

## YELLOW FEVER MASS VACCINATION CAMPAIGN USING FRACTIONAL DOSE IN KINSHASA, DRC

### Background

In response to the ongoing yellow fever outbreak in neighbouring Angola and parts of the Democratic Republic of Congo (DRC), the Ministry of Health in DRC, with the support of WHO and other partners, conducted a mass vaccination campaign from 17 August - 5 September 2016 in 47 health zones (32 in Kinshasa, 15 along the border with Angola). In order to minimize transmission and reduce the chance of spread of the outbreak into the potentially vulnerable population of urban Kinshasa, the campaign targeted **all children over 9 months of age and all adults in urban Kinshasa** (a target population of **7,586,400**). Vaccination in Kinshasa took place over 10 days (17 August – 26 August).

Global supply of yellow fever vaccine is currently limited and in order to ensure that the entire target population of Kinshasa be vaccinated, the Ministry of Health in DRC opted for the use of a **partial or “fractional dose” approach** for the 32 health zones in Kinshasa. Children under 2 years (9 – 23 months) and pregnant women were offered a full dose of the vaccine. The inhabitants of the 15 health zones bordering Angola received full dose vaccination.

During the 10 days of vaccination activity in Kinshasa, **7,898,365** people were vaccinated, achieving an administrative coverage of 104%. Rapid convenience assessments (RCAs) reported an average vaccination coverage rate of 98.2% for all 32 health zones in Kinshasa.

### Fractional dose

A fractional dose of yellow fever vaccine (0.1 ml) is one-fifth the volume of a standard yellow fever dose and is administered subcutaneously. Fractional doses are considered in light of the fact that WHO prequalified yellow fever vaccines can contain significantly more vaccine viral particles than the minimum requirement of 1000 IU/dose. Clinical trials studying safety and immunological non-inferiority of fractional dose of yellow fever vaccine demonstrate similar seroconversion and neutralizing antibody titres as with full dose.<sup>1,2,3,4</sup>

Due to the constraints that the current yellow fever outbreaks are placing on the global stockpile of yellow fever vaccine, in June 2016 WHO reviewed the available data and recommended, in consultation with SAGE, that the use of fractional dose vaccination should be considered in response to an emergency situation in which current vaccine supply is insufficient.<sup>5</sup> Given the absence of data on the use of fractional dose in young children, it was recommended that children below the age of 2 years should preferentially be offered a full dose of vaccine during emergency campaigns. The same applies to pregnant women.

### Campaign planning and implementation

- 32 surveillance/medical/logistic/risk communication and community engagement/support staff from WHO were deployed to support the development of campaign microplans and to conduct pre-campaign training and monitoring.
- Existing microplans developed from previous yellow fever campaigns were adapted for the fractional yellow fever campaign in urban Kinshasa.
- A 1-day training session was organized to instruct all vaccination staff members supporting the fractional dose campaign on 15 August 2016.
- A press conference was held by the Ministry of Health on 10 August with the key press offices in Kinshasa to provide information about the campaign, including the use of fractional dose.
- Social mobilization for the campaign was conducted through proactive engagement of local television, print and radio media, posters, banners, microphone announcements and community mobilization, including interpersonal communication through door-to-door visits.
- Main messages were translated into four local languages.
- A total of **14,424** vaccinators supported implementation of the campaign.
- A total of **2,404** immunization posts were organized and operational over 10 days (Table 1) with 1 day for mop-up.
- Each team consisted a minimum of 5 vaccinators, 2 recorders, 1 social mobilizer/community engagement expert, and 1 volunteer to maintain order at the post, and 1 responsible for waste management.

**Table 1. Numbers of vaccination sessions, total vaccinated with fractional and full dose, and median vaccinated per day and per session**

Province	Kinshasa
Target population	7,586,400
No. campaign days	10
No. vaccination sessions conducted	24,040
No. vaccination posts	2,404
No. reported vaccinated (total)	<b>7,898,365</b> (104% of target)
No. reported vaccinated (fractional dose)	7,466,998
No. reported vaccinated (full dose)	431,367
Median no. vaccinated per day	730,469

The yellow fever vaccines used in the Kinshasa campaign were 10 full-dose vials (5 ml per vial) manufactured by Bio-Manguinhos (Brazil) (2.5 million doses received), with 0.1 ml withdrawn for each fractional dose, and 0.5 ml drawn for every full dose vaccination. Therefore, each vial had the potential to contain up to 50 doses of vaccine. As yellow fever vaccine is lyophilized and without preservative, the multi-dose vial policy requires that reconstituted vials must be kept between +2°C and +8°C and must be used or discarded within 6 hours of opening, or at the end of the vaccine session, whichever comes first.<sup>6</sup>

Fractional doses (0.1 ml) were administered subcutaneously on the outer part of the right upper arm, using an autodisable syringe with 10-13 mm length needle. Full doses (0.5 ml) were administered to children 9-23 months and pregnant women, subcutaneously on the outer part of the right upper arm, using an autodisable syringe with a 16mm length needle.

