand could exceed supply (Figure 12). If dose-sparing was used in all preventive campaigns, however, the demand for vaccine would be comfortably below the likely supply, even if this was only 65 percent of the maximum global capacity.

[82] The price quoted was not for Bio-Manguinhos vaccine but calculated as a weighted average of all manufacturers' 5-, 10- and 20-dose vials at UNICEF 2011 prices. http://www.unicef.org/supply/files/2011_Vaccine_Projection_final.pdf

[83] Alejandro Costa, WHO, written communication, March 5, 2012.

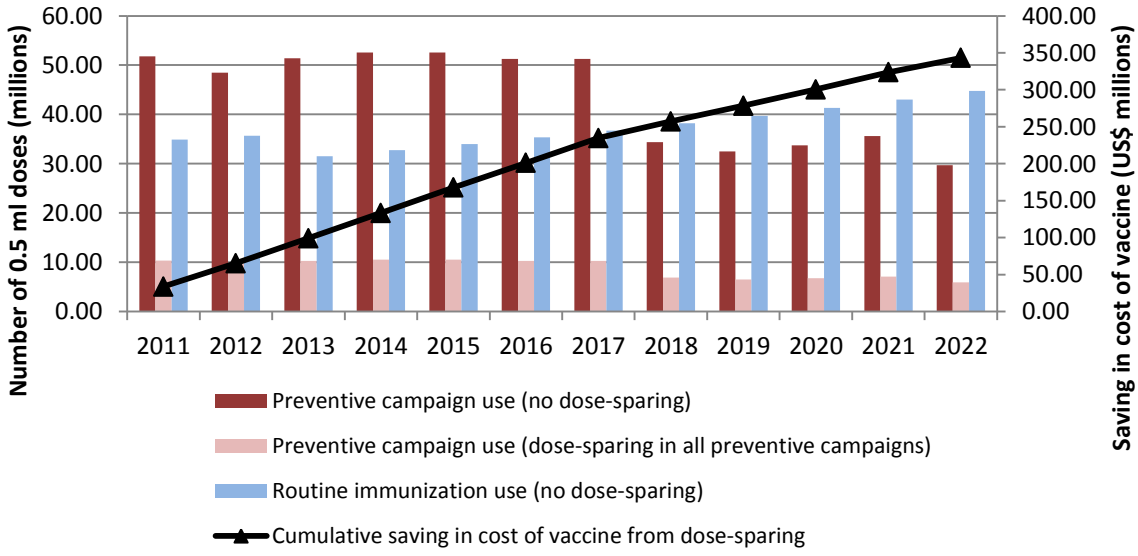
Figure 12. Impact on global YF vaccine use from implementation of dose-sparing in all preventive campaigns



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[84] The estimated supply is based on 2012 levels and does not allow for possible future changes in manufacturing capacity that could increase or decrease future supply.

Combining the information presented above for each of the three major market clusters provides an estimate of the possible impact of using dose-sparing in all YF preventive vaccination campaigns in terms of number of 0.5-ml doses (Figure 12) and vaccine costs saved (Figure 13).

Figure 13. Potential impact on global YF vaccine use and costs from implementation of dose-sparing in all preventive YF vaccine campaigns



Note: The vaccine demand data for the figure were provided by Alejandro Costa, WHO.[85] Incremental costs of change of delivery device have not been included.

[84] Alejandro Costa, WHO, written communication, March 5, 2012.

This relatively crude calculation suggests that 24 to 42 M 0.5-ml doses of YF vaccine per year could be saved, resulting in a cumulative saving of 420 M 0.5-ml doses between 2011 and 2022 and a saving of purchase costs of vaccines of approximately US$340 M.

The information in Figure 12 and Figure 13 represents a best-case scenario, and assumes:

- Dose-sparing (by reduced volume) is introduced in all preventive campaigns, but not routine immunization or outbreak response campaigns. Use of dose-sparing in these settings could provide further savings.
- The proportion of YF vaccine used for preventive campaigns in Brazil and South America remains stable.
- Implementation of dose-sparing does not result in increased vaccine wastage. For this illustrative modeling:
    - Preventive campaign settings are assumed to have sufficiently large session sizes to benefit from dose-sparing using vials containing 25- or 50-doses at 0.1 ml per dose.
    - That 25- or 50-dose vials (of 0.1 ml each dose) can be used without having to discard unused vaccine in an opened vial at the end of a session.
- 20 percent doses are used so the purchase costs of vaccine are reduced to 20 percent of the original value.
- The route of administration of the reduced dose (SC or ID) does not impact the number of vials used or cost savings.

In practice it is likely that:

- Implementation in 100 percent of preventive campaigns is very unlikely to be achieved; a sensitivity analysis of more realistic levels of dose-sparing use will be needed.
- Manufacturers might increase the purchase cost of the vaccine to offset the fact that more doses are being obtained from each vial.;
- Some reconstituted YF vaccine vials might yield more or less than the expected number of reduced-volume 0.1 ml doses, depending on the degree of overfilling of the diluent vial and the dead space of the delivery devices used. Bench testing would be required to investigate this.
- Converting existing 10-dose vials to 50-dose vials could result in some vaccine wastage, even in high-throughput preventive (or outbreak) campaigns.
- A change of route from SC to ID is likely to require use of a novel device to facilitate ID delivery, which could require retraining of vaccinators (Section 13) as well as incurring additional cost of the devices themselves (see Section 12.4).

12.4. Modeling of the impact of dose-sparing on immunization costs

The aim of the modeling was to demonstrate the relative costs per dose of the use of three types of novel ID delivery device compared with N&S Mantoux ID and gold standard N&S SC or IM. The modeling undertaken was only preliminary and did not include some of the country- and device-specific inputs that have been used in other, more complete analyses of incremental costs associated with changing the route or device used for vaccination (Griffiths et al., 2011).[86]

The three novel ID devices used in the model were:

[85] Alejandro Costa, WHO, written communication, 5 March 2012.

[86] http://www.path.org/publications/files/TS_IPV_econ_analysis.pdf

- ID adapter, similar to that developed jointly by PATH, West Pharmaceuticals, and SID Technologies; this is designed to fit over a standard needle and syringe to control the depth and angle of ID injection.
- DSJI, powered by a spring, similar to those developed by PharmaJet and Bioject.
- A syringe-mounted hollow microneedle (MN) array, similar to that produced by Nanopass.

The devices are described in more detail in Appendix Table 4. Other ID devices that were not included in the model are:

- Gas-powered DSJIs, similar to those produced by Bioject and Medical International Technologies; the requirement for compressed gas is thought to make them less suitable for campaign use in LMICs.
- Prefilled syringes with ID needles, such as Becton Dickinson's Soluvia device, were not included because they are not compatible with lyophilized vaccines such as YF.
- Microneedle patches might be suitable for YF vaccine delivery in the longer term, but reformulation of the vaccine would be required.
- All-in-one syringes with an easy-to-use ID needle that can be filled onsite might become available in the short to medium term, but these are too early in development to estimate pricing; however, it is likely that they will be benchmarked to AD syringes.

12.4.1. Impact of dose-sparing on immunization costs: assumptions

The inputs and assumptions used for the model are presented in Appendix Table 5 and are summarized below:

- *Purchase cost of vaccine.* A single price of US$0.82 was used for the cost of vaccine (see Section 12.3 and Appendix Table 5).
    - It was assumed that a 20 percent volume of vaccine would be delivered (0.1 ml compared with 0.5 ml by volume) so that the purchase cost of the vaccine would also be reduced by 80 percent.

      In practice it is likely that vaccine manufacturers would not "pass on" the full savings achieved by dose-sparing, particularly if all YF vaccine delivery was to be reduced dose. In that case, a 20 percent reduction in price for an 80 percent reduction in dose might be more realistic, as has been used previously (Griffiths et al., 2011).

      However, if ID reduced doses are to be used in specific settings only (preventive campaigns, but not routine immunization) it is more difficult to predict the likely price of the vaccine, so a simple relationship between price and volume was used.
- *Vaccine wastage.* Overall vaccine wastage was assumed to be 5 percent, which is a midpoint for estimates in campaign use and similar to the observed rate of 4.6 percent for a YF vaccination campaign in Cameroon (Wiysonge et al., 2008).
- *Cost of delivery devices.* Three types of novel delivery device were considered.
    - A single price estimate for each type of delivery device was used, rather than manufacturer-specific estimates. This also protected confidential pricing estimates from individual manufacturers.
    - The price estimates used were generated by PATH based on a production of greater than 100 M devices per year; it should be noted that this level of production might or might not be achieved in the future.
- *Introduction and implementation costs***.** No costs were included in the model for clinical studies prior to label change or introduction, nor for training and any other capital costs.
- *Needle-stick injuries.* Costs associated with the consequences of needle-stick injuries and unsafe injections were not included in the model, even though they might be avoided by

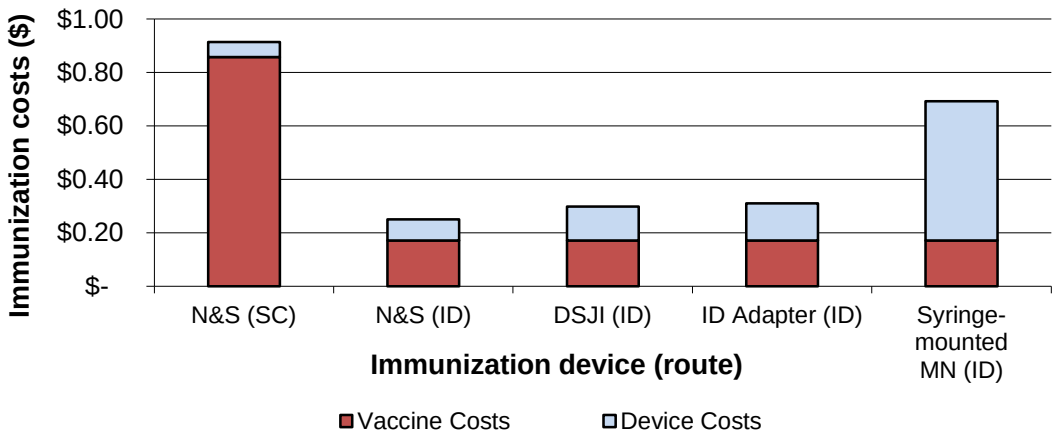
use of DSJIs. Estimates of unsafe injection costs involve a great deal of uncertainty, and immunization practices and the prevalence of blood-borne infections have changed since estimates of these costs were published (Miller and Pisani, 1999).

- *Transport, storage, or waste disposal.* Estimates for these costs were not available so were not included the model.
- *Countries.* As examples of the impact of dose-sparing, two planned preventive campaigns were used: Ghana (22 M doses) and Nigeria (104 M doses). These examples have been selected for illustrative purposes only; it should be noted that the first phase of the preventive campaign in Ghana started in November 2011 and has been completed.[87,88]
- *Sensitivity analyses.* No sensitivity analyses have been performed to date.
    - Given the preliminary nature of the modeling, it was felt that more detailed analysis would be warranted once a more complete set of input values for a specific territory had been obtained.
    - In addition, the primary reason for considering dose-sparing for YF vaccine is to smooth out supply issues and avoid vaccine shortages rather than reduce the purchase cost of the vaccine.

12.4.2. Relative costs of YF immunization using ID delivery

The results of modeling immunization costs with different delivery devices, using the assumptions described above are shown in Figure 14.

Figure 14. Costs of YF vaccination with different delivery devices, per individual



From this simple modeling:

- Using N&S for ID delivery of a 20 percent dose of vaccine reduces the costs modeled by 72.6 percent compared with delivery of the standard dose by the standard SC route (US$0.25 compared with US$0.91 per immunized individual).
    - If reduced-volume doses delivered by the SC route are shown to be immunogenic, then this approach could be used in campaign settings.

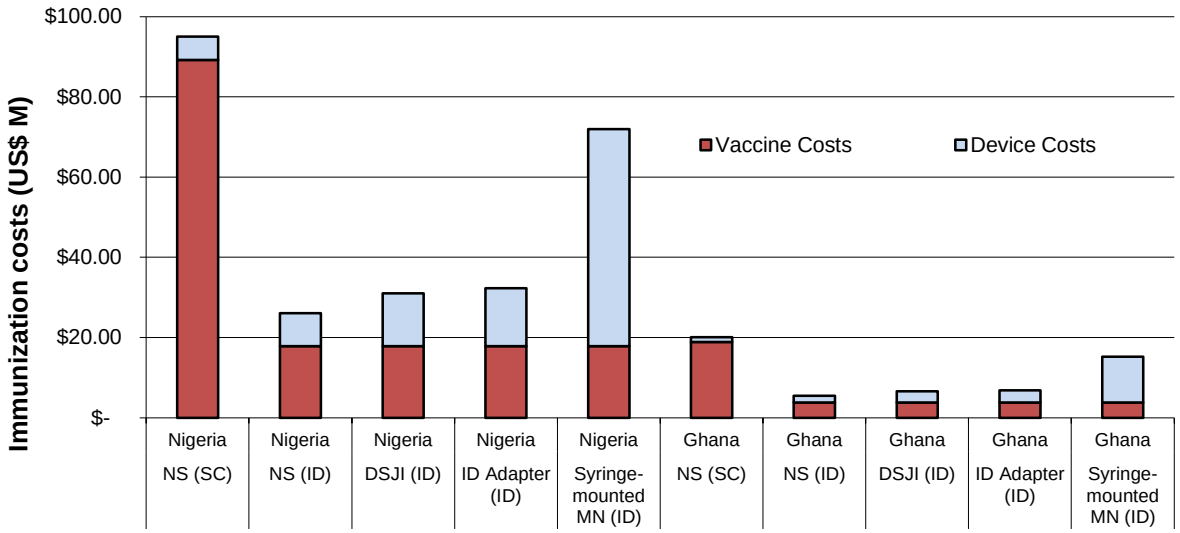
[87] Erin Staples, CDC, written communication, October 5, 2012.

[88] http://www.destinationsante.com/Yellow-fever-vaccination-campaign-in-Cameroon-and-Ghana.html, accessed November 5, 2012.

  - Dose-sparing might, however, require a change to the ID route and use of a novel ID device because, as discussed in Section 13.2, the Mantoux technique is considered to be unsuitable for use in YF campaigns.
- The DSJIs and the ID adapter have higher device costs than N&S, but ID delivery with either DSJIs or the ID adapter still results in potential savings of 67.3 percent or 66.0 percent, respectively.
- Use of a syringe-mounted microneedle array appears to be less attractive. The same amount of vaccine would still be saved, but the overall cost savings would be less due to the higher device costs.

The costs of YF vaccination per individual using ID delivery have been applied to two planned YF campaigns in Nigeria and Ghana (Figure 15).

Figure 15. Potential impact of dose-sparing on immunization costs in mass campaigns



From this simple modeling:

- The cost of immunization devices plus vaccine purchase costs in the planned YF preventive campaign in Nigeria could be reduced from ~US$95 M (standard SC dose) to ~US$31 to US$32 M, if either DSJI or the ID adapter were used for ID delivery.
- If reduced volume doses were sufficiently immunogenic when delivered subcutaneously by N&S (which would be compatible with use in campaigns), the cost of immunization devices plus vaccine purchase costs for the campaign in Nigeria could be reduced to ~ US$ 26 M (equivalent to the N&S ID cost)
- In Ghana, with a smaller population for immunization, the costs could be reduced from ~US$20 M (standard SC dose) to ~US$6.6 M (ID, DSJI) or ~US$6.8 M (ID adapter).

12.4.3. Future work

The modeling conducted in the report is very preliminary and used many assumptions. More detailed assessment of the potential impact of dose-sparing should be carried out:

- Using more realistic estimates of the proportion of preventive campaigns likely to use this vaccination strategy.

- To include the potential beneficial impact of dose-sparing on routine immunization and outbreak response campaigns.
- To assess the costs involved in implementing a dose-sparing strategy, including clinical trials, implementation and training, wastage, storage, transport, and costs associated with novel devices that might be required to facilitate ID delivery, which might impact the number of doses that can be administered per clinic hour (see Section 13).

