Vaccinating Against Monkeypox in the Democratic Republic of the Congo with JYNNEOS

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WHO Global Consultation – Monkeypox Research Priorities
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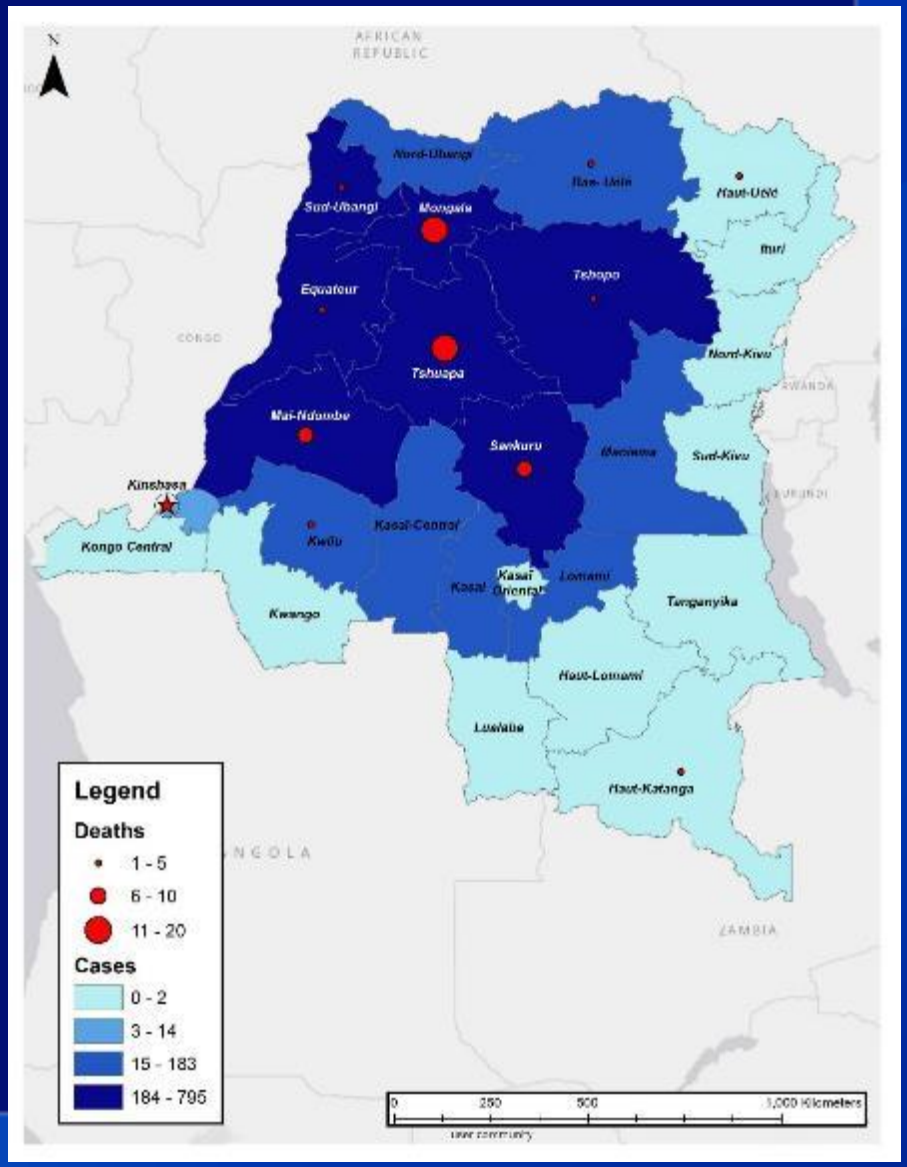
National Center for Emerging and Zoonotic Infectious Diseases
Division of High Consequence Pathogens and Pathology

