Efficacy of Bivalent Versus Monovalent Covid-19 Vaccines, A Randomized Trial from 2022-2024

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Acknowledgements

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Background

Previously, randomized trials have not compared the efficacy of booster dose with a monovalent mRNA vaccine (targeting the ancestral WA-1 strain) versus a bivalent mRNA vaccine (targeting WA-1 plus BA.4/BA.5) in the African setting with high HIV and SARS-CoV-2 prevalence.

Research Questions

Efficacy: What is the relative risk of symptomatic and severe Covid-19 among individuals who received the monovalent (mRNA-1273) booster versus the bivalent (mRNA-1273.222) booster?

Compare efficacy by immune status: Do results differ based on HIV status, HIV viral load, CD4 cell count, or SARS-CoV-2 antibodies?

Methods – CoVPN 3008 Trial

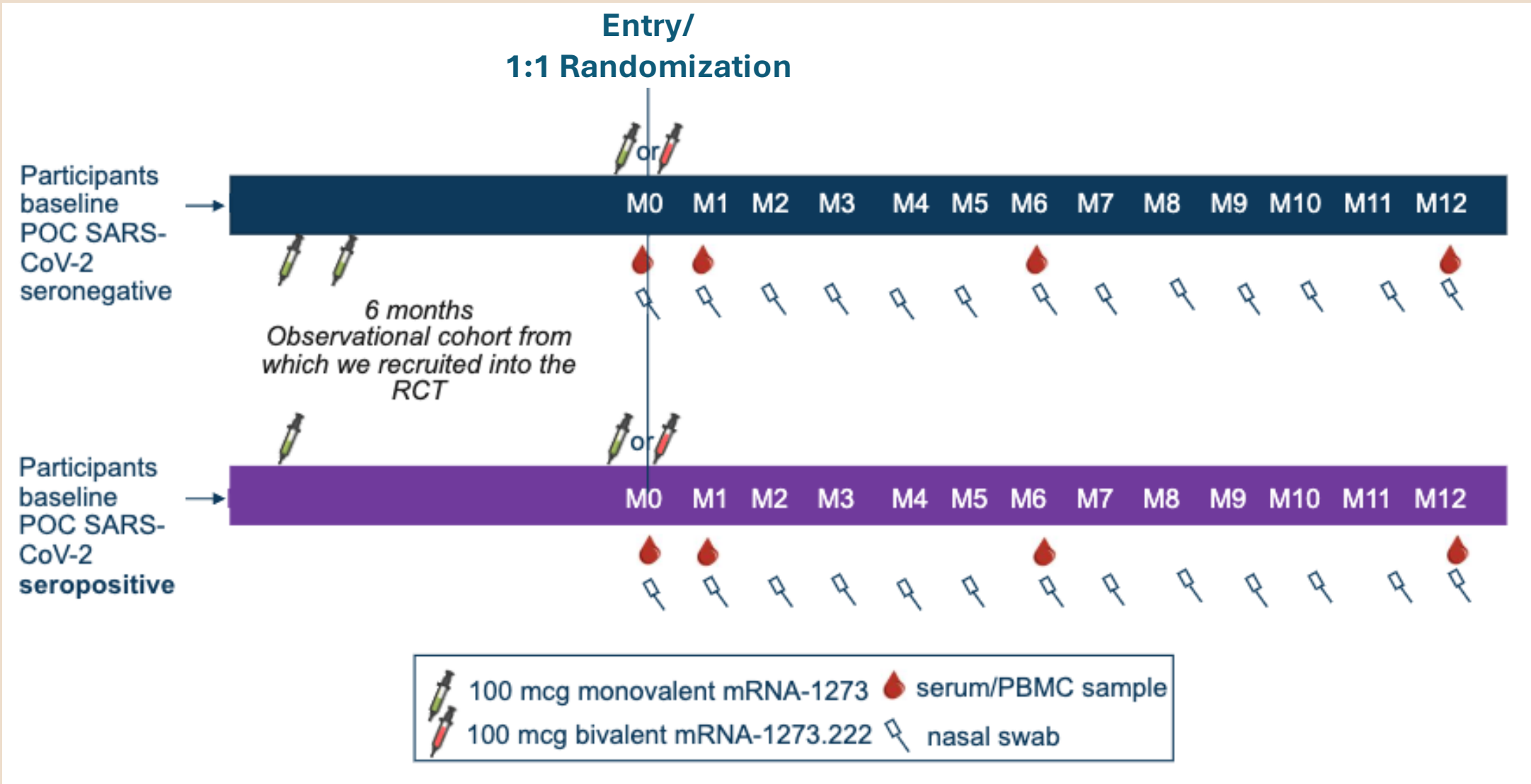
- **Design**: Double-blind, 2-arm randomized trial, **43 sites, 7 countries** in East and Southern Africa,

- **Eligibility**: People with HIV (PWH) or another co-morbidity linked to severe Covid-19 using CDC criteria (most common in our cohort: obesity, hypertension, diabetes, smoking history); 1 or 2 prior doses of monovalent mRNA vaccine; no exclusions for pregnancy, HIV VL, CD4 count, ART status.