12.5. Summary

- Preliminary modeling of the impact of dose-sparing using the WHO's conservative demand forecast data for YF vaccine suggests that even if reduced-volume dose-sparing was applied only to mass, preventive vaccination campaigns, it could:
    - Have a significant impact in Africa, reducing the projected demand for vaccine to levels within or below the expected vaccine availability (using 2012 estimates). This could be particularly important to avoid possible supply constraints resulting from the planned preventive campaign in Nigeria.
    - Smooth the demand for vaccine in South America and Brazil by reducing the amount of vaccine used in preventive campaigns.
    - Reduce the number of 0.5-ml doses of YF vaccine required so that demand can still be met in the event of actual supply falling short of what was predicted (for example, due to unforeseen manufacturing problems).
    - Result in overall savings in vaccine demand of 24 to 42 M 0.5-ml doses per year, equivalent to approximately 420 M 0.5-ml doses and up to US$340 M in vaccine purchase costs from 2011 to 2022.
- Preliminary modeling of the costs associated with using novel ID delivery devices that might be required in campaign settings to deliver reduced doses of YF vaccine suggest that:
    - ID delivery of a 20 percent dose using a DSJI or ID needle adapter could reduce the costs per immunization by approximately 67 percent.
    - In preventative campaigns such as those planned for Nigeria and Ghana this could lead to savings of US$64 M or US$13 M, respectively.

13. Programmatic issues facing implementation of dose-sparing

A number of practical or programmatic issues need to be considered to determine whether reduced-volume dose-sparing might be beneficial in practice and how it might be implemented.

13.1. Matching vaccine presentation to session size

If dose-sparing were achieved by reducing the volume of standard concentration vaccine delivered (this is most likely to be a change from 0.5 to 0.1 ml if delivered by the ID route), the benefits in terms of improving vaccine availability will be dependent on the presentation of the vaccine (doses per vial) and the session sizes in which the vaccine is used, as unused vaccine has to be discarded six hours after reconstitution:

- For example, in a case of routine childhood vaccination and with an average session size of two infants per session and vaccine in 10-dose vials, the "current" vaccine wastage would be eight doses per session. If ID delivery of a 20 percent dose were introduced to this example, this would increase the potential number of (reduced-volume) doses wasted to 48 doses per session (for a 10-dose vial that could yield 50 reduced-volume doses). There would therefore be no benefit, or drawback, to the price of the vials used or the amount of vaccine used per session.
- For larger session sizes, as is the case during larger throughput routine vaccination, mass preventive campaigns, or outbreak responses, then a reduced-volume strategy could be increasingly useful. Most PQ YF vaccines are purchased at 10 doses per vial, so the highest dose-sparing benefit would be achieved in settings with session sizes of greater than 11 doses, which would need two vials at standard dose and which are most likely to occur during vaccination campaigns.

When considering the possible impact of ID delivery of fractional doses on YF vaccine availability (Section 12), it has, therefore, been assumed that the benefits of dose-sparing would only be realized in high-throughput preventive (or emergency) immunization campaigns.

Other presentation-related issues to be considered are:

- Because dose-sparing would increase the effective number of doses per vial, the cold-chain volume required per dose would be reduced, as would transportation and storage costs.
- It is unlikely that dose-sparing would impact vaccine wastage due to problems in cold chain storage, but this should be included in an analysis.[89]
- The acceptability to policymakers of extraction of multiple doses (up to 250 per vial) because increased handling of the vial increases the risks of microbiological contamination of its contents.

Presentations of YF vaccine that are currently available, and the potential impact of implementation of a dose-sparing strategy (20 percent doses), are summarized in Table 10.

[89] Joachim Hombach, IVR WHO, written communication, August 23, 2012.

Table 10. Effect of YF vaccine presentation on suitability for dose-sparing

Current presentation (0.5 ml doses per vial); Typical settings for use.	Manufacturer (country), PQ status	Number of reduced-volume doses per vial (0.1 ml per dose)	Current availability; Population or settings for use of reduced volume vaccine; Practical issues.
1 Travel for HICs.	Sanofi Pasteur (USA), not PQ.	**5**	**Current availability**: low. **Potential settings for use of reduced volume:** all, including low-throughput routine. **Practical issues**: not PQ and not widely available; 5 doses per vial might be sub-optimal for very high throughput use.
2 Routine.	Chumakov Institute (Russia); PQ.	**10**	**Current availability**: low. **Potential settings for use of reduced volume:** all, including low-throughput routine. **Practical issues**: Currently only available in ampoules, which makes it unsuitable for repeated extraction of doses.
5 Routine.	Chumakov (Russia), PQ; Institute Pasteur Dakar (Senegal), PQ; Bio-Manguinhos (Brazil), PQ.[a]	**25**	**Current availability**: moderate, for international public health use; standard presentation for use in within Brazil (Bio-Manguinhos). **Potential settings for use of reduced volume:** less useful in low-throughput routine settings; useful in larger throughput campaign settings. **Practical issues**: policymakers might not support the extraction of 25 doses from one vial (although there is a precedent for 50 doses per vial).
10 Routine, campaign, including outbreak.	Sanofi Pasteur (France), PQ; Bio-Manguinhos (Brazil), PQ; Institute Pasteur Dakar (Senegal), PQ.	**50**	**Current availability**: high for international public health use; **Potential settings for use of reduced volume:** less useful in low-throughput routine settings; useful in larger throughput campaign settings. **Practical issues**: policymakers might not support the extraction of 50 doses from one vial (although there is a precedent for this number of doses per vial).
20 Campaign, including outbreak.	Institute Pasteur Dakar (Senegal), PQ.	**100**	**Current availability**: low. **Potential settings for use of reduced volume:** difficult to justify use in low-throughput routine settings; might be useful in the largest throughput campaign settings. **Practical issues**: policymakers might not support the extraction of 100 doses from one vial.
50 Campaign, including outbreak (not in Brazil).	Bio-Manguinhos (Brazil), PQ.[a]	**250**	**Current availability**: very low for international public health use. **Potential settings for use of reduced volume:** might be useful in the largest throughput campaign settings. **Practical issues**: some policymakers might not support the extraction of 250 doses per vial, and it is likely to be technically difficult.

Notes: a. PQ (prequalification) status of this presentation currently suspended.

If the presentations of currently available YF vaccines are not changed, then the most appropriate application for reduced-volume delivery (at 20 percent) is in mass campaigns, with perhaps more than 25 recipients per session. In these settings, the currently available 5-, 10-, (and possibly 20-) dose presentations could be used to yield approximately 25, 50, (and up to 100) doses per vial, respectively.

13.2. Suitability of the Mantoux technique for YF vaccination

ID injection of vaccines is currently achieved using needle and syringes and the Mantoux technique. In mass campaigns, success is dependent on very high throughput and simple and reliable technique; all KOLs consulted considered that in the most pressurized environments, delivery of YF vaccine intradermally using the standard Mantoux technique (by N&S) would not be practical for one or more of the following reasons: [90,91,92,93,94,95]

- The Mantoux technique is probably too slow.
- It requires too much concentration, in what are often "noisy and pressured environments."
- It requires high levels of skill, gained from both training and frequent practice.
- It might be too variable between vaccinators and also between vaccinees.
- Needle-free devices for ID delivery would be preferable for campaign use.

At this point, however, it has not been demonstrated that a change to ID delivery will be required. It is possible that a lower dose (0.1 ml, or a volume between 0.1 to 0.5 ml) delivered subcutaneously might be sufficiently immunogenic, as suggested by the data from a recent dose-response trial with YF vaccine (Martins et al., 2013). The need to change the route of delivery to ID needs to be established by studying the immune response in clinical trials, including studies of longevity of immune response.

If the ID route were shown to be necessary, then an improvement in administration from N&S Mantoux technique would probably be essential (but needs to be demonstrated in clinical studies). If this delivery method were also needle-free, this could also be advantageous from a safety and acceptability point of view.

A number of devices are being developed and evaluated for ID delivery of liquid vaccines (reviewed in PATH, 2009), some of which could be commercially available in the next 12 to 24 months. These include: DSJIs, intradermal "mini" needles, hollow microneedles, and adapters fitted to needles to control the depth and angle of ID injections (see Appendix Table 4).

13.3. Effects on the safety profile of YF vaccine

It is difficult to predict the effects of changing the dose of YF vaccine and route of administration, but evidence indicates that this could be an important issue.

Studies with Chimerivax™-JE (based on 17D YF vaccine virus) given by skin micro-abrasion or ID microneedles in cynomolgus monkeys reported apparent changes in the pattern of viremia compared with SC injection. All three animals in the ID group and all three animals in the micro-abrasion group had detectable viremias compared with only one animal in the SC group. Viremias in the ID groups were of a longer duration than the SC group, but of similar magnitude. All three mice in the micro-abrasion group had delayed viremia, possibly suggesting that these animals had received a lower dose. None of these differences were associated with any changed clinical signs in the animals (Dean et al., 2005).

[90] Olivier Ronveaux, WHO AFRO, oral communication, January 21, 2011.

[91] Brendan Flannery, PAHO, oral communication, January 25, 2011.

[92] Alba Maria Ropero, PAHO, oral communication, February 15, 2011.

[93] Alejandro Costa, WHO, oral communication, January 31, 2011.

[94] Edward Hayes, CRESIB, oral communication, January 20, 2011.

[95] Oyewale Tomori, Redeemer's University, Nigeria, January 21, 2011.

In a phase II clinical dose-escalation study by the SC route (Monath et al., 2003) of the same Chimerivax™-JE vaccine, lower doses of the vaccine were associated with a higher proportion of subjects having viremia, ($p = 0.018$) and with higher viremia titers (not statistically significant). Overall, 50 to 100 percent of the recipients of the JE vaccine had measurable viremia on at least one occasion post-vaccination, compared with 64 percent of recipients of YF vaccine. Larger groups would be required to confirm these observations, and it would be useful and more relevant to study different doses and routes with YF vaccine itself.

Viremia "reflects the level of replication in extra-neural tissues and reflects the balance between virus replication and its clearance by the immune system. It is, however, regarded as a measure of viscerotropism of YF vaccine virus" (cited in Monath et al., 2009).

Overall, these studies suggest that relationship between the dose and route of delivery of YF vaccine and subsequent viremia (which might be a marker of viscerotropism) is not easy to predict and is an issue that will need to be addressed in clinical, and possibly preclinical, studies of ID delivery of reduced doses of vaccine.

13.4. Effects on immunogenicity, protection, and other issues

Other consequences or risks associated with implementing dose-sparing of YF vaccine that need to be considered include:

- Reduction of the "margin of safety" as the potency of the vaccine declines during storage. This might be a concern when the vaccine nears the end of its shelf life and/or if it has been stored incorrectly.
- Reduction of immunogenicity (and protection) by affecting immune responses that are not measurable by a simple 28-day serological response. This might have most clinical impact in sub-populations for which little is known about the immunogenicity of YF vaccines (such as people with HIV infection).
- The use of at least two immunization protocols; for example, a standard dose subcutaneously for routine immunization and a reduced dose intradermally (or subcutaneously) for use in campaigns. This could lead to errors in administration, but was not considered to be a significant barrier by at least one KOL.[96]
- Eligibility for International Health Regulation travel certification. Even though an individual might be protected from YF disease, they would not be allowed entry to some countries unless the International Health Regulations were changed to allow reduced-dose immunization. This issue requires more investigation; people who want and need to be protected against YF also want and need to be able to travel between countries.

13.5. Regulatory issues

In general, policymakers will not approve a change to the way a vaccine is used without clinical evidence of non-inferiority in immune response and safety, and also formal regulatory approval of such a change. There are several routes for achieving such a change in use of vaccines, including not aiming for an initial change of label.

13.5.1. Formal change of label

This would cover all subsequent use of YF vaccine and be sponsored by the vaccine manufacturer. Evidence to support the label change would be reviewed by the relevant national regulatory

[96] Martin Friede, WHO; oral communication, March 3, 2011.

authorities (NRAs) and/or WHO. This is likely to be the preferred approach for policymakers, but requires cooperation between vaccine manufacturers and the NRAs, and for the manufacturers to conduct the appropriate trials.

13.5.2. Off-label use

Off-label ID use of YF vaccine by clinicians could lead eventually to regulatory approval for ID administration. There is a precedent for this model, namely ID injection of rabies vaccine for post-exposure vaccination:

- Various reduced-volume ID rabies vaccine regimens have been developed in the past few years in several LMICs.
- In addition, some clinics use reduced-dose ID rabies vaccine regimens for pre-exposure immunization (e.g., in one travel clinic in the Netherlands).[97]
- The clinical evidence for this change of route and dose was developed empirically by several clinical groups, responding to the need to increase access to a too-costly vaccine.
- After several years, the evidence base was deemed sufficient by policymakers to gain support from NRAs and WHO (WHO 2005a; WHO 2010b). NRAs can, however, insist that clinical studies are repeated with each rabies vaccine of interest and the new regimen be reflected on its label in that territory.

During off-label use, the consent process needs to reflect the off-label status, with consequent effects on liability.

13.5.3. Alternate use (delivery route) depending on settings

Clinical studies could support alternate delivery techniques for YF vaccine for use in specific settings. A precedent for off-label use of reduced volume of vaccine was the clinical trial of Menomune (Sanofi Pasteur), a tetravalent, unconjugated polysaccharide meningitis vaccine, which showed non-inferior immunogenicity for all but one *Neisseria* strain (Guerin et al., 2008). This was considered by policymakers to be "useful evidence in case of scarcity of vaccine during an epidemic."[98]

This type of off-label use of reduced-volume YF vaccine would have needed to be reflected in the consent process.

13.5.4. Dual labeling

At least one KOL[99] considered that it would be both feasible and attractive (if clinical data supported this) to aim for a formal label amendment to permit reduced-volume use of YF vaccine in some settings, but to retain the standard route and volume for others. For example, a full 100 percent dose could be used for routine childhood immunization (where session size suggests no benefit of dose-sparing), but a reduced dose could be used in mass campaigns or other situations where vaccine access was limited.

Delivery of reduced doses could also be used when the full dose of vaccine could increase the risk of SAEs for that vaccine recipient. This approach has been used for egg-allergic individuals (Roukens et al., 2009).

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[97] Leo Visser, Leiden University Medical Centre, oral communication, August 14, 2009.

[98] Alejandro Costa, WHO; oral communication, January 31, 2011.

[99] Martin Friede, WHO; oral communication, March 3, 2011.

13.6. Summary

- Use of dose-sparing with the currently available WHO PQ presentations of YF vaccine mean that vials will typically contain at least 25 to 50 ID doses per vial; therefore, the maximum benefit of using this approach will be in mass immunization campaigns, either preventative or for outbreak control.
- The type of label change required to support ID delivery needs to be determined and a clinical and regulatory strategy to support this change needs to be developed. A dual label supporting delivery of reduced doses in campaign settings and full doses for routine use is an attractive and potentially feasible approach.
- A change of dose and route would impact travel certification under IHRs and so needs to be planned with this consideration.

14. Developing a clinical evidence base for YF dose-sparing

Before dose-sparing by delivering reduced-volume doses of YF vaccine can be introduced, clinical evidence to support its use and to address key questions will be required.

Some of the clinical issues to be addressed are outlined in Section 13.4 and are discussed in more detail below, along with a preliminary outline clinical trial program. Background information on previous clinical trials with YF vaccines is provided in Appendix Table 9, Appendix Table 10, and Appendix Table 11.

Prior to clinical trials, it is possible that preclinical studies could also be useful in addressing safety issues associated with a change of dose and/or route (Section13.3). These would give additional confidence around changes in interactions between YF vaccine virus and host cells that might interact with other host factors to change the risk of SAEs.

14.1.1. Preclinical models for assessing YF vaccine safety

The recent development of a preclinical mouse model of viscerotropic disease with YF vaccines (Meier et al., 2009) could be a useful, and possibly essential, step in the assessment of lower-dose or alternative route YF vaccine regimens.[100]

Mice deficient in IFN-α/β receptor (A129) or STAT1 signalling molecule (STAT129) have been found to develop viscerotropic disease similar to that in human clinical YF cases (or primate models) when infected (subcutaneously) with wild-type YF virus (Meier et al., 2009). The model is preferable to the hamster models that need to use adapted strains of YF virus or other mouse models that have predominantly encephalitic disease and can require intracerebral administration.

14.2. Clinical questions to be addressed

Some of the key clinical questions to be addressed before implementation of ID delivery of reduced doses could take place include:

- Is a change of route from SC to ID required for reduced-volume doses of YF vaccine to be non-inferior? Data from a dose-response clinical trial with YF vaccine in healthy adults (Martins et al., 2013) suggest that this might not be the case. However further trials are required. Clinical studies should compare directly the same dose in terms of amount of antigen (potency) delivered subcutaneously and intradermally, ideally in the same volume. In addition, these should be compared with the standard dose and route.