After vaccination, each vaccine recipient was given a specially designed card indicating which dose (full or fractional) was received. The cards also included a disclaimer that the cards were not considered yellow fever vaccination certificates valid for international travel. Recipients were asked to report any adverse events occurring within a week of receiving the vaccine, including illness, hospitalizations or death.

19,416 safety boxes of waste were collected/destroyed during the Kinshasa campaign: 4,677 incinerated by MSF, 2,022 incinerated by Save the Children and 12,717 stored in the World Food Programme (WFP) warehouse, to be transported and incinerated at a central cement plant in Kinshasa.

### **AEFI surveillance**

Since 2014, DRC has been involved in a process of strengthening the national system for monitoring Adverse Events Following Immunization (AEFI), culminating in June 2016 with the validation of a national manual for AEFI surveillance with clear identification of activities, actors and their roles and responsibilities. This campaign was an opportunity to launch the new AEFI surveillance system. An ad hoc committee was formed to steer the AEFI surveillance activities during the campaign, with membership from the Direction of Pharmacies (DPM), the National Centre of Pharmacovigilance (CNPV), the Expanded Programme on Immunization (EPI), the National Program for Emergency and Humanitarian Action (PNUAH) and the Provincial Division of Health (DPS) in Kinshasa. Information on AEFI was drawn from four main sources of information.

Through the passive surveillance system of DRC, as of 22 September, 123 AEFI were reported, of which 8 were serious. Among the reported AEFI, Kinshasa reported 78 cases of which 7 were serious (notification rate: 1 per 100,000 doses). Severe AEFI were followed up by investigations in three hospitals and seven mobile clinics. The results of the investigations are currently being analysed.

In addition to the passive surveillance system, an alert system to specifically report and follow up on severe AEFI was put in place in Kinshasa. 41 suspected serious AEFI were reported through this system.

A country-wide surveillance system that was put in place at the beginning of the epidemic to identify yellow fever cases detected 4 cases of yellow fever symptoms in people vaccinated during the preventive campaign in August 2016.

Finally, a community survey was led by the National Pharmacovigilance Centre to complement passive surveillance efforts. This survey yielded 4350 AEFI reports. The analysis of these reports is ongoing, but preliminary results as of 13 September indicate that from 1650 reports analysed, 500 have been classified as AEFI.

### **Campaign monitoring**

32 WHO supervisors and 96 independent campaign monitors were assigned across 32 health zones in Kinshasa. A total of **2,404** vaccination sessions (1 visit to each post) were observed during the campaign. Supervisory checklists were modified to capture additional information unique to the fractional dose aspect of the campaign. Of over 350 supervisory checklists collected, data was consolidated from **335 reports** (the rest were rejected as incomplete).

According to the compiled reports, 96% of visited sites were well organized and full teams were present for 99% of sessions. Overall, the use of fractional doses was well understood by health workers (100%) and in 94% of sessions observed, fractional dose was administered correctly. In a few instances the health workers had difficulties with the use of the 0.1 ml syringes but this was corrected early in the campaign by supervisors. Injection safety was a concern as monitors reported seeing recapping of syringes in 24% of sessions observed. Monitors noted that despite multiple punctures to the vial septum, no leakage or bits of septum degradation/debris were observed in any of sessions. Average numbers of fractional doses able to be drawn from each vial were not accurately counted, as scoring errors resulted from overly busy sites and the combination of fractional and full dose delivery. However, an average wastage rate of only 3.2% (0.3% - 8.8%) was calculated overall.

Given the low thermostability of yellow fever vaccine following reconstitution, cold chain maintenance at the immunization sessions was a concern. In addition, the Bio-Manguinhos vials used in Kinshasa did not have VVMs attached. Only 31% of sites observed had a temperature monitor in the vaccine carrier. 89% of vaccine carriers observed had sufficiently cold ice packs and 84% of sites were correctly keeping the reconstituted vaccine vials in the foam cushion of the carriers. Diluent was sometimes kept out of the cold chain (6%). The multi-dose vial policy was properly adhered to in nearly all sites monitored. However, in 2 sites it was observed that reconstituted vials were put back in the refrigerator for use the following day. This was rapidly corrected by supervisors.

Fractional dosing (designated as “minimal dose”) was well understood by the population (97% of vaccine recipients questioned). However, health workers reported questions being raised on the duration of protection and on the validity for travel. Questions were also raised about vaccination of pregnant women as they have not been included in previous yellow fever vaccination campaigns. Correct messaging by health workers was observed in 95% of sites monitored. 9% of sites monitored reported having encountered cases of resistance to receiving the fractional dose, but 10% reported having encountered cases of resistance to the full dose as well.