Monkeypox

- Causative agent: *monkeypox virus*
- Clinical presentation: disseminated vesicular/pustular rash associated with fever, malaise, and lymphadenopathy
- Transmission: primarily zoonotic following contact with infected animals; human-to-human via respiratory droplets and lesion exudates
- Animal reservoir: likely small rodents (rope squirrel, Gambian rat, dormouse)

Monkeypox in the Democratic Republic of the Congo

- **5,060 MPX cases were reported with 103 deaths (CFR 2%) from 18 provinces in 2019**
- **Enhanced surveillance in Tshuapa Province**
  - ~ 500 suspect samples submitted/year
  - ~ 300 confirmed cases/year
  - Annual incidence rate of 4.4/10,000
  - Annual incidence of 17.4/10,000 in healthcare workers (1/100 of confirmed cases)



Prevention of Monkeypox

- Avoid contact with animals that could harbor the virus
- Isolate infected patients
- Use personal protective equipment (PPE) when caring for patients
- Practice good hand hygiene after contact with infected animals or humans

- Smallpox vaccination (administered 3–19 years previously) appeared to provide over 85% protection against disease acquisition in studies of close contacts of cases

Smallpox Vaccine Advances

- 1st generation vaccines – propagated in calf skin
  - Dryvax, **Aventis Pasteur Smallpox Vaccine (APSV or Wetvax)**
- 2nd generation vaccines – propagated in tissue culture, produced using modern good manufacturing practices
  - **ACAM2000**
- 3rd generation vaccines – attenuated live virus propagated in tissue culture, produced using modern good manufacturing practices
  - **JYNNEOS/IMVAMUNE/IMVANEX**, LC16M8
- 4th generation vaccines – protein subunit vaccines, DNA vaccines
  - 4Pox

JYNNEOS Smallpox and Monkeypox Vaccine

- **Modified Vaccinia Ankara (attenuated)**
  - Tested in >7,000 human participants (including >400 HIV+ individuals and >380 individuals with atopic dermatitis)
- **No severe adverse events**
- **Efficacy demonstrated in animal models**
- **Administered subcutaneously**
  - No vaccine site lesion or “take”
  - No risk of inadvertent transmission
- **Approved by US FDA for prevention of smallpox and monkeypox (September 2019)**
- **Effectiveness had not been evaluated in the setting of natural orthopoxvirus disease**

JYNNEOS Vaccine Study

- **Collaboration between the DRC Ministry of Health, the Kinshasa School of Public Health, and CDC began in 2015**
- **Developed Investigational New Drug (IND) Protocol**
  - Prospective cohort study of adult healthcare workers at risk for monkeypox in the Democratic Republic of the Congo
- **Objectives**
  - Evaluate safety of JYNNEOS
  - Evaluate immunogenicity of JYNNEOS
  - Evaluate effectiveness of JYNNEOS to prevent human monkeypox

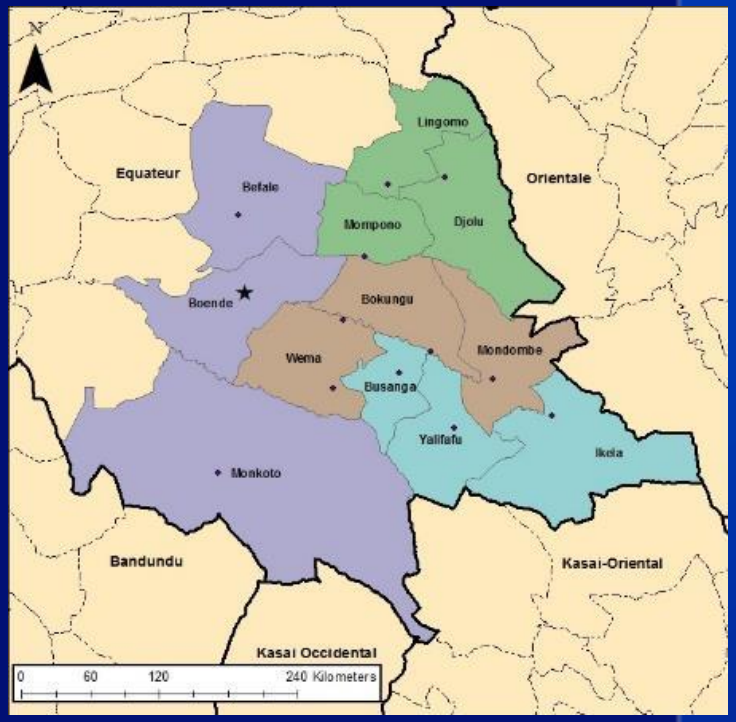
JYNNEOS Vaccine Study

- Vaccine administered to study participants on days 0 and 28
- Study visits on days 0, 14*, 28, 42, 180, 1yr, 1.5 yr, 2 yrs
  - (*subset of participants)
- Blood draws on each study visit
- Adverse event diaries given on each vaccination day
- Exposure diaries completed throughout the study to document contact with monkeypox patients and disease occurrence

JYNNEOS Vaccine Study Results

Cohort 1: Liquid Frozen Formulation

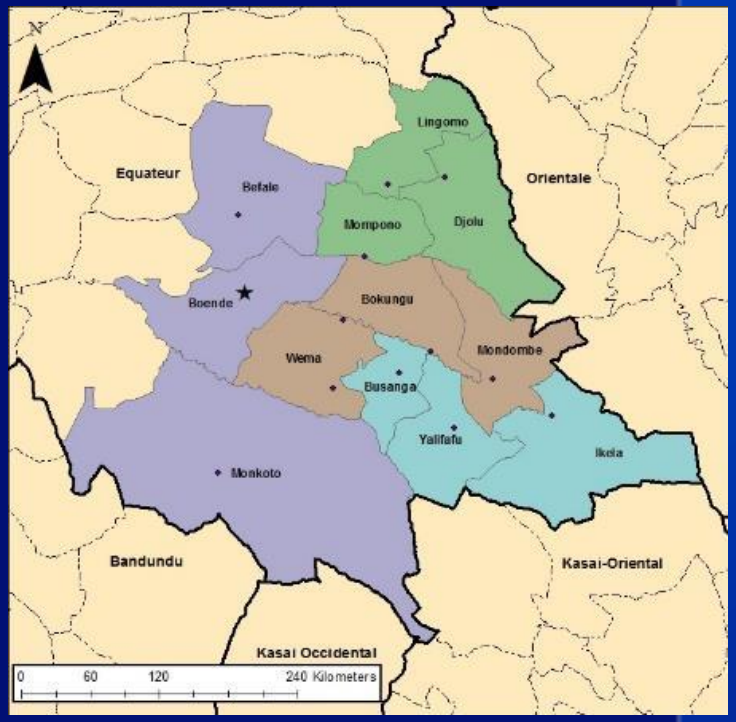
- **1,000 participants enrolled and vaccinated in Kinshasa and four health zones in the Tshuapa Province in 2017**
  - >97% received two doses
  - Excellent return rate for follow up study visits
    - >88% through day 730
- **No monkeypox disease identified among participants during 2 year monitoring period**
  - One study participant vaccinated with JYNNEOS in May and June 2017 developed Monkeypox in November 2019



JYNNEOS Vaccine Study Results

Cohort 2: Lyophilized Formulation

- **600 participants enrolled and vaccinated in two health zones in the Tshuapa Province in 2019**
  - >95% received two doses
  - Excellent return rate for follow up study visits
    - >85% at day 545
- **No monkeypox disease identified among participants during 2 year monitoring period**



Preliminary Safety Analysis - Cohort 1 (Liquid Frozen)

✓ 771 previously vaccinated, 221 unvaccinated (naïve) estimated based on age

	10-14%	6-9%	3-5%	0-2%
Local Vaccine Site Reactions	Pain, 14%	Tenderness, 7% Induration, 6% Edema, 7% Pruritis, 8%	Erythema, 5%	
General Systemic Systems			Fever, 4% Sweating, 4% Fatigue/Malaise, 4%	Chills, 2% Pain in the Arm, 2%
Lymphatic				Underarm Swelling, 2%
Gastrointestinal				Nausea/Vomiting, 2%
Cardiac and Respiratory				Chest Pain, 2% Difficulty Breathing, 0.7%
Nervous System		Headache, 7%		Dizziness, 2%
Musculoskeletal			Myalgia, 4% Arthralgia, 3%	

- No significant increase in any reported adverse reactions compared to clinical trial data

Preliminary Safety Analysis - Cohort 1 (Liquid Frozen)

	Previously Vaccinated	Naïve
Local Vaccine Site Reactions		
Pain	161/765 (21%)	78/221 (37%)
Tenderness	75/765 (10%)	39/220 (18%)
Erythema (redness)	53/765 (7%)	24/221 (11%)
Induration (hard lump)	66/765 (9%)	31/220 (14%)
Edema (swelling)	88/765 (12%)	33/221 (15%)
Pruritis (itching)	95/765 (12%)	35/221 (16%)
General Systemic Symptoms		
Fever	51/765 (7%)	24/220 (11%)
Chills	22/765 (3%)	20/220 (9%)
Sweating	51/766 (7%)	20/220 (9%)
Nausea/Vomiting	19/765 (2%)	11/220 (5%)
Fatigue/Malaise	49/765 (6%)	28/220 (13%)
Myalgia (Muscle Pain)	49/766 (6%)	23/220 (10%)
Arthralgia (Joint Pain)	37/765 (5%)	18/220 (8%)
Headache	85/765 (11%)	40/219 (18%)
Dizziness	38/764 (5%)	6/220 (3%)
Chest Pain	23/765 (0.3%)	14/220 (6%)
Difficulty breathing	12/765 (2%)	2/220 (1%)
Pain in the arm(s)	24/765 (3%)	16/220 (7%)
Underarm swelling	23/765 (3%)	9/220 (4%)

Preliminary Safety Analysis
Severe Adverse Events

- No vaccine-associated severe adverse events reported
- 16 study participants deaths reported
  - Acute hepatitis and severe anemia; skin infection of the leg (distant from the vaccine site injection); cerebral vascular accident secondary to hypertension; alcohol intoxication (n=2); cerebral vascular accident secondary to HIV infection and cryptococcal meningitis; traumatic head injury; acute gastroenteritis associated with severe malaria; opportunistic infections/AIDS; hepatic cirrhosis; suspected complications of tuberculosis; hepatic cancer and hepatitis B virus infection; suspect myocardial infarction; stroke in the context of acquired immunodeficiency (HIV/AIDS); hypertensive cardiopathy; and scrotal hernia complicated by septic shock
- Estimated annual average crude death rate in DRC is 9.6 deaths/1,000 population*
  - Annual average death rate of 6 deaths/1,000 among study participants

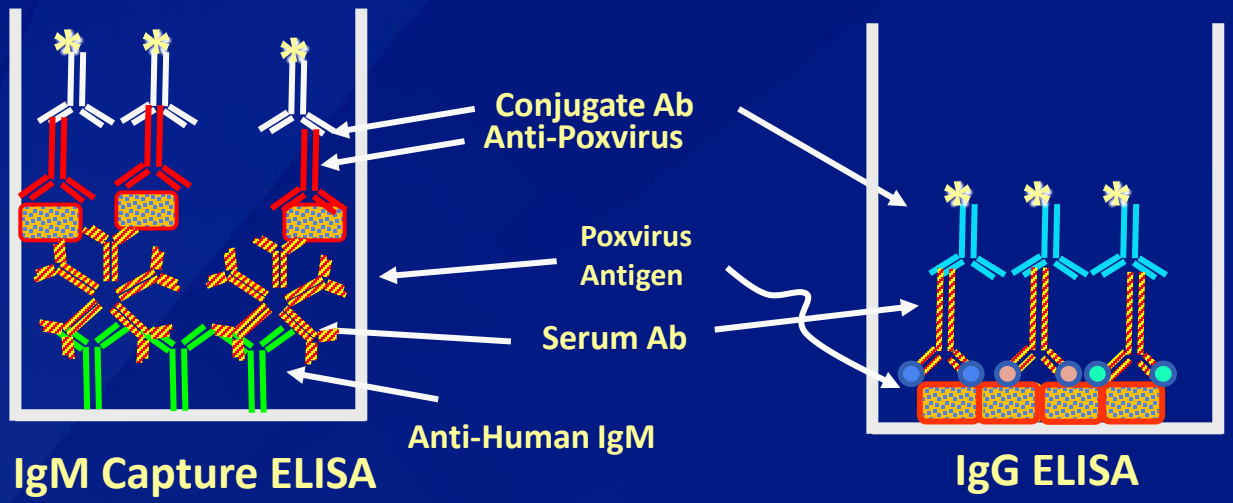
* United Nations Department of Economic and Social Affairs (https://population.un.org/wpp/Download/Standard/Mortality/)

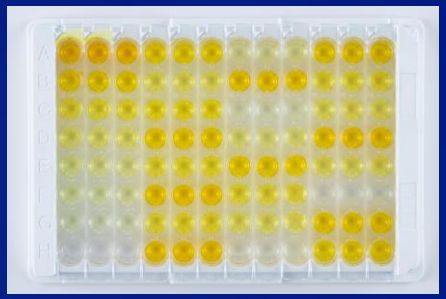
Preliminary Safety Analysis
Pregnancies

- 14 female study participants became pregnant within 6 months of receiving the study vaccine
  - All female participants were advised to avoid becoming pregnant for one month (28 days) after each study vaccine administration. However, the occurrence of pregnancies among study participants was not unexpected among this population with relatively high fecundity.
  - 13 participants delivered healthy babies and one participant experienced a stillbirth at an estimated 37 weeks gestation based on her last menstrual period
  - Estimated annual infant death rate in DRC is 65 infant deaths per 1,000 live births*

* United Nations Department of Economic and Social Affairs (https://population.un.org/wpp/Download/Standard/Mortality/)

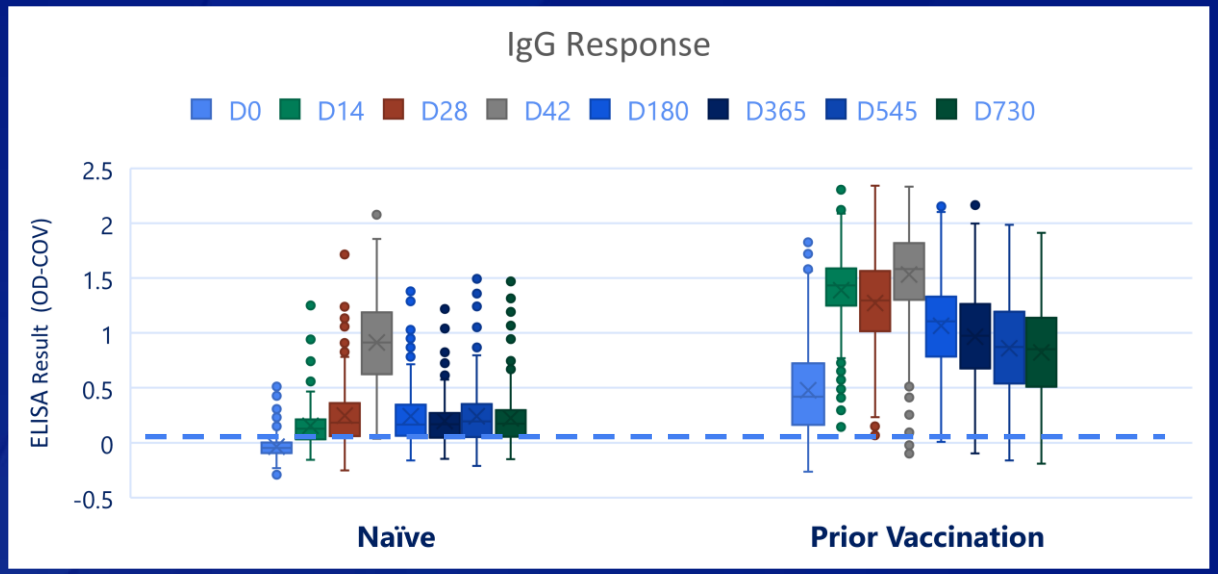
Immunogenicity Analysis
IgM and IgG Whole Virus ELISA

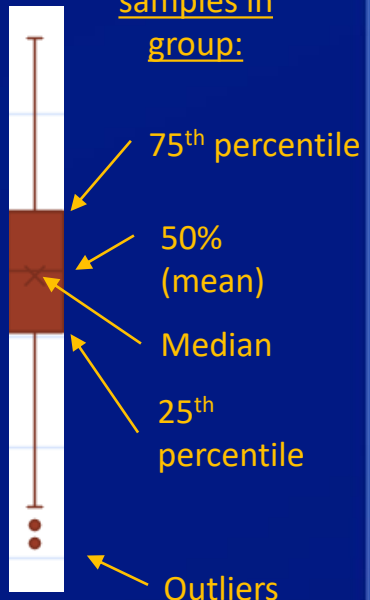




Immunogenicity Analysis
IgG Response and Seroconversion

	D14	D28	D42	D180	D365	D545	D730
All Samples (n=999)	92%	89%	98%	88%	83%	80%	77%
Naïve (n=294)	78%	75%	99%	76%	73%	74%	71%
Prior Vaccination (n=579)	99%	96%	97%	94%	89%	83%	81%





*Seroconversion defined based on a rise in OD signal of 0.1 from baseline (Day 0)

Immunogenicity Analysis
Seroconversion (IgG) Compared to Prior Studies

	Naïve		Prior Vaccination	
	DRC	BN Trials	DRC	BN-Trials
IgG D14	78%	70-99%	99%	84-96%
IgG D28	75%	68-98%	96%	80-93%
IgG D42	99%	96-100%	97%	
IgG D730	71%	72-82%	81%	97%*

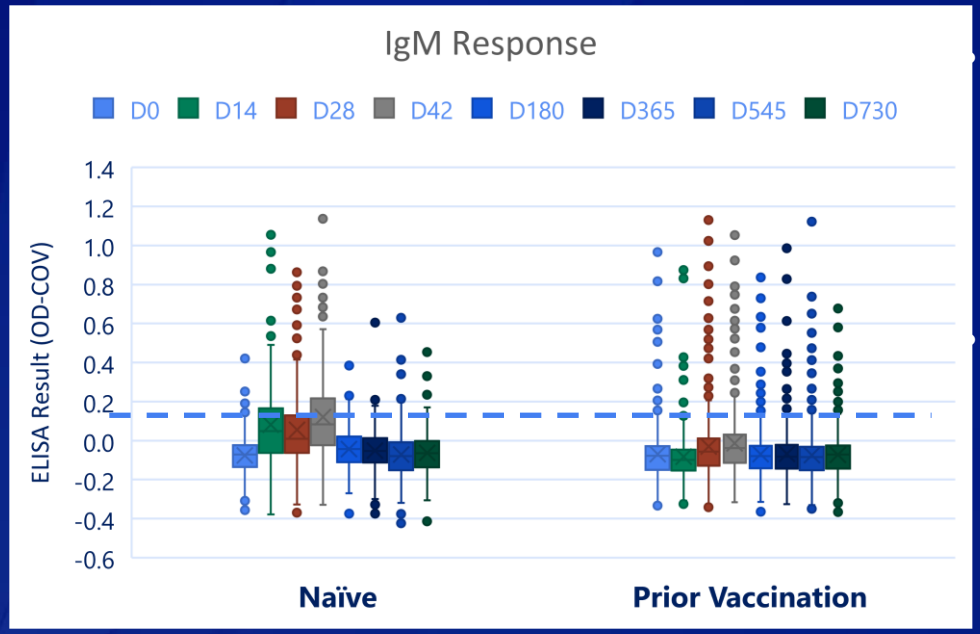
- BN Trials aggregated from Investigator's Brochure (31 Oct 2019)
  - Standard two-dose at Day 0 and Day 28
  - BN results from healthy individuals
- Overall, seroconversion rate is comparable previously reported results