- What is the optimal dose and volume? Ideally, the vaccine used in clinical trials to test reduced-volume dosing would be prepared to cover a wide range of vaccine potencies to ensure that the reduced-volume dosing is still on the “plateau” of the dose-response curve. This would give confidence that reduced doses of vaccine at the end of its shelf life could be used. The fact that YF vaccine is lyophilized means that the vaccine can be reconstituted in the field to a range of desired volumes, giving greater flexibility to control the volume of the dose administered in clinical trials.

[100] Alan Barrett, University of Texas Medical Branch at Galveston, oral communication, September 4, 2012.

- Does a reduced-volume dose of YF vaccine change the nature of immune response, including the longevity of protection? Clinical studies should probably follow (at least serological) responses to at least 10 to 12 months. Longer follow-up and effect on any booster vaccination, according to national policy or for travel certification purposes, would be desirable.

- What is the impact of reduced-volume dose regimens on short-term safety? As well as clinical studies of local and systemic AEs, it has been suggested that ID delivery of reduced doses of other flavivirus vaccines can increase the duration and titer of the viremic phase (Dean et al., 2005). There is no convincing clinical data that YF vaccine-virus viremia is directly associated with AEs, but some KOLs would expect viremia to be measured at least once, at an early time point, although the interpretation of any change in viremia profile might be difficult. There are clear requirements, established by WHO (WHO 2010a) for the preclinical and clinical testing of YF vaccines, which should be referred to when designing clinical trials for reduced dose and/or change of route of administration.[101]

- Would a change of route from SC to ID impact safety of YF vaccines? Participants given YF vaccine ID in the Roukens trial (2008) had redness and swelling at the injection site more frequently and for longer than SC vaccinees ($p < 0.001$). Itching at the vaccination site was also reported more frequently in the ID group ($p = 0.02$). Pain and myalgia were reported more frequently in the SC group.

  YF vaccines do not contain an adjuvant, but it is possible that other excipients present in some manufacturers' YF vaccine formulations might be unacceptably reactogenic when used intradermally, even if at a lower volume (and therefore a lower dose).[102]

- What is the impact of reduced-volume doses on longer-term adverse events? The SAEs associated with YF vaccine use are very rare and are only detected by surveillance in very large populations of vaccinated people. Long-term monitoring of populations vaccinated by reduced-dose by volume YF vaccine would be advisable, in case a change of dose and route was associated with a change in incidence of SAEs. The methodology and practicality of carrying this out needs to be considered and costed as part of a plan to evaluate changes in YF vaccine regimens.

- Are some YF vaccines more suitable for reduced-volume doses? The existing YF vaccines from different manufacturers have different properties (strains, starting potency, and stability) and it cannot be assumed that results obtained with dose-sparing with one vaccine will translate into similar clinical efficacy (and adverse events) with another vaccine.[103]

- Are some subpopulations more suitable recipients for reduced-volume doses? YF vaccines might be more or less immunogenic in different populations: for example, very young infants and older people. Data from a recent clinical trial indicate that adults over 60 years old mount a delayed antibody response and have higher viremia levels following

[101] Alan Barrett, University of Texas Medical Branch at Galveston, oral communication, September 4, 2012.

[102] Erin Staples, CDC. Written communication, October 5, 2012.

[103] Isabelle Delannoy (ID), Sanofi Pasteur, oral communication, February 11, 2011.

YF vaccination compared with adults aged 18 to 28 years (Roukens et al., 2011). Other groups that are likely to be less responsive to vaccine immunogens are people who are immunocompromised, which can include pregnant women and people with some stages of HIV infection. The safety profile might also differ in these populations. This might be a challenge to introduction of reduced-volume dosing of YF vaccine for some subgroups but a positive indication for others.

14.3. Framework for a clinical trial program: guidelines

The requirements for clinical evaluation of new live-attenuated YF vaccines are described by the WHO in their draft revised recommendations (WHO 2010a). These guidelines apply to testing of both new live attenuated YF vaccine strains and testing following major changes to the manufacturing process of an established YF vaccine.

Some of the main points are:

- Efficacy studies are not possible and so safety and immunogenicity endpoints should be used.
- Neutralizing antibodies pre- and post-vaccination should be measured, either by plaque-reduction neutralization test (PRNT) or $\log_{10}$ neutralization index (LNI). Geometric mean titers (GMTs), seroconversion rates, and reverse cumulative distributions should also be provided.
- A comparison vaccine should be included in the trial; either a well-established and licensed vaccine, or (if a new master seed lot is being used) a vaccine lot from the existing master seed.
- Age de-escalation: safety and immunogenicity studies should be undertaken initially in healthy adults aged 18 to 60 years, preferably in those in need of vaccination against YF. Subjects should not have had previous YF disease or YF vaccination. Studies in children should only be undertaken after adult studies have demonstrated an acceptable safety profile.

14.4. Clinical trial strategy

A stepwise strategy (Table 11), building on the studies of Roukens et al. (2008; 2009), could be taken.

Table 11. Strategy for clinical evaluation of fractional doses (by volume) of YF vaccine

Trial	Hypothesis	Arms of study	Population or setting	Endpoints	Notes
1	Delivery of 0.1 ml of the current formulation of YF vaccine (by SC or ID route) is immunologically non-inferior to 0.5 ml.	**Comparator**: 0.5 ml SC N&S. **Essential:** 0.1 ml SC N&S; 0.1 ml ID N&S. **Desirable:** 0.1 ml ID DSJI and/or other ID device[a]; 0.1 ml ID adapter [a]; 0.5 ml SC DSJI.	**Africa** (e.g. Ghana, Uganda, Kenya): in preventive campaign; age de-escalating (adults, then infants aged 9 months); select for non-immunes by history (analyze pre-immunes in separate group; could stratify for HIV$^+$). **Brazil**: adults, then infants aged 9 months.	**Immunogenicity:** antibody (at 30 days and preferably at 12 months), GMTs and seroconversion. **Reactogenicity:** local and systemic (10 days). **Programmatic:** acceptability, feasibility of RD SC, ID N&S and ID DSJI. **Safety**: Viraemia should be measured, duration TBD.	Need pilot study for acceptability/feasibility of DSJI or other ID device first. Use 30-day data to decide if elective revaccination after trial is needed. **Vaccine:** Stamaril (Sanofi Pasteur, France) is PQ, widely used and was used in the 'Roukens trials'. Vaccine from Institute Pasteur Dakar could be an alternative in West Africa. Bio-Manguinhos' vaccine could be used, unless a reduced potency formulation is introduced, which might preclude reduced-volume dosing and/or be less representative of other YF vaccines.
2	Delivery of 0.1 ml of same or second vaccine to test for equivalent results in different population and setting.	As above; or select comparators based on data from trial 1.	**South America** (other than Brazil) e.g. Peru/Colombia: as above, but infants aged 12 months.	As for trial 1.	**Vaccine**: repeat study with the vaccine used in the first study, plus one other vaccine used in the territory selected for preventive campaigns.
3	Vaccination by ID route improves immunogenicity of YF vaccine in HIV$^+$ people. Builds on data from trial 1.	**Comparator:** 0.5 ml SC N&S. **Essential:** 0.1 ml ID, possibly by DSJI. **Desirable:** 0.5 ml SC possibly by DSJI. 50% and/or100% potency, ID in 0.1 ml.	**Africa:** (high HIV prevalence): age-de-escalation; select HIV$^+$ by history; select non-immunes by history (stratify for pre-immunes by day 0 serology); de-select those with advanced HIV disease.	**Immunogenicity:** antibody (30 days and 12 months), GMTs and seroconversion. **Safety:** TBD.	**Vaccine**: possibly Stamaril (Sanofi Pasteur, France) vaccine as first choice; this would build on retrospective study in Switzerland (Veit et al., 2009) and coordinate with prospective studies in HIV$^+$ in Europe. Including ID dose-response groups will show whether ID route can improve responsiveness in hard to immunize populations.
4	Vaccination with reduced-volume of YF vaccine to determine if ID induces qualitatively different immune response to full dose SC.	**Comparator:** 0.5 ml SC N&S. **Essential:** 0.1 ml SC N&S; 0.1 ml ID N&S. **Desirable:** 0.1 ml ID DSJI.	**Europe or USA**: healthy volunteers (medical students?). Small numbers of subjects (to allow detailed immunological analysis).	**Immunogenicity:** antibody (20, 30, 180 days and 12 months), GMTs, seroconversion; cell-mediated immunity (CMI) Viremia: days 2–12. **Reactogenicity:** local and systemic (for 10 days).	**Vaccine:** Consider re-vaccination at 12 months to study memory response. Trial is not a high priority for programmatic use but scientifically novel and interesting.

Notes: DSJI = Disposable syringe jet injector, a device for needle-free delivery of vaccines SC, IM or ID; GMTs = geometric mean titers; N&S = needle and syringe; ID = intradermal; PQ = prequalified; SC = subcutaneous; TBD = to be determined; YF = yellow fever; a. The ID adapter is a device fitted to a 1.0 ml syringe that aids ID delivery by controlling the angle and depth of injection (reviewed in PATH, 2009).

The outline presented in Table 11 is proposed only as a simple description of a possible clinical program. More work, probably from a multidisciplinary working group, would need to be done to define endpoints, but it includes the following points for discussion:

1. The first clinical trials should use a vaccine likely to have non-inferior immunogenicity delivered intradermally at 20 percent dose, and preferably one that is also PQ and widely purchased for mass campaigns. Currently available YF vaccines have much higher PFU per dose than those used in some historical trials (including those in the 1950s),[104] which impacts the interpretation of published data and should inform the design of safety investigations.
2. The initial clinical trials should demonstrate whether a change of route is required, and whether doses other than 20 percent could be used subcutaneously instead of 20 percent intradermally (Trial 1).
3. The trials would be conducted in adults, and then in younger ages, preferably in YF at-risk areas (Trial 1).
4. The effects of lower dose and changed route on viremia could be assessed in the initial trials, as one potential (or expected) marker for safety (Trials 1 and 2).
5. Trial 1 could then be repeated with other YF vaccines and in other settings to test the reproducibility of the results (Trial 2).
6. The potential for increased immunogenicity of the ID route for YF vaccination in subgroups who might be more difficult to seroconvert could also be investigated (Trial 3, Table 11).

All the trials could provide an opportunity to compare N&S with needle-free delivery systems such as DSJI, and/or with enabling technologies such as the PATH ID adapter, or other ID delivery devices (Trials 1 to 3). Additional issues with these novel technologies might include those arising from the variation in dermal thicknesses (and hair distribution) with age (adults and children) and between sites on the body. These will need to be taken into account in studies optimizing ID delivery.[105]

14.5. Summary

There appears to be a rationale for using dose-sparing by reduced volume to improve the availability of YF vaccine (Sections 9 and 12) and some clinical data to support ID delivery of reduced volumes of YF vaccine (Roukens et al., 2008 and 2009) or SC delivery or reduced potency YF vaccines (Martins et al., 2013). However, several issues need to be addressed before the approach can be implemented, including

- Clinical trials are required to determine:
    - Whether a change to the ID route is required, or whether reduced doses will be sufficiently immunogenic when delivered subcutaneously.
    - Whether a 20 percent dose (80 percent dose-sparing) is the optimal dose, or whether more antigen (e.g., 40 or 50 percent dose) is required.
    - That changing the route and volume of vaccine delivered does not adversely affect the safety or immunogenicity of the vaccine, including in different subpopulations known to have differing responses to standard dose YF vaccine.
    - Which delivery device(s) might be required to support simple, reproducible ID delivery, which is currently carried out using N&S and the Mantoux technique.

[104] Alan Barrett, University of Texas Medical Branch at Galveston, oral communication, September 4, 2012.

[105] Erin Staples, CDC, written communication, October 5, 2012.

- A regulatory strategy will be required to support a label change covering the change in volume of YF vaccine to be used and the change in route to ID (if this is shown to be necessary); this might be for all use or just in certain settings or subgroups.

15. Conclusions

Through the analysis undertaken for this report, the authors have identified the following key points:

1. *YF vaccine supply.* The issues affecting the supply of the vaccine are complex and up-to-date information is not always available in the public domain. In theory, sufficient global manufacturing capacity already exists and could even be expanded to fit better the likely future demand, but:
    a. The limited number of YF vaccine producers, combined with unpredictable surges in demand, mean that periodically acute shortages of vaccine have occurred in the past decade and may well occur in the future.
    b. Interruptions to the vaccine production process, such as upgrading production equipment, restrictions in SPF egg supply, contamination or low yields of vaccine, cannot always be predicted, but are likely to occur in the future and will limit the amount of vaccine produced.
    c. The bottlenecks in production of YF vaccine appear to be mainly at the lyophilization and fill-finish step. Supply of SPF eggs can also limit production.
    d. Modifications to the production process, such as reducing the potency of the vaccine, are unlikely to be undertaken and/or are not likely to have a significant effect on global supply of YF vaccine without an expansion in lyophilization capacity. This is unlikely in the short to medium term.
    e. In general, vaccine manufacturers are unwilling to commit to expanding production of vaccines (including YF vaccine) in the absence of a secure and predictable future market.
    f. The supply for YF vaccine for travel use in HICs is separate, and insignificant in volume, to that for use in areas at risk of YF. Innovations in vaccines for the (higher price) travel market, such as inactivated YF vaccines are not likely to be available in the short to medium term and, even then, might not be transferred to the (lower price) nontravel market in LMICs.

2. *YF vaccine demand.* The issues affecting the demand side of the equation are also complex and vary between and within market clusters:
    a. The market and demand for YF used to be highly volatile but is now more stable, thanks to international efforts to predict, plan, and smooth out demand, and to fund and manage a stockpile for surges in demand due to outbreak response.
    b. The level of volatility in demand varies between countries and can be due to the capacity for detection of outbreaks and/or change in vaccination policy.
    c. The market for YF vaccine remains difficult to predict, in terms of “real need” (expansion of populations at risk) and also “expressed need” (demand), which is influenced by many factors including financial and human resources.
    d. The public sector market is very dependent on funding and purchasing mechanisms such as GAVI, UNICEF, and the PAHO Revolving Fund. It is also dependent on purchase (and use) by LMICs that have many competing priorities for health care spending and human resources.

e. The demand for YF vaccine in the African market cluster is higher overall than in South America or Brazil, but probably more predictable. Although large amounts of vaccine are used in preventive campaigns in Africa, several have been successfully completed. Campaigns planned for areas at lower risk of YF can be "spread" in time to some extent, to match vaccine availability.
f. Overall, demand for YF vaccine continues to exceed supply, resulting in delays to preventive campaigns.

3. *Increasing the availability of YF vaccine.* This could be achieved in a number of ways:
    a. Long-term strategies include modifications to vaccine manufacturing processes (including to change to cell-based production), changes to the nature of the vaccine (including inactivated and novel live vectored vaccines), development of effective therapies for YF disease and vector control (especially in cities). The probability of success and impact of these on the public-sector market in LMICs is low.
    b. In the short to medium term, based on information in the public domain, it appears that most YF vaccine manufacturers are unlikely to be willing (without external incentives) to invest large amounts of money and resources in developing new vaccines or reformulating the existing vaccine.
    c. At least one manufacturer (Chumakov Institute) has recently scaled up its production capacity for YF vaccine by increasing either bulk production and/or lyophilization capacity.
    From publicly available information, it is not possible to predict whether similar increases in capacity will be made by other manufacturers or, conversely, whether YF vaccine manufacturers will reduce annual production.
    d. In the short to medium term, pragmatic modifications to the use of the existing vaccine could be considered. For example, dose-sparing by reducing the volume of vaccine delivered (for example 0.1 ml rather than 0.5 ml) and probably by changing the route of administration from SC to ID could be both feasible and have an impact on vaccine supply and vaccine purchase cost.
    e. One or more manufacturers might be developing new seed stocks, which could be an opportunity to trial reduced dose and/or changes in route of administration.

4. *Dose-sparing by reduced volume.* Current clinical evidence suggests that dose-sparing (for example, delivering a 20 percent dose) could be possible with YF vaccine, inducing protective levels of immunity; however:
    a. This concept is only supported by a limited amount of clinical data from HIC use. Additional studies are required to analyse this further, especially in populations in countries at risk of YF.
    b. Recent data (Martins et al., 2013) suggest that reduced doses of YF vaccine might still be effective when given subcutaneously, so a change to the ID route might not be necessary. Further clinical trials are required to confirm whether:
        i. This finding applies to YF vaccines from more than one manufacturer.
        ii. Similar results are obtained in different populations (infants as well as adults).

iii. Similar results are obtained with reduced volume doses (which can be implemented at the point of use) to those seen with reduced potency vaccine (which will require reformulation) as tested by Martins et al.

5. *Vaccine presentation and use.*
    a. Data suggest that dose-sparing by reduced volume could increase the availability of the number of doses of vaccine per vial up to five fold (if a 20 percent dose was used).
    b. YF vaccine is already available in single-dose vials for the travel market (one 0.5-ml dose per vial) but this presentation is not PQ or available for public-sector purchase in at-risk countries. Increasing the number of 0.5-ml vials produced could reduce the overall supply of vaccine vials and increase costs per reduced-volume dose. This needs to be investigated.
    c. If current presentations of YF vaccine are not changed, then dose-sparing by volume for routine immunization is likely to result in wastage of vaccine due to the small immunization session sizes. This is less likely to be a problem in campaign settings where there is a high throughput of vaccinees per session:
        i. The view of KOLs was that dose-sparing in preventive or outbreak campaign settings would be a valuable tool to increasing the availability of vaccine.
        ii. If delivery of fractional doses required the use of the ID route, then a novel device to facilitate ID delivery (such as PATH's ID adapter or DSJIs) would probably be needed to replace the Mantoux technique, which is not suitable for high-pressure, high-throughput settings. This would need to be confirmed in clinical studies.

6. *Impact of implementation of dose-sparing by reduced volume.* Some very preliminary forecasts of the impact of dose-sparing suggest that:
    a. 24 to 42 M standard 0.5-ml doses of vaccine per year could be saved by using dose-sparing in preventive campaigns, amounting to savings of up to 420 M 0.5-ml doses by 2022.
    b. Use of novel devices for ID delivery of reduced volume doses could reduce the "device plus vaccine" cost per immunization by up to approximately 67 percent compared with the current cost of NS delivery of a 0.5-ml dose of YF vaccine.
    c. A much more detailed analysis of the costs involved is required, which would be strengthened by clinical evidence to identify the optimum dose volume required.

7. *Next steps.* Dose-sparing by reduced volume could be easier to implement than developing new YF vaccines or making significant changes to the formulation of existing vaccines. However, significant obstacles remain that will require cooperation between vaccine manufacturers, regulators, vaccine purchasers, and delivery-device manufacturers if they are to be overcome.

    Many questions remain to be answered, including:

a. Does dose-sparing require the use of the ID route? If so, which delivery devices should be used and tested?
b. If dose-sparing is to be used for campaign, but not routine immunization, will this be acceptable and what issues does having a "dual" indication raise?
c. Can dose-sparing by either route be introduced off label, or if a label change is preferred, what clinical trials are required to achieve this?
d. What are the implications of dose-sparing in terms of long-term immune responses and also maintaining a safety margin in the potency of the vaccine, so that it still induces a protective immune response at the end of its shelf life?

A pragmatic dose-sparing strategy with existing YF vaccines has significant promise for increasing YF vaccine supply, increasing access to vaccines and reducing purchasing costs, which could benefit vaccine manufacturers, public-sector funders, purchasers, and end users.

The authors hope that this report will stimulate interest among a wider group of key stakeholders involved with YF vaccination (including the YF working group of the WHO SAGE).[106,107]

[106] http://www.who.int/immunization/sage/working_mechanisms/en/index.html

[107] http://www.who.int/immunization/sage/SAGE_wg_call_yellow_fever.pdf

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Appendix 1. Methodology, interviews, and contacts

The information for this report was obtained from a literature review (peer-reviewed and gray literature) and interviews with the key opinion leaders (Appendix Table 1) some of which were conducted at the Flavivirus Vaccination Conference, Les Pensieres Conference Centre, Veyrier-Du-Lac, France, December 6 to 8, 2010.

Appendix Table 1. Key opinion leaders and stakeholders consulted

Name	Affiliation	Interview method	Rationale/expertise
YF vaccine manufacturers			
Antonio **de Padua Barbosa**, Deputy Director of Production; Akira **Homma**, President of Political and Strategic Council; Reinaldo de Menezes **Martins**, Scientific Consultant	Bio-Manguinhos, Brazil	Email (February 7, 2011)	YF vaccine manufacturer.
Alexandra **Sinyugina**, Head of Quality Control; Andrew **Malkin**, Head of Quality Assurance	Chumakov Institute, Russia	Telephone (January 26, 2011)	YF vaccine manufacturer.
Jaco **Smit**, Global Immunization Policy; Isabelle **Delannoy**, Head of Yellow Fever Franchise; Michael **Attlan**, Senior Director, Endemic and Innovation Franchise; Isabelle **Dechamps**, Vaccination Policy Director; Cecile **Tricoire**	Sanofi Pasteur, France	Telephone (February 11, 2011) Telephone (May 9, 2012)	YF vaccine manufacturer.
Individual key opinion leaders			
Alan **Barrett**	Sealy Center for Vaccine Development, University of Texas Medical Branch, United States	Informal interviews at Flavivirus Vaccination Conference (December 6-8, 2010; not cited in the report) Review of the second draft of the report (Summer 2012) Telephone follow-up (September 2012)	Virologist specializing in bunyaviruses and flaviviruses including YF.
Alejandro **Costa**	Global Alert and Response, WHO, Switzerland	Telephone interview (January 31, 2011 and April 12, 2011) Review and revisions of report, with email correspondence (March 5, 2012) Telephone follow-up (May 28, 2012)	Closely involved with supply of YF vaccine and interactions with manufacturers.

Name	Affiliation	Interview method	Rationale/expertise
Morag **Ferguson**	National Institute for Biological Standards and Control, United Kingdom (retired)	Email correspondence (January 17, 2011; not cited in the report)	Expert on YF potency requirements and assays.
Brenan **Flannery**	PAHO, Brazil	Telephone interview (January 25, 2011)	Focus on vaccine use in Brazil and also liaise with Brazil-based manufacturers for PAHO.
Lauren **Franzel**	PATH, France	Email and telephone interview (March 28, 2011)	YF strategic demand forecasting (amongst other vaccines purchased by the GAVI Alliance/UNICEF).
Martin **Friede**	WHO, Switzerland	Telephone interview (March 3, 2011)	Interest in intradermal route and regulatory pathways to change dose/route of vaccines.
Ulla **Griffiths**, Health Economist	London School of Hygiene and Tropical Medicine, United Kingdom	Review of the second draft of the report, plus correspondence (Summer 2012)	Previous study on impact of jet injector uses on vaccine costs including YF.
Edward "Ned" **Hayes** Research Professor	Barcelona Centre for International Health Research, Spain	Telephone interview (January 20, 2011)	Interest in YF vaccine safety, efficacy and economic modeling.
Joachim **Hombach**, Acting Head of the Initiative for Vaccine Research	Initiative for Vaccine Research, WHO, Switzerland	Review of the second draft of the report, plus correspondence (Summer 2012)	Responsible for flavivirus vaccine portfolio.
Tom **Monath**	Kleiner Perkins Caufield & Byers, United States	Telephone interview (2009) Brief discussion at Flavivirus Vaccination Conference (December 6-8, 2010)	Expert in YF and flavivirus vaccines.
Olivier **Ronveaux**, Medical Officer Yellow Fever Control	WHO African Regional Office, Burkina Faso	Telephone interview (January 21, 2011) Review and revisions of initial draft of report, plus correspondence (September 26, 2011)	Medical Officer Yellow Fever Control
Alba Maria **Ropero** (Alvarez)	Immunization Unit, Family and Community Health, PAHO, United States	Telephone interview (February 16, 2011)	Regional advisor on immunization.
Francois **Simon**	APHP, France	Informal interview at Flavivirus Vaccination Conference (December 6-8, 2010)	Former director of Institut Pasteur, Dakar—now based in Paris. About to start trial of YF vaccine in HIV-positive subjects.
J Erin **Staples**	Centers for Disease Control and Prevention, Georgia, United States	Review of the second draft of the report, plus correspondence (Summer 2012)	Medical epidemiologist; arbovirus specialist.
Oyewale **Tomori,** Professor of Virology	Redeemer's University, Nigeria	Telephone interview (January 24, 2011)	
Dennis **Trent**	Sealy Center for Vaccine Development, United States	Informal interview at Flavivirus Vaccination Conference (December 6-8, 2010; not cited in the report)	Worked in industry on inactivated YF vaccine; interest in regulatory affairs.

Name	Affiliation	Interview method	Rationale/expertise
Leo **Visser**	Leiden University Medical Center, the Netherlands	Telephone interview (February 1, 2011)	Corresponding author on two primary publications on intradermal route for YF vaccine.
Michel **Zaffran**, Simona **Zipursky**	Project Optimize, WHO, Switzerland	Telephone interview (March 18, 2011)	Vaccine presentation and transport/storage of vaccines; interest in stability of YF vaccine.

Notes: APHP = Assistance Publique Hopitaux de Paris; PAHO = Pan American Health Organization; UNICEF = United Nations Children's Fund; WHO = World Health Organization; YF = yellow fever.

Appendix 2. Yellow fever vaccine potency measurements

For several decades, the World Health Organization (WHO) requirements for yellow fever (YF) vaccines stated that "…the titer of the vaccine shall not be less than 1,000 mouse lethal dose $_{50}$ or its equivalent in plaque-forming units, in the dose recommended by the manufacturer for use in humans" (cited in Ferguson and Heath 2004); however, in practice, plaque assays are used by manufacturers because they are more reproducible than MLD_{50} assays.

In 2003, the first international standard for a YF vaccine was assigned to improve comparisons between laboratories. Originally assigned a potency of $10^{4.5}$ international units (IUs) per dose, this was subsequently amended because the minimum potency recommended for use in humans should not be less than 3.0 $\log_{10}$ IU per dose (1,000 IU per dose)[108, 109]

Information provided to WHO in 2008 and 2009 by YF vaccine manufacturers and national control laboratories on the relationship between MLD_{50}, plaque-forming units, and IUs and the potency of YF vaccine lots is presented in Appendix Table 2 and Appendix Table 3. Manufacturers might have changed their potency since this date, but it gives an indication of relative potencies at that time.

Appendix Table 2. Summary of the relationship between different measures of yellow fever vaccine potency

	PFU equivalent to 3.0 $\log_{10}$ MLD_{50} per dose		Relationship between IU and PFU		
Manufacturer or laboratory	**PFU per dose**	**$\log_{10}$ PFU per dose**	**Assay results**	**Conversion factor**	**Number of PFU equivalent to 1 IU**
Manufacturers					
Bio-Manguinhos (Brazil)	5,370	3.73	4.48 $\log_{10}$ PFU per dose = 4.2 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU - 0.28	1.91
Crucell (The Netherlands)	15,000	4.2	Information not provided	Information not provided	Information not provided
Institut Pasteur, Dakar	Information not provided	Information not provided	4.48 $\log_{10}$ PFU per dose = 4.2 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU - 0.28	1.91
Sanofi Pasteur (France)	6,309	3.8	4.54 $\log_{10}$ PFU = 4.2 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU - 0.34	2.19
National laboratories					
AFSSAPS (France)	5,012	3.7	Information not provided	Information not provided	Information not provided
INCQS (Brazil)	9,772	3.99	4.86 $\log_{10}$ PFU per dose = 4.2 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU - 0.66	4.57
NIBSC (United Kingdom)	2,692	3.43	4.87 $\log_{10}$ PFU per dose = 4.2 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU - 0.67	4.7
NICPBP (China)	5,623	3.75	4.03 $\log_{10}$ PFU per dose = 4.2 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU + 1.48	0.68
SwissMedic (Switzerland)	Information not provided	Information not provided	3.8 $\log_{10}$ PFU per dose = 4.2 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU + 0.40	0.40
Tarassevich (Russia)	1,584	3.2	3.95 $\log_{10}$ PFU per dose = 4.13 $\log_{10}$ IU per dose	$\log_{10}$ IU = $\log_{10}$ PFU + 0.18	0.66

[108] Ferguson M, et al. *WHO Working Group on Technical Specifications for Manufacture and Evaluation of Yellow Fever Vaccines.* May 13-14, 2009; Geneva, Switzerland. *Vaccine.* 2010;28(52):8236-8245.

[109] WHO (2010a). Yellow fever fact sheet. *Weekly Epidemiological Record.* 2010a;85(5):33-36.

Notes: AFSSAPS = French Agency for the Safety of Health Products; INCQS = National Institute of Quality Control in Health Care; IU = international unit; MLD = 50-percent mouse lethal dose; NIBSC = National Institute for Biological Standards and Control; NICPBP = National Institute for the Control of Pharmaceutical and Biological Products; PFU = plaque-forming units.[110]

The titer of live YF virus per dose of vaccine (equivalent to the vaccine potency) at the point when the vaccine is released varies between manufacturers and varies between different batches from the same manufacturer. Typical ranges of YF vaccine potency are summarized in Appendix Table 3. This is from the most recent publicly available information; some manufacturers might have changed their formulation since these data were reviewed.

Appendix Table 3. Potencies of currently available yellow fever vaccines

Manufacturer	Potency of vaccine lots			Stability data	Approximate "excess potency"[a]
	log_{10} MLD_{50} per dose	log_{10} PFU per dose	log_{10} IU per dose	log_{10} IU per dose	
Bio-Manguinhos (Brazil)		2000–2009: average = > 4.0; range = 3.81 - 4.92 (5-dose vial);[b] 3.56 - 4.39 (50-dose vial).[b]		Range = 3.28 - 4.11, after stability test.	5-dose vial: 3.4 - 43.7 fold excess. 50-dose vial: 1.9 - 12.9 fold excess.
China National Biotech Institute (China)	1973–2000: average = 5.5; range: 3.5 - 6.5.[c]	2001–2006: average = 5.5; range = 4.5 - 6.1.[c]	2006: range = 5.3 - 6.4.[c]	2006: range = 5.2 - 5.9.[c]	
Chumakov Institute (Russia)	1973–2000: average = 5.5; range= 3.5 - 6.5.		2004–2007: range= 3.87 - 4.7.[c]	3.73, range = 3.3 - 4.26.[c]	7.4 - 50.1 fold excess.
Institut Pasteur, (Senegal)			Range = 3.98 - 4.92.[c]	Range = 3.58 - 4.59, after stability test.[c]	9.5 - 83.2 fold excess.
Sanofi Pasteur (France)			2004–2007: average = 4.2;[c] range = 3.90 - 4.31.[c]	Range = 3.48 - 4.03.[c]	7.9 - 20.4 fold excess.
Sanofi Pasteur (United States)		2006: range = 4.99 - 6.28.[c]		Range = 4.87 - 6.17; log_{10} PFU after 12 months.[111]	

Notes: IU = international unit; MLD = 50-percent mouse lethal dose; PFU = plaque-forming units;[112] a. excess potency was calculated by comparing potency range of vaccine lots (in IU/dose) with WHO minimum recommended potency of 3 log_{10} IU/dose; b. 5- and 50-dose vials contain different stabilizers.

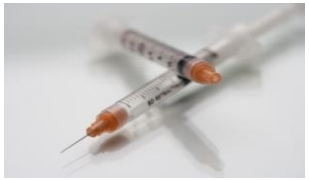
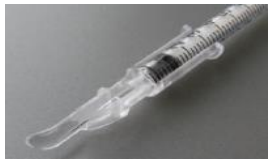
[110] WHO (2008e). *WHO Informal Consultation of the Minimum Potency Specification for Yellow Fever Vaccines, National Institute for Biological Standards and Control (NIBSC)*. Potters Bar, UK: November 19-20, 2007. Available at: http://www.who.int/biologicals/publications/meetings/areas/vaccines/yellow_fever/FINAL%20WHO%20Report-YFpotency-29%20July%202008%20clean%20for%20web.pdf.

[111] WHO (2008e). *WHO Informal Consultation of the Minimum Potency Specification for Yellow Fever Vaccines, National Institute for Biological Standards and Control (NIBSC)*. Potters Bar, UK: November 19-20, 2007. Available at: http://www.who.int/biologicals/publications/meetings/areas/vaccines/yellow_fever/FINAL%20WHO%20Report-YFpotency-29%20July%202008%20clean%20for%20web.pdf.

[112] Ferguson M et al. *WHO Working Group on Technical Specifications for Manufacture and Evaluation of Yellow Fever Vaccines.* May 13-14, 2009; Geneva, Switzerland. *Vaccine.* 2010;28(52):8236-8245.

Appendix 3. Devices for intradermal delivery of vaccines

Appendix Table 4. Summary of key features of some of the intradermal delivery devices considered to be suitable for use with yellow fever vaccine

Device and manufacturer	Image	Description	Availability and status	Notes
Autodisable syringe Manufacturers include BD (United States); www.BD.com Star Syringe (United Kingdom) www.starsyringe.com	 ©PATH/Scott Areman	Needle and syringe with AD features. Some have staked needles, others interchangeable Luer needles.	Widely available.	Widely used for ID delivery of Bacillus Calmette-Guérin using the Mantoux technique. Key opinion leaders consulted for the report felt that the Mantoux technique would not be suitable for mass immunization campaigns.
ID adapter West Pharmaceuticals, Inc. (United States) www.westpharma.com	 ©PATH/Scott Areman	Plastic sleeve that fits over a commercially available needle and syringe to limit the depth and angle of the needle to facilitate giving a reliable ID injection.	Has regulatory clearance.	
Biojector B2000 Bioject Inc. (United States) www.bioject.com	 ©Bioject	Needle-free DSJI powered by an internal CO_2 cartridge or an external CO_2 tank. Different delivery depths achieved by the use of spacers.	Commercially available.	Requires procurement and transport of CO_2, which is likely to preclude use in campaign and possibly routine immunization settings.
Bioject ID pen injector Bioject Inc. (United States) www.bioject.com	 ©PATH/Patrick McKern	Spring-powered DSJI with needle-free AD syringe. Designed for ID delivery. User activates the spring by pulling on the integrated reset lever.	In development.	Designed to have similar performance characteristics for ID delivery as the B2000 device but without the requirement of a compressed-gas power source.

Device and manufacturer	Image	Description	Availability and status	Notes
Bioject Zetajet Bioject Inc. (United States) www.bioject.com	 ©Bioject	Spring-powered DSJI with needle-free AD syringe. User activates the device by turning a dial on the bottom of the device.	Commercially available. Investigational use only for ID delivery.	Designed for use in low-resource settings; however, the twisting action required to reset the device may not be compatible with high-volume campaign settings.
Med-Jet Dart Medical International Technologies (China, Canada) www.mitcanada.ca	 ©Medical International Technologies	Spring-powered DSJI with needle-free AD syringe. User activates the device by turning a dial on the bottom of the device.	In development.	In early stage development; clinical data not yet available.
Med-Jet H-4 Medical International Technologies (China, Canada) www.mitcanada.ca	 ©Medical International Technologies	Compressed gas-powered DSJI with needle-free AD syringe. Gas pressure is adjusted to control depth of delivery.	In development.	Requires an external compressed-gas propulsion system, which is likely to preclude its use in campaign and possibly routine immunization settings.
PharmaJet Generation 1 needle-free injector PharmaJet Inc. (United States) www.pharmajet.com	 ©PharmaJet	Spring-powered DSJI with needle-free AD syringe and separate manual resetting station. Separate versions are available for subcutaneous/intramuscular or ID delivery.	Has regulatory clearance.	Design improvements have been made to more recent PharmaJet DSJIs to improve usability.
PharmaJet Tropis PharmaJet Inc. (United States) www.pharmajet.com	 ©PharmaJet	Spring-powered DSJI with needle-free AD syringe and integrated manual resetting via lever built-into the handpiece. Designed specifically for ID delivery.	In development.	Designed to be easy to use and portable.

Device and manufacturer	Image	Description	Availability and status	Notes
MicronJet NanoPass (Israel) www.nanopass.com	 ©Nanopass	Luer hub that attaches to a standard syringe. The hub has three hollow microneedles mounted at one end.	Has regulatory clearance.	The microneedles are smaller than standard needles and might pose less risk of needlestick injury, but are still likely to be considered as sharps.

Notes: AD = autodisable; DSJI = disposable syringe jet injector; ID = intradermal; devices included in the table were selected to be compatible with existing lyophilized formulations and presentations of YF vaccine, capable of ID delivery and available in the short-medium term; a. estimated cost of disposable components per dose delivered; most devices are in development, so cost of components can only be estimated; estimates assume devices are produced at large scale (> 100 million units per year). Other devices, such as ones similar to Soluvia, or other types of DSJI, might be available.

Appendix 4. Assumptions and inputs for models

Appendix Table 5. Incremental cost model; inputs and assumptions

General model inputs	SC	ID	Source and notes
Price per dose of vaccine (US$).	0.82		Based on weighted average of United Nations Children's Fund prices for 5-, 10-, and 20-dose vials in 2011:[113] • 6.69 million 5-dose vials purchased at $0.66 per dose. • 25.2 million 10-dose vials purchased at $0.85 per dose. • 0.68 million 20-dose vials purchased at $0.61 per dose. The price might increase as it did during the period 2004 to 2010 (CEPA 2010).
Volume of vaccine, delivered per injection (ml).	0.5	0.1	Assume dose sparing by delivering 20 percent of standard dose. The actual "reduced volume" dose that is non-inferior to full-dose might not be at 20 percent but could be more or less than this and will need to be established in clinical studies.
Number of injections per schedule per infant or other vaccine.	1	1	This is the standard immunization schedule for yellow fever vaccination. Some countries use booster doses (especially for travel vaccination every 10 years).
Vaccine wastage (as a percent of the number of doses purchased).	5%	5%	Based on observed wastage rates in one preventive yellow fever vaccine campaign (Wiysonge et al., 2008). This probably refers to number of doses not delivered rather than wastage due to dead space in the delivery device or from cold chain failure. A larger dataset of wastage would be useful for modeling purposes.
Cost of vaccine transport, sharps disposal and biomedical waste disposal (US$).	-	-	Not included in model; no data available for "large market"-level analysis.
Unsafe injection cost (US$ per injection).	-	-	Not included in model; see main text for explanation.

Notes: ID = intradermal; SC = subcutaneous.

[113] http://www.unicef.org/supply/files/2011_Vaccine_Projection_final.pdf

Device-specific inputs	SC	ID	Source and notes
Needle and syringe			
Price of autodisable N&S (US$)—the baseline recurrent cost.	0.05	0.08	2011 UNICEF catalogue: Syringe, A-D , 0.5 ml, w/ndl/BOX-100 = $5.40); Syringe, A-D, bacillus Calmette-Guérin, 0.1 ml, w/ndl/BOX-100 = $7.85.
Price of reconstitution N&S (US$).	0.03	0.03	Assumes use of 5-ml syringe and needle at $3.44 per 100 (UNICEF catalogue 2011).
Disposable syringe jet injector			
Price of (non-disposable) DSJI handpiece (includes reset station if this is needed for the device) (US$), [capital cost].		48	PATH estimate[114] for high volume production.
Number of injections possible with the re-useable DSJI component during its lifetime.		5,000	PATH estimate. Device PQS specification requires 20,000 injections but there might be breakage or loss.
Price of the DSJI disposable syringe (US$) (includes price of vial adapter), [recurring cost].		0.12	PATH estimate for high-volume production.
Intradermal needle adapter			
Price of the (disposable) ID adapter (US$), used with a needle and syringe, [recurring cost].		0.06	PATH estimate for high-volume production.
Hollow microneedle array			
Price of the (disposable) microneedle array (US$), used with syringe instead of a needle.		0.5	PATH estimate based on conversations with microneedle developers.
Device-specific inputs not included in the model at this stage			
Wastage rates of the disposable parts of each device.			No data available.
Amount of vaccine wastage due to dead-space in the device.			Excluded. The dead-space volume will vary between devices (and might vary between currently used N&S). Novel devices for ID delivery are currently undergoing development and design changes, so dead-space volumes are likely to change.

Notes: DSJI = disposable syringe jet injector; ID = intradermal; N&S = needle and syringe; SC = subcutaneous; UNICEF = United Nations Children's Fund.

[114] "PATH estimate" refers to estimates made by PATH's Vaccine Delivery Technology Group (PATH VDTG) in 2011.

Appendix 5. Use of yellow fever vaccine in routine immunization

Appendix Table 6. Use of yellow fever vaccine for routine immunization by country[a]

Country	Age for routine immunization (if used for travelers)[b]	2009 birth cohort (thousands)[c]	Estimated % coverage YF and MCV for 2010 (UNICEF data)[d]	Reported vaccine stockouts[e]
Angola	9 months old (and international travelers)	789	YF 40; MCV: 93	2008: 46 districts; 2009: 138 districts; 2010: 3-month stockouts in 150/164 districts.
Argentina	1-year old, subnational (risk areas)	691 subnational	YF 14; MCV 99	
Benin	9 months old	349	YF 69; MCV 69	
Bolivia (Plurinational State of)	12 to 23 months old	262	YF 63; MCV 79	2009: 2-month vaccine shortage.
Brazil	9 months old, 10 years old, subnational (where indicated)	3,026 subnational	YF 34; MCV 99	
Burkina Faso	9 months old	738	YF 93; MCV 94	
Cameroon	9 months old	711	YF 79; MCV 79	
Central African Republic	9 months old	154	YF 62; MCV 62	
Chad	9 months old	508	YF 61; MCV 46	2008: decline due to vaccine shortage.
Colombia	12 months old and for people from risk areas and travelers	917	YF 79; MCV 88	2008: decline attributed to vaccine shortage.
Congo	36 weeks old	126	YF 77; MCV 76	
Congo, Democratic Republic	9 months old	2,930	YF 62; MCV 68	2008: decline attributed to vaccine shortage.
Cote d'Ivoire	9 months old	729	YF 69; MCV 70	2009: 10-month stockout; 2010: 1-month vaccine stockout.
Ecuador	12 months old; > 1 year in Amazon region	279	YF 65; MCV 98	
France (French Guiana)	12 months old; 11, 21, 31, 41, 51 years old; subnational	(not listed) subnational	Not reported	
Gabon	9 months old	40	YF 55; MCV 55	
Gambia	9 months old	62	YF 68; MCV 63	
Ghana	9 months old	766	YF 64; MCV 71	
Guinea	9 months old	397	YF 38; MCV 51	

Country	Age for routine immunization (if used for travelers)[b]	2009 birth cohort (thousands)[c]	Estimated % coverage YF and MCV for 2010 (UNICEF data)[d]	Reported vaccine stockouts[e]
Guinea-Bissau	9 months old	66	YF 61; MCV 61	
Guyana	12 months old	13	YF 94; MCV 95	
Honduras	Greater than 1 year, travelers	202	YF not reported; MCV 99	
Kenya	9 month, subnational	1,530 subnational	YF 1; MCV 86	
Liberia	9 months old	149	YF 64; MCV 64	
Mali	9 months old	551	YF 68; MCV: 63	
Niger	9 months old	815	YF 64; MCV 71	
Nigeria	9 months old	6,081	YF 69; MCV 71	
Panama	1-year old (and every 10 years), subnational (high-risk areas)	7 subnational	YF data not sufficient to produce an estimate; MCV 95	
Paraguay	1-year old	154	YF 69 (country report on childinfo.org); MCV 94	
Peru	15 months old, subnational	605 subnational	YF 61; MCV 94	2009: shortages led to subnational (at risk) delivery only.
Sao Tome and Principe	9 months old	5	YF 93; MCV 92	
Senegal	9 months old	476	YF 60; MCV 60	
Seychelles	12 months old (and travelers)	3	YF not reported; MCV 99	
Sierra Leone	9 months old	227	YF 82; MCV 82	
South Sudan	Greater than 2 year, subnational	New country so not yet listed subnational	Not applicable	
Suriname	1-year old, subnational	1 subnational	YF 11 (80 in targeted area); MCV 89	
Togo	9 months old	215	YF 84; MCV 84	
Trinidad and Tobago	1 and 11 years old	20	YF 95; MCV 92	
Venezuela	12 months old, (preschool and travelers)	600	YF 48; MCV 79	2010: 12-month vaccine stockout.

Notes: MCV = measles containing vaccine; UNICEF = United Nations Children's Fund; YF = yellow fever; a. Other African countries are considered "at-risk of yellow fever"[115] but do not have yellow fever vaccine in their routine childhood schedule—these include Burundi, Equatorial Guinea, Ethiopia, Eritrea (low potential for exposure), Mauritania, North Sudan (in the Eastern Mediterranean Region), Rwanda, Somalia (in the Eastern Mediterranean Region, low potential for exposure), Uganda, and United Republic of Tanzania (low potential for exposure); b. Schedule correct as of September 20, 2011, from World Health Organization (WHO) Vaccine Preventable Diseases Monitoring System (WHO website); countries have not been included if they vaccinate only travelers to other countries; [116] c. 2009 annual birth data, not adjusted for survival, listed where there is no indication that the coverage is subnational only. From the United Nations Children's Fund's (UNICEF's) State of the World's Children 2011 report;[117] d. 2010 estimated immunization coverage data for yellow fever vaccine, and (for comparison) measles-containing vaccine from UNICEF's data; [118] e. Recent stockouts reported in "country" immunization reports from WHO and UNICEF (data updated July 15, 2011).[119]

[115] Olivier Ronveaux, WHO AFRO, written communication, September 26, 2011.

[116] http://apps.who.int/immunization_monitoring/en/globalsummary/ScheduleResult.cfm

[117] http://www.unicef.org/publications/files/SOWC_2011_Main_Report_EN_02242011.pdf

[118] http://www.childinfo.org/immunization_countrydata.php

[119] http://www.childinfo.org/immunization_countryreports.html

Appendix 6. Recent history of reported yellow fever outbreaks and vaccine responses

Africa

Outbreaks can be dispersed across multicenter rural areas or in urban settings (e.g., Abijan in Cote d'Ivoire in 2001). The emergency vaccination response can range from none (when the population immunity is sufficiently high, [e.g., Senegal in 2010]) to mass vaccination of an entire city or (e.g., Cote d'Ivoire vaccinated approximately 3 million people in eight days) or the entire population (e.g., Gambia in 1978, achieving 97-percent coverage).

Outbreak sizes in Africa range from a single confirmed case (e.g., Senegal in 2007) to 200,000 (e.g., Ethiopia in 1960 to 1962); Appendix Table 7.

Appendix Table 7. Yellow fever outbreaks in Africa since 1940 and outbreak-control response

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
1940	Sudan	Under war conditions, ingress of non-immunes to Nuba region, 15,000 cases.		Mutebi and Barrett, 2002; reviewed in McMullan et al. 2012.
1941, 1952, 1959	Uganda	1 case each year.		Reviewed in McMullan et al. 2012.
1958–1962	Zaire (Democratic Republic of Congo), Upper Nile Region of Sudan	Severe outbreaks; 1,800 cases in Sudan (1959), spread to Ethiopia.		Tomori, 2004; reviewed in McMullan et al. 2012.
1960–1962	Ethiopia	Largest outbreak reported: 200,000 cases, 30,000 deaths; civil unrest.	Following a "warning" outbreak the previous year (1959), mass vaccination could have prevented this outbreak.	Mutebi and Barrett 2002; Ellis and Barrett 2008; reviewed in McMullan et al. 2012.
1965	Senegal	20,000		Mutebi and Barrett 2002; Nathan et al. 2001.
1967–1969	Uganda	Endemic for YF but only 1 case reported in 1964.		Reviewed in McMullan et al. 2012.
1969	Burkina Faso, Nigeria	About 100,000.		Mutebi and Barrett, 2002; Nathan et al. 2001.
1969–1970, 1974	Nigeria	Yes	Not well controlled.	Tomori, 2004.
1971	Angola	Yes		Tomori, 2004.

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
1975	Sierra Leone	Yes		Mutebi and Barrett, 2002; Tomori, 2004.
1977	Ghana	Yes		Tomori, 2004.
1978	Gambia	8,400 cases.	Entire population vaccinated with 97-percent coverage, and routine EPI to > 80-percent coverage; "successful control of YF."	WHO, 2007a; Mutebi and Barrett, 2002; Tomori, 2002; Tomori, 2004.
	Ghana	Yes		WHO, 2007a; Mutebi and Barrett, 2002; Tomori, 2002; Tomori, 2004.
1979	Ivory Coast	Yes		Tomori, 2004.
1986–1991, 1994	Nigeria	Greater than 20,000 cases (by 1994) longest running, uninterrupted epidemic in entire country.	30 million doses imported and used: 30-percent wasted, failure to control due to slow response to outbreak. In 1987, some vaccinees had fever and rapidly progressing swelling of arm (within hours of vaccination) and 5 died—probably from bacterial contamination of vaccine (poor handling).	WHO, 2007a; Tomori, 2002; Nathan et al. 2001; Tomori, 2004.
1992–1993	Kenya	Mostly in woodland due to movement of non-immunes during drought—after 20 years without an outbreak.		WHO, 2005b; Mutebi and Barrett, 2002.
1994	Gabon	Yes, started as jungle cycle in remote mining camp, spread to rural areas and then urban areas.		Tomori, 2002.
1995–1996	Liberia	359		Mutebi and Barrett, 2002.
	Benin	86		Mutebi and Barrett, 2002.
	Ghana	27		Mutebi and Barrett, 2002.
1997	Liberia	1		Mutebi and Barrett, 2002.
1998	Burkina Faso	2		Mutebi and Barrett, 2002.
2000–2001	Guinea	About 833 cases (CFR 33 to 60 percent), after 50 years without an outbreak (no YF vaccination since 1950s).	Yes, vaccine supply caused delays.	WHO 2005b; Nathan et al. 2001.
	Liberia	102	About 150,000 doses planned.	WHO GAR alerts, YF[120] Mutebi and Barrett, 2002; WHO, 2005b.

[120] http://www.who.int/csr/don/archive/disease/yellow_fever/en/

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
	Nigeria	2	Mass vaccination planned for presumed urban outbreak in Kano.	WHO GAR;[120] Mutebi and Barrett, 2002; WHO, 2005b.
2001	Ivory Coast	Abijan: 203 in urban outbreak.	2.6 to 3 million doses, all aged > 9 months but not if vaccinated in past 10 years delivered within 8 days; plus active surveillance for adverse events; It was estimated that about 30,000 deaths were prevented.	Mutebi and Barrett, 2002; Fitzner et al. 2004.
2002	Senegal	Dakar: 60+ including Touba.	Mass vaccination about 800,000 doses (up to 99-percent coverage).	WHO GAR;[120] WHO, 2005b.
	Nigeria and Gambia		In 2002, Nigeria was thought to have achieved 1-percent coverage for YF compared with 87percent in Gambia.	Tomori, 2002.
2003	Burkina Faso	About 1+.	Rapid vaccination.	WHO GAR.[120]
	Guinea		About 600,000 doses.	WHO GAR.[120]
	Liberia	Yes, in internally-displaced person camps.		Huhn et al. 2006.
	Sierra Leone	About 1+.	+, about 250,000 doses.	WHO GAR.[120]
	Sudan	17+	Reactive campaign.	WHO GAR.[120]
2004	Burkina Faso	Yes, Dioulasso,: 4+, risk of urban outbreak.	Mass campaign (with measles in kids aged > 9 months).	Briand et al. 2009.
	Liberia	4+	Reactive campaign.	WHO GAR.[120]
2005	Benin	Yes		WHO, 2006.
	Burkina Faso	About 14.		WHO, 2006.
	Cameroon	2		WHO, 2006.
	CAR	Yes		WHO, 2006.
	Congo			WHO, 2006.
	Cote d'Ivoire	3	290,000 doses, mostly from the European Commission Humanitarian (Aid) Office stockpile.	WHO, 2006.
	Democratic Republic of Congo			WHO, 2006.
	Gambia			WHO, 2006.
	Ghana	2		WHO, 2006.
	Guinea	74 including in transport hub	900,000 doses, 100,000 from national stock	WHO, 2006.
	Liberia			WHO, 2006.
	Mali	12	2.5 M doses, some from national stock	WHO, 2006.
	Niger			WHO, 2006.

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
	Senegal	7	150,000 doses, none from GAVI	WHO, 2006.
	Sierra Leone			WHO, 2006.
	Sudan		2.8 M doses, 60% from global stockpile, 28% from MSF,rest from UNICEF	WHO, 2006.
	Togo		In total ~4.8 million doses were required from global stockpile	WHO, 2006.
2006	Burkina Faso		Start of risk assessment.	UNICEF, 2008c.
	Cameroon	1+52	Large reactive campaign.	WHO, 2008b.
	CAR	1	Small reactive campaign.	WHO, 2008b.
	Cote d'Ivoire	Greater than 16.	Large reactive campaign.	WHO, 2008b.
	Ghana	1	Large reactive campaign.	WHO, 2008b.
	Guinea	1	No reactive campaign; reinforced routine EPI.	WHO, 2008b.
	Mali	5	No reactive campaign because in 2005, those aged < 15 years had been vaccinated.	WHO, 2008b.
	Senegal		Planned start of risk assessment.	UNICEF, 2008c.
	Togo	3	Reactive campaign; planned start of risk assessment.	UNICEF, 2008c.
2007		No cases in urban environments.		WHO, 2007b; WHO, 2009.
	Benin		UNICEF: risk assessment.	UNICEF, 2008c.
	Burkina Faso	2	No reactive campaign.	WHO, 2007b; WHO, 2009.
	Cameroon	3	Reactive campaign after first two; start of risk assessment.	WHO, 2007b; WHO, 2009; UNICEF, 2008c.
	Mali	1	Reactive campaign; planned start of risk assessment.	WHO, 2007b; WHO, 2009; UNICEF, 2008c.
	Nigeria		In 2007, it was estimated that 4.5 million people might be infected if there was an outbreak in Lagos, population at the time was 15 million.	Roberts, 2007.
	Senegal	1 suspected.	Campaign later in year. December 2007: Senegal; preventive campaign (funded by IFFIm); 3 million doses.	WHO, 2007b; WHO, 2009; UNICEF, 2008c; UNICEF, 2008d.
	Togo	5	Two reactive campaigns; about 1.5 million doses; "the population" aged > 9 months; previous campaign in 1987; September 2007, implemented preventive campaign (funded by IFFIm) of 4 million doses.	WHO, 2007b; WHO, 2009; UNICEF, 2008c; UNICEF, 2008d.
2008	Burkina Faso	2 infants (7 months and 6 years old, not vaccinated, in context of 85-percent EPI coverage), order with Mali.	About 366,000 doses (start of preventive campaign) achieved 95-percent coverage.	WHO, 2008a; WHO GAR;[120] UNICEF, 2008c; WHO, 2011a.
	Cameroon	2 (100-percent CFR) 28 and 45 year old unvaccinated.	Planned start of preventive campaign; 125,000 doses at start of 2009; 92-percent coverage in that area.	UNICEF, 2008c; WHO, 2011a.
	CAR	5 cases (three outbreak events). Last outbreak was 24 years earlier. Risk of epidemic in capital (Bangui)	Reactive campaigns to separate outbreak events: 55,000 doses 92-percent coverage; about 183,000 doses with about 78-percent coverage About 201,000 people 94-percent coverage rate; about 297,000 people	WHO, 2008a; WHO GAR;[120] WHO, 2011a.

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
		great; high risk in South, lower risk in North.	76-percent coverage.	
	Ghana		Planned start of risk assessment.	UNICEF, 2008c.
	Guinea	25 (CFR 12 percent).	About 140,000 doses planned; planned start of risk assessment.	WHO, 2008a; WHO GAR;[120] UNICEF, 2008c.
	Cote d'Ivoire	Urban (capital). 2 cases in different districts (one 48 years old woman vaccinated in 1997; 20-year old man unvaccinated). Risk of urban outbreak in Abijan, despite mass vaccination in 2001, coverage likely to be ≤ 60 percent. Vectors in capital.	About 1.9 million doses 105-percent coverage. Start of risk assessment.	WHO, 2008a; WHO GAR;[120] UNICEF, 2008c; WHO, 2011a.
	Liberia	2 (32-year old; CFR 50 percent.)	About 294,000 doses 99-percent coverage; planned start of risk assessment.	WHO, 2008a; WHO GAR;[120] UNICEF, 2008c.
	Mali		April 2008: preventive campaign (funded by IFFIm) completed: 6 million doses.	UNICEF, 2008c; UNICEF, 2008d.
	Nigeria		Planned start of risk assessment.	UNICEF, 2008c.
	Senegal		Preventive campaign completed.	UNICEF, 2008c.
	Sierra Leone	9	Planned start of risk assessment.	UNICEF, 2008c.
	Togo		Preventive campaign completed.	UNICEF, 2008c.
2009	Benin		2009: UNICEF start of campaign. November 2009: with Liberia (3 million, 90-percent of population, not pregnant or < 9 months old, via schools, community centers, and clinics, 25 injections per hour).	UNICEF, 2009a; UNICEF, 2009b; UNICEF, 2008c.
	Burkina Faso		Late 2008: preventive campaign planned.	UNICEF, 2008c.
	CAR	4 Index: 18-year old male cattle breeder.	About 327,000 doses 85-percent coverage.	WHO GAR.[120]
	Cameroon	1 (61-year old).	Subnational reactive campaign of about 165,000 doses: 102-percent coverage.	WHO GAR[120] UNICEF, 2008c; WHO, 2011a.
	Chad	Suspected cases not confirmed. No cases since 1950s.	No reactive campaign (security reasons). Previous vaccination in 1930s to 1950s.	WHO, 2011a.
	Cote d'Ivoire	3+ (12-year old unvaccinated).	About 154,000 doses 87-percent coverage.	WHO, 2011a.
	Democratic Republic of	1 (55-year old male farmer). No confirmed cases since 1981.	About 74,000 doses 71-percent coverage. Vaccination in 1930s–1960s.	

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
	Congo			
	Ghana		Planned start of preventive campaign.	UNICEF, 2008c.
	Guinea	2 (24-year olds, unvaccinated). 2+ (40-year olds).	About 140,000 doses (in low-coverage areas) 101-percent coverage; then about 60,000 doses. Planned start of preventive campaign.	WHO GAR;[120] UNICEF, 2008c; WHO, 2011a.
	Liberia	1+ (32-year old).	About 96,000 doses 99.7-percent coverage; November 2009: with Benin (see above). Planned start of preventive campaign.	WHO GAR;[120] UNICEF, 2009a; UNICEF, 2009b; UNICEF, 2008c.
	Republic of the Congo	1+	About 73,000 doses planned.	WHO GAR.[120]
	Sierra Leone	2+	About 527,000 doses 84-percent coverage; November 2009: mass campaign: 11.9 million doses, with vitamin A, de-worming, measles.	WHO GAR;[120] UNICEF, 2009a; UNICEF, 2009b.
2010	Benin	3	Planned end of preventive campaign.	UNICEF, 2008c; WHO AFRO Surveillance Network September 5, 2011.
	Burkina Faso	8		WHO AFRO Surveillance Network, September 5, 2011.
	Cameroon	19 4 outbreak events in area considered at low-risk (bordering on Nigeria) and therefore not included in previous 2009 preventive campaign.	Field-based risk assessment; Plans to vaccinate about 234,000, 346,000, and 258,000 people in 2+ areas (reported coverage about 99 percent and 98 percent). No mass campaign could be organized for fourth outbreak (no further cases reported).	WHO GAR;[120] WHO AFRO Surveillance Network September 5, 2011; WHO, 2011c.
	Central African Republic	8		WHO AFRO Surveillance Network September 5, 2011.
	Cote d'Ivoire	51	About 180,000 doses; planned start of preventive campaign.	WHO GAR;[120] UNICEF, 2008c; WHO AFRO Surveillance Network September 5, 2011.
	Democratic Republic of Congo	2 (two areas).	Previously mass vaccination from 1930 to 1960 (last outbreak 1981). About 65,000 vaccinated (about 72-percent coverage).	WHO GAR;[120] WHO, 2011c; WHO AFRO Surveillance Network September 5, 2011.
	Gabon	1		WHO AFRO Surveillance Network 5, September 2011.
	Ghana	2		WHO AFRO Surveillance Network 5, September 2011.
	Guinea	1+ (35-year old woman).	2008 campaign was delayed due to supply problems; about 290,000 doses vaccinated about 95-percent coverage.	WHO GAR;[120] WHO, 2011c. WHO AFRO Surveillance Network 5,

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
				September 2011.
	Liberia	1		WHO AFRO Surveillance Network 5, September 2011.
	Mali	3		WHO AFRO Surveillance Network 5, September 2011.
	Senegal	2	No mass vaccination because low risk of epidemic. Both cases believed to be imported from Gambia (which also has high levels of immunization coverage).	WHO GAR;[120] WHO 2011c.
	Sierra Leone	1		WHO AFRO Surveillance Network 5, September 2011.
	Uganda	226 cases. Yes, in five districts (near border with South Sudan). 5+ cases, 53 deaths. Concern that YF could spread to Kampala.	First case in Uganda since 1964, which is endemic for multiple hemorrhagic fever viruses. January 4, 2011: requested vaccine from International Coordinating Group stockpile (shipped on January 11, 2011). January 5, 2011: "global shortage of vaccine," procured from UNICEF and Centers for Disease Control and Prevention. January 13, 2011: 1 million doses arrive two months after outbreak started, due to limited supply; vaccination planned to start January 22, 2011 in the five affected districts (> 905,000 people) and then "once we get more resources" would expand to 7 neighbouring ones (cost $3.5 million). Initially planned for 2.5 million doses in 26 districts. Also strengthening surveillance.	WHO AFRO Surveillance Network 5, September 2011; WHO 2011b; allAfrica.com;[121] McMullan, et al. 2012.
2011	Cameroon	4		WHO AFRO Surveillance Network September 5, 2011.
	Cote d'Ivoire	About 12 to 66 cases since November 2010 (CFR 35 percent). 1	Planned end of preventive campaign (end of November campaigns delayed twice due to unrest); January 22, 2011: start of reactive campaign about 840,000 in four districts (7 days) aged > 9 months (4/61 districts slated for mass preventive campaign).	UNICEF 2008c; allAfrica.com;[122] UNICEF, 2011b; WHO, 2011b; WHO AFRO Surveillance Network September 5, 2011.
	Democratic	1		WHO AFRO Surveillance Network

[121] allAfrica.com news article: January 3, 2011: http://allafrica.com/stories/201101040067.html; January 13, 2011: http://allafrica.com/stories/201101140088.html; January 5, 2011: http://allafrica.com/stories/201101070288.html; http://allafrica.com/stories/201101060067.html

[122] January 5, 2011: http://allafrica.com/stories/201101060154.html

[5] January 2011: http://allafrica.com/stories/201101060154.html

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
	Republic of Congo			September 5, 2011.
	Ghana	2	WHO recommended reactive campaign—6 districts planned for November +.	WHO AFRO Surveillance Network September 5, 2011; ProMed November 12 and 18, 2011.
	Senegal	October: 3 YF cases (one with no history of vaccination).	Increase in susceptible (since 2007 campaign) die to influx into area from neighbouring countries). Planned for December—doses from stockpile.	ProMed December 1, 2011; February 10, 2012.
	Sierra Leone	2 (one male, one female; both previously unvaccinated). Both in Bonthe district.	Response vaccination campaign targeting 144,479 people aged nine months and above, excluding pregnant women. Sierra Leone had mass vaccination campaign in 2009, which covered 11 out of 13 districts in the country, excluding Bonthe and Bombali districts.	WHO GAR;[120] WHO AFRO Surveillance Network September 5, 2011.
2012	Nigeria		Planned start of preventive campaign.	
	Senegal	October 2011 cases.	February 2012: 412 vaccination teams to cover the entire population of 3 health districts—Kedougou, Saraya, and Salemata—are being covered with the exception of pregnant women, children under 9 months of age and people who were already vaccinated during previous campaigns during the last 10 years. 160,000 doses.	ProMED, February 10, 2012.
	Cameroon	23 cases (7 deaths) notified (about 13 confirmed) since October 2011. Six districts.	January 23, 2012: Reactive campaign planned about 1.2 million people in 8 districts (previously not considered at risk or included in 2009 preventive campaign).	ProMED, February 3, 2012.
2014	Nigeria		Planned end of preventive campaign.	UNICEF, 2008c.

Notes: AFRO = African Region; CAR = Central African Republic; CFR = case fatality rate; EPI = Expanded Programme on Immunization; GAR = Global Alert and Response; IFFIm = International Finance Facility for Immunisation; 'number +' = that number of cases and possibly more; UNICEF = United Nations Children's Fund; WHO = World Health Organization; YF = yellow fever.

The Americas

In South America, most yellow fever (YF) virus transmission is in "sparsely populated forested areas" (Staples et al. 2010) and there have been no urban outbreaks (Appendix Table 8). Since 1999, there have been YF outbreaks in approximately seven countries in the YF belt of the Americas (Argentina, Bolivia, Brazil, Colombia, Paraguay, Peru, and Venezuela); (confirmed) outbreak sizes have ranged from 1 (Argentina 2008) to 66 (Peru 2005). Vaccination responses have varied from emergency reactive campaigns (e.g., Paraguay 2008) to catch-up campaigns and large-scale mass vaccination (e.g., Venezuela 2006).

Appendix Table 8. Yellow fever outbreaks in the Americas since 1918 and outbreak-control response

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
1918	Venezuela	Last human case or urban YF.		Rifakis et al. 2006.
1942	Brazil	Last cases of urban YF.		Massad et al. 2003.

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
1998	French Guyana	Yes	First since 1902.	Tomori, 2004.
1999	Bolivia	Small urban outbreak.		Mutebi and Barrett, 2002.
2000	Brazil	3		WHO GAR;[120] reviewed in Moreno and Barata, 2011.
2001	Brazil	20+	Reactive campaign including intensive house to house campaign in rural areas.	WHO GAR.[120]
	Peru	8+	About 400,000 doses planned.	WHO GAR.[120]
2003–2005	Brazil	4+	Reactive campaign.	WHO, 2008b; WHO GAR[120] reviewed in Moreno and Barata, 2011.
	Venezuela	60		WHO, 2008b; WHO GAR.[120]
2004	Venezuela	2	Catch-up campaign—in 2003, started 10 million-dose campaign; from 2002 to 2004: Venezuela vaccinated 1.9 million people in enzootic areas.	WHO GAR;[120] Rifakis et al. 2006.
2005	Brazil	3		WHO, 2006.
	Bolivia	16		WHO, 2006.
	Colombia	20		WHO, 2006.
	Peru	66		WHO, 2006.
	Venezuela	12		WHO, 2006.
2006	Bolivia	16		WHO, 2008b.
	Brazil	2		WHO, 2008b.
	Colombia	5		WHO, 2008b.
	Peru	63		WHO, 2008b.
	Venezuela		Aims to have 7 million people in high-risk cities and towns vaccinated.	Rifakis et al. 2006.
2007	Americas	No urban cases.	Four countries all have YF in EPI.	WHO, 2009.
	Bolivia	6	About 81-percent EPI coverage.	WHO, 2009.
	Brazil	13	100-percent EPI coverage.	WHO, 2009.
	Colombia	6		WHO, 2009.
	Peru	23	87-percent EPI coverage.	WHO, 2009.
2008	Argentina	7	Preventive campaign about 1.5 million (one serious adverse event).	Reviewed in Pires-Marczeski et al. 2011.
	Brazil	30 (2 vaccinated > 20 years ago) in three states (plus epizootic).	About 7 million doses planned.	Reviewed in Moreno and Barata., 2011.
	Paraguay	Urban (capital). About 24 cases including suspected cases in urban area.	Reactive campaign: 1.5 million, about 850,000 from Brazil, 144,000 doses from Peru; UNICEF supplied 2 million doses from the International Coordinating Group	WHO, 2008c; Tauil, 2010; Lancet, 2008; WHO GAR;[120] UNICEF, 2008e.

Year(s)	Country	Outbreak; number of cases	Outbreak response/routine activities	References
			stockpile.	
Since 2008	Various		Circulation of sylvatic YF increased and enzootics in some areas of Argentina, Brazil, Columbia, Trinidad and Tobago, and Venezuela.	WHO, 2001a.
2009	Bolivia	YF is endemic in tropical regions (60 percent of country) but much migration so whole population is at risk.		Reviewed in Pezzoli et al. 2009.
	Brazil	30 (plus nonhuman primates) in 5 different municipalities.		Reviewed in Moreno and Barata, 2011.
2010	Bolivia	2	Neither had been vaccinated.	WHO, 2011c.
	Brazil	2 (both died). In general, outbreaks (no urban) are often separated by 4–7 years.	Neither had been vaccinated.	Ferguson et al. 2010; WHO, 2011c.
	Peru	18		WHO, 2011c.
2011	Peru	Maternal death (3 days post-partum), confirmed YF.	Vaccination sweep.	ProMED, November 10, 2011.
2012	Peru	January 2012: 1 case, 45-year old farmer, confirmed, another one suspected.	Shipment of 27,500 doses and requested another 50,000 doses. Vaccination sweep. Four districts. Population to be vaccinated will be between 2–59 years old.	ProMed, February 10, 2012.

Notes: EPI = Expanded Programme on Immunization; GAR = Global Alert and Response; 'number +' = that number of cases and possibly more; UNICEF = United Nations Children's Fund; WHO = World Health Organization; YF = yellow fever; information on outbreaks and outbreak response is listed by date and country on WHO Global Alert Response yellow fever website.[120, 123]

[123] http://www.who.int/csr/don/archive/disease/yellow_fever/en/

Appendix 7. Clinical trials and clinical studies of yellow fever vaccines

Appendix Table 9. Clinical trials and studies of yellow fever vaccines: primarily infants

Publication	Vaccine	Design, endpoints	Population or setting	Notes
Luiza-Silva et al. 2011	17DD (BioMan 0.5-ml dose).	Observational; n = 60; PRNT on pre-bleeds and day 30 post vaccination.	Infants aged 9–43 months. Belo-Horizonte and Brasilia, Brazil.	60 subjects recruited. After vaccination, 30 were seropositive, and 10 were seronegative. Revaccinated 10 seronegative subjects; all seroconverted. Correlated cytokine profiles with seroconversion and PRNT antibody titer.
Study outline: Collaborative Group for Studies with YF Vaccine 2007 Results: Nascimento Silva et al. 2011	17DD (BioMan 0.5-ml dose) versus 17D-213/77 (investigational) ± MMR simultaneously or 30 days apart.	Designed to compare vaccine strains, test MMR interference and maternal Ab; RCT: serology day 0 and 30 (MMR, dengue and YF); mothers of participants aged < 12 months gave blood sample (maternal Ab YF); parents asked about events at day 30 (by form); n = 860 (approximately) in each group.	Brazil: infants aged 9–23 months.	Subjects injected with YF vaccine and MMR simultaneously had lower seroconversion rates for YF, rubella and mumps, compared with those vaccinated 30 days apart. Seroconversion rates for measles were high, and similar in both groups.
Agnandji et al. 2010 GlaxoSmithKline; PATH Malaria Vaccine Initiative	Stamaril (Aventis Pasteur, intramuscular) with measles (intramuscular), within routine EPI vaccines ± RTSS (GlaxoSmithKline vaccine).	RCT; YF serology (PRNT, GMT) at 7 and 8 months.	Ghana, Gabon (not Tanzania): aged 7 months.	YF was included to study interference; 97 and 94 percent seroconversion (± RTSS). Eligible infants were 6–10 weeks at study entry. YF virus given at study month 7.
Poo et al. 2010	YF used as control vaccine for tetravalent dengue vaccine; one injection at month 0 with two of tetravalent dengue vaccine.	Phase 1 RCT (n = 126) to test safety and immunogenicity of a tetravalent dengue vaccine and to test effect of prior immunity to YF virus.	Mexico: children aged 2–5, 6–11, or 12–17 years; adults < 45 years.	Two doses of dengue vaccine given to YF-vaccinated subjects were as immunogenic as three doses of dengue vaccine. No YF specific parameters were measured.
Belmusto-Worn et al. 2005 Acambis sponsor; US Naval Medical Research Detachment, Lima	Arilvax (Evans), YF-Vax (Aventis-Pasteur).	Phase III: RCT (stratified for four age groups and vaccine lots), double-blind; per-protocol analysis. N = 1107 (738 + 369); safety and efficacy (seroconversion). 0.5-ml SC YF; no other vaccines 30 days before or after; screened out those with prior YF immunity; stratified for prior dengue immunity. 30-day follow up; sera day 1 and 31; no routine viremia study.	Northern Peru (city, 5 centers): first immunization of healthy children aged 9 months to 10 years; May to November 2002.	Seroconversion significantly higher and non-inferior (in all age groups) for Arilvax (94.9 percent) than YF-VAX (90.6 percent); differences most striking in youngest age groups; Log neutralization titers similar at 30 days; similar proportions had at least one adverse event; no serious adverse events.
Osei-Kwasi et al. 2001	Institut Pasteur Dakar vaccine (20-dose vials) 0.5 ml SC, with measles	N = 421.	Ghana: aged 6 or 9 months (non-endemic	Seroconversion similar: 6-months: 98.6 percent; 9-months: 98 percent; similar GMTs (158, 129);

Publication	Vaccine	Design, endpoints	Population or setting	Notes
	at other timepoint.	Serology at day 0 and at + 3 months. Adverse events at day 10. Tested vaccine potency.	area) had completed bacille Calmette-Guérin, diphtheria, tetanus, pertussis vaccine, oral polio vaccine.	No YF+ pre-bleeds; Some malaria in groups.
Soula et al. 1991	Combined YF-measles versus separate.	RCT; n = 453.	Mali: aged 4–8 and 12–24 months.	Abstract only reviewed. 92–96 percent seroconversion (in four age groups) (Robertson 1993).
Mouchon et al. 1990	Combined YF-measles versus separate.	N = 319.	North Cameroon: aged 6–10 months.	Abstract only reviewed. About 93-percent seroconversion; trend for higher titers and seroconversion when combined (Robertson 1993).
Lhuillier et al. 1989	Combined YF-measles versus separate.	Trial.	Cote d'Ivoire: aged 6–9 months.	Abstract only reviewed. > 90 percent seroconversion (Robertson 1993).
Yvonnet et al. 1986	YF ± hepatitis B vaccine booster.		Senegal: aged 9–35 months.	Abstract only reviewed. 92/94 percent seroconversion (Robertson 1993).
Georges et al. 1985	(Stabilized). Pasteur vaccine.		Central African Republic: aged 12–59 months.	Abstract only reviewed. 94 percent seroconversion (Robertson 1993).
Ruben et al. 1973	0.5 ml (SC) by Ped-O-Jet jet injector: with one or more of smallpox (ID), measles, diphtheria, tetanus, pertussis vaccine at different sites (all by jet injector).		Nigeria: aged 6–23 months.	95–97 percent seroconversion (at 3 months); some reduction in measles seroconversion in those > 9 months (Robertson 1993).
Meyer et al. 1964	Measles, smallpox (ID), YF (separately or combined) by jet injector ID.intradermally		Upper Volta, Africa: aged 5–56 months.	About 97-percent seroconversion, (Robertson 1993).

Notes: Ab = antibody; EPI = Expanded Programme on Immunization; MMR: measles, mumps, and rubella; N = population size; n = sample size; PRNT = plaque-reduction neutralization assay; RCT = randomized controlled trial; RTSS: candidate malaria vaccine; SC = subcutaneous; YF = yellow fever.

Appendix Table 10. Clinical studies of yellow fever vaccines: primarily adults (or older children)

Publication	Vaccine	Design, endpoints	Population or setting	Notes
Martins et al. 2013 ISRCTN38082350[124]	17DD YF vaccine (BioMan). SC: 1 dose; 27,476 IU, 10,447 IU, 3,013 IU, 587 IU, 158 IU, 31 IU.	RCT: n = 900. Serology: neutralizing Ab (seroconversion and titer); Blood chemistry day 0, 5, and 30; viremia (day 5, plaque assay and RT-PCR); dengue IgG measured prevaccination. Follow-up: 1 month and (9–15) months. Those not protected to receive reference dose of vaccine.	Brazil: adult healthy men, army conscripts, (no previous exposure to vaccine).	Approximately 16 percent of volunteers were seropositive for YF at baseline (excluded from the analysis). 87 percent of the volunteers were seropositive for dengue at baseline. Doses from 27,476 IU to 587 IU induced similar seroconversion and neutralizing GMTs. Viremias were "transient and low intensity." Viremias (by plaque assay, but not PRNT) were higher in dengue and YF seronegative subjects.
De Melo et al. 2011	YF 17DD (BioMan).	Prospective cohort (2005 to 2007, followed to 2009); followed by blood sampling: pre-vaccination, and post-vaccination at 30 days, range of months from 1–17; annually to 4–5 years; ELISA before and PRNT after vaccination. Related retrospective study (randomized) n = 40 to 5 and 10 years.	Recife, Pernambuco, Brazil (non-endemic for YF, no routine YF vaccination, does have dengue fever). N = 238 of 260, first time vaccines; aged > 10 years presenting for travel vaccination.	No anti-YF pre-immunes (by GAC ELISA); 82 percent pre-immune to dengue. Post-vaccination: 70.6 percent had IgM to YF and 98.3 percent IgG; all > seroprotective by PRNT; mean GMT 892; 86.6 percent anti-dengue IgG (no interference with seroconversion to YF vaccine. Kinetics with GMTs. All 5- and 10-year samples PRNT positive for anti-YF IgG; GMTs reduce with time. ELISA was less sensitive. AEs: 1.7 percent (fever, discomfort).
Kay et al. 2011	YF-VAX (Sanofi).	Prospective study. Pre-bleed; seroconversion at 21 days (± 1 day) and 8 months (± 30 days) after vaccination (baseline for inactivated vaccine trials); PRNTs; n = 30.	Healthy adult travelers aged 18–49 years; primary vaccination. United States.	100-percent seroconversion by day 21; GMT 6,451; 8 months: all seropositive GMT 1,246.
Martinez et al. 2011	Not specified. Vaccinations took place at a travel clinic in Barcelona so probably used Sanofi vaccine.	Exploratory study: to test for presence of YF vaccine virus RNA in urine samples donated up to one year after YF vaccination; n = 44.	Healthy vaccine recipients (25–59 years). Travel clinic in	2/44 samples were positive (one at 21 days and one at 198 days post-vaccination). Vaccine virus could persist for at least 6 months after vaccination (after expected period of

[124] http://www.controlled-trials.com/ISRCTN38082350

Publication	Vaccine	Design, endpoints	Population or setting	Notes
			Barcelona, Spain.	viremia). Larger study planned—needs culture of live virus.
Monath et al. 2011	XRX-001 inactivated vaccine with aluminum. Two injections of one of two doses (4.8 µg per dose and 0.48 µg per dose) or placebo.	Phase I; RCT; n = 60; safety to 42 days, 3, 6, and 12 million; serology (seroconversion, PRNT, GMT).	United States; healthy volunteers aged 18–49 years (no previous exposure to flaviviruses or vaccines).	Neutralizing antibodies induced in 100 percent and 88 percent subjects receiving 4.8 µg and 0.48 µg per dose, respectively. Levels were significantly higher with the 4.8 µg formulation.
Nasveld et al. 2010 Acambis/Sanofi (July 2004–April 2005)	Stamaril SC at 3–4 $\log_{10}$ PFU (Sanofi), concomitant or sequentially with Japanese encephalitis chimeric virus.	RCT; serology PRNT (followed to 6 months); n = 108.	Queensland Australia: healthy adult volunteers aged 18–53 years.	100-percent seroconversion to YF.
Pacanowski et al. 2011	Unknown.	Prospective cohort: proportion of HIV positive people with YF vaccine failure (neutralizing titers < 1:10), by HIV status at vaccination and CD4+ status; n = 364; n = 240 vaccinated after HIV diagnosis.	HIV positive outpatients who had at least one YF vaccine; serology at 0.9–23.3 years after vaccination. Paris (2007–2008).	98 percent had PRNT > 10 at one year after vaccination, 92 percent at 10 years. Higher HIV RNA risk factor for vaccine failure; no association between Ab response and CD4+.
Qiao et al. 2011	Stamaril YF vaccine (Sanofi) 12 months before 4-valent dengue vaccine (Sanofi).	Part of trial for dengue vaccine n = 8 for YF prior vaccination (small numbers).	Healthy volunteers (18–40 years). Australia.	Prior vaccination with YF vaccine increased immunogenicity of chimeric dengue vaccine without increasing AEs.
Roukens et al. 2011	YF-17D (Stamaril, Sanofi), SC into arm.	Prospective cohort study; n = 30 for younger groups and n = 28 for older group; PRNT and viremia (by PCR) at pre-bleed and 3, 5, 10, 14, and 28 days after vaccination. Aim: to see if immune response to YF is slower in the elderly as this might be related to why there are more SAEs in older age groups.	Healthy volunteers aged 18–28 years or 60–81 years. Netherlands travel clinic (2008 to 2009).	2 of elderly excluded based on pre-bleeds (had been vaccinated many years before). No Ab at days 3 or 5. At day 10, 77 percent of younger group and only 50 percent of older group had seroconverted. GMTs were higher in younger than older group. Ab responses were delayed in older group but no difference by day 28. Viremia was more common in older group (86 versus 60 percent); 2 had viremia at day 10 and a higher copy number. Both groups peaked at day 5. Fewer adverse events in elderly.
Roukens et al. 2009	17D Arilvax (Medeva) or Stamaril (Sanofi Pasteur), 0.1 ml, ID (N&S).	Retrospective. N = 7 (4 males, 3 females). Outcomes: serology (titers and IU by PRNT	Travel clinic, Leiden, Netherlands.	7 out of 7 had serology above protective threshold.

Publication	Vaccine	Design, endpoints	Population or setting	Notes
		assay) once, at 3–32 weeks.	Volunteers, aged 1–53 years (1, 2, 17, 20, 26, 28, 53), egg allergic.	
Veit et al. 2009	71 percent had Stamaril (83 percent were primary vaccinees).	Retrospective study in prospective cohort (medical records, vaccination cards, blood sample): serology after past vaccination at different time intervals; SAEs within 6 weeks after vaccination.	102 HIV positive travelers aged 28–41 years (versus 209 age-matched HIV^- people). 7 centers in Switzerland (SHCS cohort); some also hepatitis C virus positive or hepatitis B positive.	Higher proportion (13 percent) of HIV positive had non-reactive PRNTs versus HIV^- (3 percent) within the first year after vaccination and greater difference (23 versus 12 percent) over first 1–10 years after vaccination. GMTs were lower. People with lower $CD4^+$ cell counts were more likely to non-respond.
Ripoll et al. 2008	Stamaril (Sanofi Pasteur) $10^{4.52}$ PFU (10-dose vials) and VCFA (Bio-Manguinos; 5-dose vials) single dose (at least 10^3 MLD_{50}) 0.5 ml intramuscularly into deltoid.	Randomized (no placebo control), vaccinators and patients blinded; n = 2,514. AEs to 21 days; no.	Enzootic region of Argentina: primary care, aged 1–80 years (more females than males).	Approximately twice the proportion had local and systemic AEs with VCFA about 2 percent had SAEs.
Roukens et al. 2008	17D (Stamaril): 3.5 x 10^4 PFU per 0.5-ml dose or 5 x 10^3 MLD_{50}. 0.1 ml/dose ID, (dorsal forearm; > 6mm wheal), N&S.	RCT (block randomization), non-inferiority n = 155 primary vaccinations plus 20 booster vaccinations. Serology at 2, 4, and 8 weeks and 1 year (by PRNT). AEs by 3-week diary; viremia at 5 days.	Leiden University, Netherlands. Healthy adult volunteers (aged over 18 years).	No difference ID versus SC in terms of antibody responses (including kinetics); all above World Health Organization protective level. Greater proportion of primary ID vaccinees had redness and itching and for longer versus SC. Greater proportion of SC primaries had pain and myalgia. Viremia detected in 50 percent of primary but not booster doses (ID and SC).
Hepburn et al. 2006	17D vaccine; manufacturer(s) unknown.	Retrospective review (data to 2002); annual serology for PRNT to YF after vaccination; boosted if titers fall below 1:40 (or from 1996 below 1:20); n = 1029.	Laboratory workers, United States Army Medical Research Institute of Infectious Diseases (United States).	Few maintained 1:40 titers for 10 years Pre-vaccination serology influenced the initial and long-term response to YF booster vaccination. Divided into three groups and calculated time to titer failure. Higher titers pre-boost gave lower responses than lower titers.

Publication	Vaccine	Design, endpoints	Population or setting	Notes
Monath et al. 2005	YF-VAX (Sanofi-Pasteur) and Arilvax (Chiron).	RCT: serology and AEs (Monath et al 2002) n = 1440. Open label: AEs to 30 days n = 3,092. Retrospective: SAEs versus age.	RCT: United States = > 18 years (no previous vaccination). Open-label = United Kingdom (travelers) > 9 months (no previous vaccination); only 23 > 75 years. Retrospective study = United Kingdom (travelers) aged > 15 years.	Humoral responses were similar at different ages (97–100 percent seroconversion; primary failures in younger age groups only); Older people (> 65 years) had less local and systemic AEs (60 versus 83 percent), but more SAEs 65–74 years: RR 2.82; 45–64 years: RR 1.82 versus 25–44 years (reference RR of 1) [other studies have RR as high as 16].
Camacho et al. 2004 Camacho et al. 2005	3 lots of vaccines from different seed lots (WHO-17D seed lot; Bio-Manguinhos old and new) 0.5 ml SC (> 1000 MLD_{50}/dose); 50-dose vials.	RCT: double-blind, placebo control (block randomisation); equivalence; n = 1087. Neutralizing Ab titers; viremia. Bloods: day 0, 4–20, 30+. Liver enzymes.	Brazil: Rio (non-endemic); healthy adults aged 14.8–67 years old (soldiers) no past YF vaccine; no plan to travel to endemic areas.	About 22–28 percent were already seropositive at day 0. 98-percent seroconversion (2-fold increase) for primary and 90 percent overall (16 percent in placebo group); 2.7 percent (not reported in detail) had viremia days 3–7 (although viremia collected between days 4 and 20); Only 55–63 percent returned diaries of AEs.
Monath et al. 2002	Arilvax (Evans), YF-Vax (Aventis-Pasteur).	Phase III: RCT, double blind. N = 1440. N = about 600 for serological endpoint; no placebo group. Serology (including to other flaviviruses) and adverse events. Follow-up: day 5 by phone, day 11 (diary, serum) and day 31.	United States (9 centers): healthy adult volunteers > 18 years old without previous YF immunity.	Seroconversion with YF-VAX (99.3 percent) versus Arilvax 98.6 percent (non-inferior). Higher LNIs for YF-VAX (2.21) versus Arilvax (2.06; > 0.7 is considered protective) and in males, caucasians and smokers. Less local reactogenicity in Arilvax group. Detailed list of frequency of AEs. More injection site pain in those aged < 60 years. Injection site reactions between days 1–5; systemic until day 11. Frequency of local reactions less in those with pre-existing immunity; fewer AEs in elderly group.
Lang et al. 1999	2 batches Stamaril (Pasteur Merieux) versus Arilvax (Evans/GlaxoSmithKline). 1 x SC 0.5 ml (> 1000 MLD_{50}).	RCT: clinical validation of new seed (past lots exhausted). N = 211. Serology at days 0, 10-14, and 28 (including GMTs). Safety (liver tests but not viremia).	United Kingdom: healthy adults > 18 years, no past vaccine.	Seroprotection equivalent: 100 percent and 99 percent.

Publication	Vaccine	Design, endpoints	Population or setting	Notes
Reinhardt et al. 1998		N = 17. Viremia. $CD8^+$ T-cell responses.	Healthy adults aged 18–50 years (12 primary and 5 boosters).	
Lopes et al. 1988	Bio-Manguinos ± stabilizers and 6 different lots diluted to 1: 10, 60, 100, and 1000 (from about 5,000 to about 3 PFU); presume 0.5 ml SC.	N = 300. Serology at day 0 and 28. Adverse events.	Healthy adult (military) volunteers aged 18–47 years (unknown past history of vaccination).	100-percent seroconversion (neutralizing Ab > 1:32) if > 200 PFU (600 MLD_{50}). About 10-percent antibodies in day-0 sample (excluded from analysis). About 3 percent dropout rate. Low reactogenicity. Pre-immunes showed lower day 28 response than non-immunes.
Roche et al. 1986	Heat-stable 17D and non-stabilized vaccine (Pasteur Vaccins) 0.5 ml SC.	RCT. N = 115, 143. Serology at day 52. Reactogenicity.	Seronegative (French Naval) adults.	Neutralizing Ab (1:5) in 99/100 percent of subjects at day 52.
Freestone et al. 1977	Stabilized or un-stabilized (Wellcome) YF vaccine, SC dose-study from ($10^{5.3}$ PFU) down to 9 PFU.	N = 68. Serology at day 0 and 28. Liver function, adverse events.	United Kingdom: seronegative volunteers.	50 percent immunizing dose of 42 PFU. Greater neutralizing antibodies to lower doses.'
Dick 1952	17D (Rockefeller, New York) and French neurotropic vaccine (Pasteur, Dakar), SC or scarification by 0.5-cm scar through two drops (equivalent in dose to usual dose). Both vaccines were out of the cold chain for some of the time.	N = 300 (3 groups) then n = 75. Adverse events by "sick parade." Serology at day 32 (assayed *in vivo* in mice).	Ugandan male prisoners, and then 75 patients of mental hospital.	High dropout for day 32 bleed. No reactions.

Notes: Ab = antibody; AE = adverse event; CD4, CD8 = T-cell markers; ELISA = enzyme-linked immunosorbent assay; GAC ELISA = immunoglobulin G antibody capture enzyme-linked imunosorbent assay; GMT = geometric mean titer; ID = intradermal; IU = international unit; IgG = immunoglobulin G; IgM = immunoglobulin M; IU= international units; LNI = log neutralization index; MLD_{50} = 50-percent mouse lethal dose; N = population size; n = sample size; N&S = needle and syringe; PCR = polymerase chain reaction; PFU = plaque-forming units; PRNT = plaque-reduction neutralization assay; RCT = randomized controlled trials; RR = relative risk; RT-PCR = reverse transcription polymerase chain reaction; SAEs = serious adverse events; SC = subcutaneous; SHCS = Swiss HIV cohort study; VCFA = yellow fever vaccine (Portuguese); YF = yellow fever.

Appendix Table 11. Clinical studies; unpublished, in progress or being planned

Institution and investigators (country); status	Vaccine	Design, endpoints	Population or setting	Notes; reference
Bio-Manguinhos (Brazil) Status: Planned; recruitment not yet started	17-DD YF vaccine. 1-dose SC reference vaccine (60,000 plaque-forming units) versus 20,000, 6,000 plaque-forming units (some with addition of protamine sulfate).	Dose-response study—RCT; n = 1800; follow-up: 1, 9–15 months after vaccination; 6 groups; reactogenicity, serology, viremia at 5 days.	Infants aged 9–11 months. Brazil.	ISRCTN36905484[125]
Sanofi PI: Sanofi medical director Status: Ongoing; December 2011 to June 2014	Chimeric dengue vaccine ± YF-Vax (Sanofi).	RCT Phase II; mostly dengue endpoints but also plaque-reduction neutralization test to YF vaccine; n = 390.	Healthy adults 18–45 years. United States.	NCT01488890[126]
Sanofi Status: Ongoing; September 2011 to December 2013	Chimeric dengue concomitant with YF (Stamaril)—at two different sites (0.5-ml SC) plus usual vaccines (including measles, mumps and rubella vaccine).	Phase III: To test for non-inferiority of YF at 28 days if given concomitantly with chimeric dengue vaccine; n = 792.	All eligible (regardless of flavivirus status at baseline. Babies at 12–13 months old (for YF); Colombia and Peru.	NCT01436396[127]
Novartis Status: Not yet recruiting	MenACWY-CRM at same time as other travel vaccines including YF (17D-204, manufacturer not known); 0.5 ml SC/IM.	Phase IIIb; interventional, open label, safety immunogenicity; includes YF Ab at day 28; n = 550.	Adults 18–60 years; travelers to Africa/Latin America (could be booster vaccine to YF > 5 years ago). Czech Republic and Germany.	NCT01466387[128]
GlaxoSmithKline Status: Ongoing; November 2011 to December 2016	YF (IM), within EPI ± malaria vaccine (257049), which contains hepatitis B vaccine Ag.	RCT (phase III); 11 groups; not clear if response to YF will be measured. N = 700; some follow to 48 months.	Ages 8–12 weeks (YF 6 months later) Burkina Faso and Ghana.	NCT01345240[129]
GlaxoSmithKline (sponsor)	YF (Stamaril, IM) as part of EPI given with	RCT; mostly about pneumo; 8 groups; 3-month follow up of	Aged 2–4 years; YF at 9	NCT01262872[130]

[125] http://www.controlled-trials.com/ISRCTN36905484

[126] http://clinicaltrials.gov/ct2/show/NCT01488890

[127] http://clinicaltrials.gov/ct2/show/NCT01436396

[128] http://clinicaltrials.gov/ct2/show/NCT01466387

[129] http://clinicaltrials.gov/ct2/show/NCT01345240

Institution and investigators (country); status	Vaccine	Design, endpoints	Population or setting	Notes; reference
PATH, Medical Research Council Gambia, London School of Hygiene & Tropical Medicine Status: Completed February 2011 to May 2013	GlaxoSmithKline Pneumo vaccine candidate.	YF responses (also measles); n = 1320.	months old. Gambia.	
French National Agency for Research on AIDS and Viral Hepatitis PI: Francois Simon Status: Ongoing August 2011 to December 2013	Stamaril YF.	Interventional (not RCT)—to develop tools to monitor immunity (including cell-mediated immunity) and virological endpoints (YF and HIV); follow up to 12 months after YF vaccine; n = 70.	Adult volunteers (18–55) ± HIV+; primary YF vaccination. France.	NCT01426243[131]
Serum Institute of India (India) and PATH (sponsor) PI: Abraham Hodgson, Navrongo, Ghana Status: Completed August 2008 to December 2012	MenA-conjugate vaccine (1–2 doses at different ages) in EPI schedule. YF is given with measles and MenA at 9 months.	Phase II, RCT. Safety and immunogenicity of MenA within EPI schedule.	Ghana: infants aged 14 weeks and 9 months.	ISRCTN82484612[132]
Emory University (sponsor) with University of California (both United States) PI: Srilatha Edupuganti Status: February 2011 to February 2013	Standard dose and route of YF vaccine (manufacturer not known).	Interventional (non-randomized non-controlled); follow up to day 52; n = 40. Processing and life-span of CD8+ T cells after vaccination.	Healthy adult volunteers (18 to 45 years); primary vaccination. United States.	NCT01290055[133]
Emory University	YF vaccine (manufacturer unknown).	Observational; human memory T-cell responses; n = 100.	Adults >18 years with past	NCT01244802[134]

[130] http://clinicaltrials.gov/ct2/show/NCT01262872

[131] http://clinicaltrials.gov/ct2/show/NCT01426243

[132] http://www.controlled-trials.com/ISRCTN82484612

[133] http://clinicaltrials.gov/ct2/show/NCT01290055

Institution and investigators (country); status	Vaccine	Design, endpoints	Population or setting	Notes; reference
PI: Srilatha Edupuganti Status: Recruiting; November 2010 to December 2013			history of YF vaccination. United States.	
Emory University (United States) PI: Sri Edupuganti Status: Recruiting; May 2008–December 2015	YF-VAX (standard 1-dose).	Immune memory to YF vaccine; Up to 8 blood samples 1–12 months (T- and B-cells); n = 50.	Travel clinic, United States; healthy adults aged 18–70 years (younger versus older comparison).	NCT00694655[135]
Emory University and Sanofi Pasteur PI: Carlos del Rio Status: Completed; 2006–2008	YF-VAX ± immunoglobulin (GamaSTAN S/D) or placebo.	RCT Phase I; n = 80; viremia, immunogenicity, safety; T-cell and dendritic cells response.	United States; healthy volunteers aged 18–40 years (no prior exposure to YF or vaccine).	NCT00254826[136]
Oregon Health & Science University; National Jewish Health; University of California, San Diego (all United States); National Institute of Allergy and Infectious Diseases (sponsor) PIs: Mark Slifka, Eric Simpson, Henry Milgrom, Richard Gallo Status: Completed; 2008 to August 2011	YF SC or scarification (1/50 dose).	Phase I and II. Immune responses: serology (kinetics); viremia (days 3, 5, 7, 10, 14); T-cells.	Adults with atopic dermatitis.	NCT00723489[137]

Notes: Ab = antibody; EPI = Expanded Programme on Immunization; GamaSTAN S/D = immune globulin (human) injection; IM = intramuscular; MenA = meningitis A; MLD_{50} = 50-percent mouse lethal dose; N = population size; n = sample size; PI = principle investigator; RCT = randomized controlled trials; SC = subcutaneous; YF = yellow fever.

[134] http://clinicaltrials.gov/ct2/show/NCT01244802

[135] http://clinicaltrials.gov/ct2/show/NCT00694655

[136] http://clinicaltrials.gov/ct2/show/NCT00254826

[137] http://clinicaltrials.gov/ct2/show/NCT00723489