As a result of a rumour circulating that yellow fever vaccine was incompatible with consumption of alcohol, lower attendance was observed at sites on the weekends. There were no widespread issues with false rumours or concerns specifically related to fractional dosing.

### **Post-campaign evaluation and coverage**

A total of 7,898,365 people were reported to have been vaccinated during the campaign, representing 104% of the initially estimated target population. RCAs were conducted across 10,300 households representing 58,021 respondents. Of these, 56,974 (98%) reported being vaccinated during the campaign. Of the 2% not vaccinated, 21% (219/1,046) were reported as vaccine refusals. Reasons given for refusing the vaccine are presented in **Figure 1**.

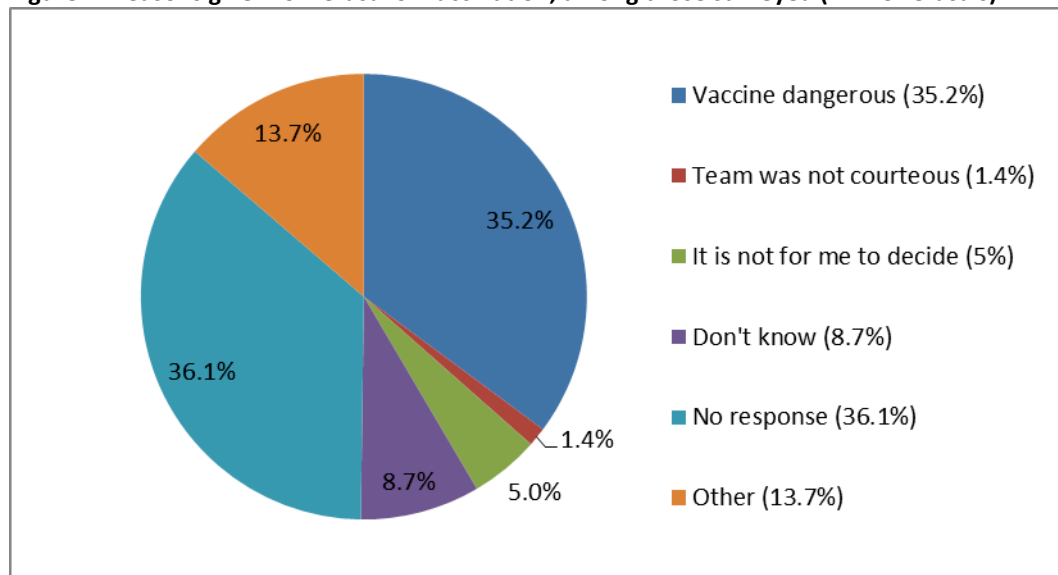
A full post-campaign assessment is currently underway, with a report expected by the end of October 2016.

### **Monitoring of immunity**

The Yellow Fever partnership, under US CDC leadership in collaboration with the National Institute of Biomedical Research (INRB) in Kinshasa and WHO, launched a study that will assess immunogenicity at 28 days

and 12 months post vaccination. If the results of this study suggest poor immunogenicity, revaccination with a full dose will be considered.

**Figure 1. Reasons given for refusal of vaccination, among those surveyed (n=219 refusals)**



## References

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- <sup>1</sup> Lopes O de S, Guimarães SDA, de Carvalho R. Studies on yellow fever vaccine. III-Dose response in volunteers. *J Biol Stand* 1988; 16: 77-82.
- <sup>2</sup> Roukens AH, Vossen AC, Bredenbeek PJ, Dissel JT, and Visse LG. Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: a randomized controlled non-inferiority trial. *PLoS One* 2008; 3.
- <sup>3</sup> Martins RM, Maia MDLS, Farias RHG, Camacho LAB, Freire MS, Galler R, et al. A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study 17DD yellow fever vaccine. *Human Vaccines & Immunotherapeutics* 2013; 9: 879–88.
- <sup>4</sup> Campi-azevedo AC, Estevam PDA, Coelho-dos-reis JG, Peruhype-magalhães V, Villela-rezende G, Quaresma PF, et al. Subdoses of 17DD yellow fever vaccine elicit equivalent virological / immunological kinetics timeline. *BMC Infect Dis* 2014; 14: 391.
- <sup>5</sup> Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response. WHO Secretariat information paper. 20 July 2016. Available online: <http://apps.who.int/iris/bitstream/10665/246236/1/WHO-YF-SAGE-16.1-eng.pdf>
- <sup>6</sup> WHO Policy Statement: Multi-dose Vial Policy (MDVP). 2014 revision. Available online: [http://apps.who.int/iris/bitstream/10665/135972/1/WHO\\_IVB\\_14.07\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf)