Revisiting Immune Interference: Evaluation of Immune Response to Yellow Fever Vaccine at Various Time Points Following Live-Attenuated Influenza Vaccination

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Abstract

Background: Due to concerns for immune interference, current recommendations are to avoid other live virus vaccines for 30 days pre- and post-mass vaccination campaigns leading to interruptions in routine vaccinations. During rapid preparations for Operation United Assistance (OUA) which supplied humanitarian assistance during the Ebola epidemic, mass yellow fever vaccine (YFV) administration to deploying personnel was needed during ongoing live-attenuated influenza vaccine (LAIV) administration. This study is the first to compare seroconversion rates for YFV when given per guidelines (VBG) to rates when YFV is given 1-29 days post-LAIV (NVBG).

Methods: All personnel who received LAIV concurrently or before YFV for OUA and had pre- and post-vaccination archived serum at the Department of Defense Serum Repository were included. VBG was defined as YFV given concurrently or ≥30 days after LAIV and NVBG as YFV given 1-29 days post-LAIV. YFV seroresponse was determined by screening ELISA followed by confirmation with plaque reduction neutralization testing (PRNT) on all positive samples. YFV PRNT ≥1:20 was considered positive. Exclusion criteria were prior YFV and pre-vaccination positive PRNT. Statistical analysis was performed using SPSS v22.

Results: During OUA preparations, 676 personnel were vaccinated with LAIV concurrently or before YFV. Sixteen were excluded due to positive pre-vaccination PRNT. Of the 660 who met inclusion criteria, 507 were VBG (482 concurrently and 25 vaccinated ≥30 days post-LAIV) and 153 were NVBG. Median age was 25 (IQR 22, 29) for both groups. Pre-vaccination serum was drawn 280 and 345 days for VBG and NVBG respectively (p=0.05). Post-YFV serum was drawn a median of 154 days following YFV in both groups. Seroconversion rates were 98% for VBG and 95% for NVBG (p=0.15). Median yellow fever titers were 320 (IQR 160, 640) in both groups post-vaccination. Seroconversion rates were 98% for those with LAIV and YFV concurrently (n=471), 100%, 95%, 92%, 100%, and 100% for those with YFV on days 1-6 (n=18), days 7-13 (n=42), days 14-21 (n=66), days 22-27 (n=8), and ≥28 days (n=44) post-LAIV respectively (p=0.12).

Conclusions: In this healthy, adult population, YFV provided high levels of protection regardless of timing following LAIV.

Background

- Yellow fever continues to be a global health threat, with outbreaks requiring aggressive massive vaccination campaigns
- Because YFV is a live virus vaccine, concerns about immune interference led to recommendations for administering this either simultaneously or 30 days apart from other live viral vaccines
- This can be challenging with competing mass vaccination campaigns
- In 2014, during urgent preparations for OUA in support of the humanitarian response to the Ebola epidemic in West Africa, YFV was administered during an already ongoing LAIV mass vaccination campaign, often not according to recommended spacing
- This study seeks to evaluate the seroconversion rates of YFV when given at various time points relative to LAIV

Methods

Study Population:

- All active-duty military personnel who received LAIV concurrently or prior to YFV in preparation for OUA and had pre- and post-vaccination serum archived at the Department of Defense Serum Repository were included
- Personnel were considered VBG if they received YFV simultaneously or ≥30 days following LAIV and NVBG if YFV was administered 1-29 days post-LAIV
- Exclusion criteria were prior receipt of YFV and pre-vaccination positive PRNT

Seroconversion Evaluation:

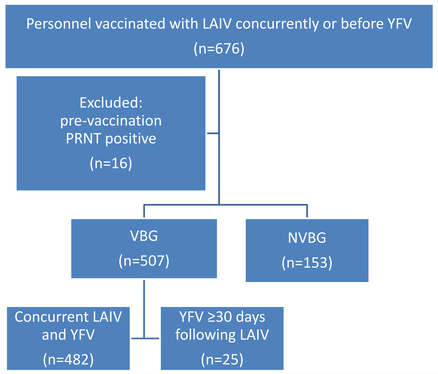
- Screening ELISA was performed, followed by confirmation on all positive samples with microneutralization PRNT and development with 4G2 monoclonal antibody on all positive samples.
- YFV PRNT50% ≥1:20 was considered positive.

Statistical Analysis:

- X^2 or Fisher's exact test as appropriate for categorical variables and Mann-Whitney U for continuous variables were performed using SPSS® Statistics (Version 22, Chicago, Illinois)

Results

Figure 1. Flowchart of included personnel

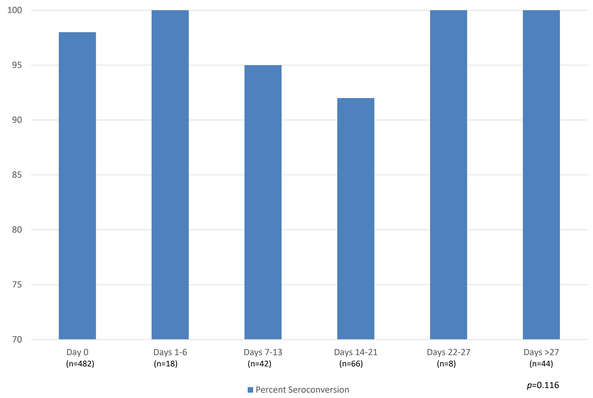


Results (cont.)

Table 1. Seroconversion of those VBG compared to those NVBG

	VBG (n=507)	NVBG (n=153)	*p* value
Age in years, median (IQR)	25 (22, 29)	25 (22,29)	0.621
Male Gender, no. (%)	424 (84%)	121 (79%)	0.194
Days prior to YFV serum drawn, median (IQR)	280 (143, 436)	345 (176, 518)	0.053
Days following YFV serum drawn, median (IQR)	154 (133, 174)	154 (132, 161)	0.069
Titer post-vaccination	320 (160, 640)	320 (160, 640)	0.428
Seroconversion, no. (%)	496 (98%)	146 (95%)	0.151

Figure 2. Percent seroconverted by time after LAIV that YFV was administered



Discussion

- Initial studies of viral interference revealed that circulating interferon induced by live-attenuated measles virus was associated with systemic protection from vaccinia
- Circulating interferon peaked on days 6-11 following measles vaccination, with peak response interference noted on days 9-10, and decreased to zero by the 20th day
- Follow-up studies have indicated that this interference phenomenon may not be universal
- A prior study evaluating seroconversion in children showed no difference in seroconversion among those receiving the YFV on days 1-6, 7-13, 14-21, 22-27, and ≥28 days following measles vaccination
- More data is needed to guide recommendations on required spacing of live virus vaccinations, which is especially important to avoid disruptions of routine vaccinations during mass live-virus vaccination
- In this healthy population, seroresponse to YFV was high regardless of timing following LAIV
- Limitations of this study are the retrospective nature, limited number of personnel vaccinated at certain time points following LAIV, and pre-vaccination serum >6 months prior to YFV (however in this population, interceding exposure to yellow fever is not expected)
- Additionally, these results may not be generalizable outside of this well-nourished adult population

Conclusions

- In this healthy adult population, seroresponse to YFV was high regardless of timing following LAIV
- This study emphasizes the need to evaluate interactions between live virus vaccines individually
- Increased awareness of live-virus vaccinations which do not display immune interference may decrease interruptions in immunizations

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