* Received single dose JYNNEOS

Immunogenicity Analysis
IgM Response and Seroconversion

	% Seroconvert*
All Samples (n=999)	24%
Naïve (n=294)	50%
Prior Vaccination (n=579)	11%

	% Seroconvert			
	D14	D28	D42	D180
Naïve (n=294)	47%	30%	46%	6%
Prior Vaccination (n=579)	6%	6%	9%	2%



CDC Dryvax/ACAM vaccine study

- ~75% IgM positive after primary vaccination (n=15)
- ~4% after secondary or subsequent vaccinations (n=43)

USAMRIID Kole MPX Study (2005-2011)**

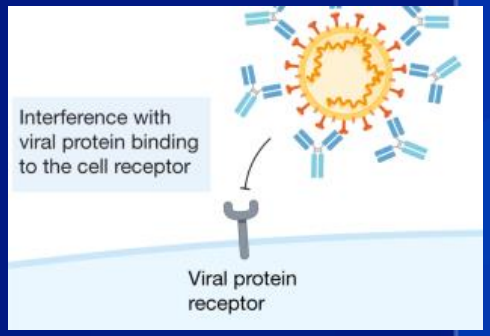
- Using DOB with 1980 vaccination cut-off
- Likely not Vac: 85% IgM Seroconv. (n=206)
- Likely Vac: 64% IgM Seroconv. (n=17)

**Unpublished findings

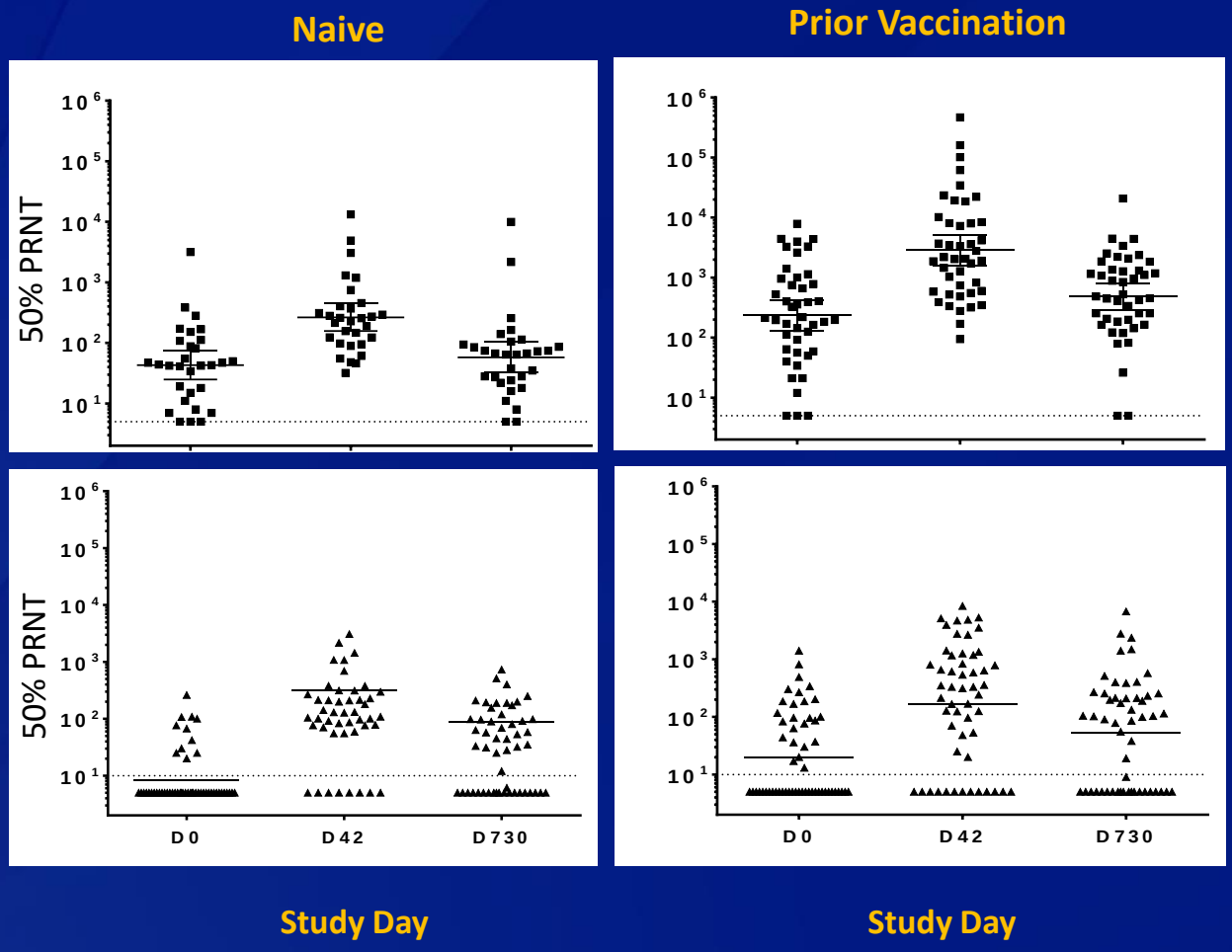
*Seroconversion is determined based on a rise in OD signal of 0.15 from baseline (Day 0)

Immunogenicity Analysis
Neutralization Testing

- Test a limited sample set (n=73) at key timepoints
  - Day 0: pre-vaccination
  - Day 42: peak response after vaccination
  - Day 730: end of study to assess longevity of responses
- Assay Format: 96-well, medium throughput
  - Vaccinia WR and Monkeypox (WA strain)
  - ImmunoSpot S6 Microanalyzer and BioSpot software



Immunogenicity Analysis
Neutralization Testing



Conclusions

- Binding antibody (ELISA) and neutralization (PRNT) results are comparable to prior studies
  - Peak responses observed at Day 42
  - Rapid decline after peak in vaccinia naïve participants
  - Levels were more stable in those with prior vaccination
  - Slow decline up to 2 years post vaccination
- MPXV Neutralization
  - Peak responses observed at Day 42
  - Durability was similar to VACV, with responses out to Day 730

Next Steps

- Effectiveness
  - Compare to retrospective surveillance data from areas of enhanced surveillance
  - Evaluate reported exposures to monkeypox
  - Comparison with non-vaccinated health zones
- Safety
  - Finalize safety data analysis including comparisons with previously collected clinical study data
- Immunogenicity
  - Complete neutralization testing with monkeypox virus
  - Correlation studies with collected data/diaries/exposures
- Additional Studies
  - Persistence of immunity evaluation in 2022
    - Vaccine booster study will administer a single dose of JYNNEOS to a cohort of previous study participants 3+ years following primary vaccination with JYNNEOS
    - Serum will be collected at days 0, 7, and 14 for immunogenicity and evaluation of memory response

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Questions?

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