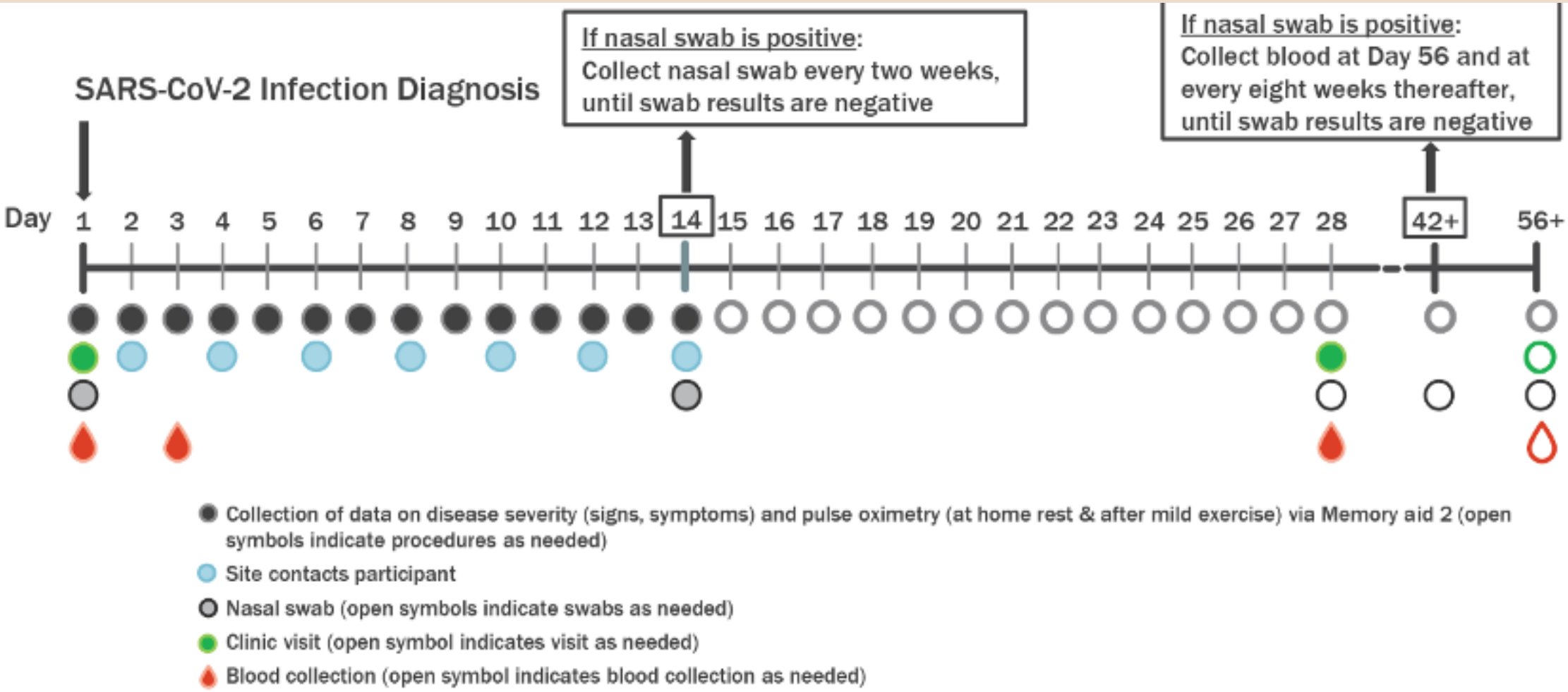
- **Statistical analysis:** Risk of Covid-19 compared between boost arms using cumulative incidences and Cox regression
  - Month 6 and month 12
  - Overall and by HIV status, SARS-CoV-2 serology, CD4 cell count, HIV viremia
  - Events (cases) were included if they occurred >13 days after boost
  - CDC case definitions

- **Characterize immune response in PWH:** Measured neutralizing anti-Spike antibody ID50 titers against BA.4/5 and XBB.1.5 (dominant during the trial) at baseline (before booster), and 1 month post-booster, in 100 PWH per arm. Absolute nAb titers compared by arm.

Methods: Study Procedures



Methods:
Procedures for SARS-CoV-2 PCR Positive



Results: Study Population

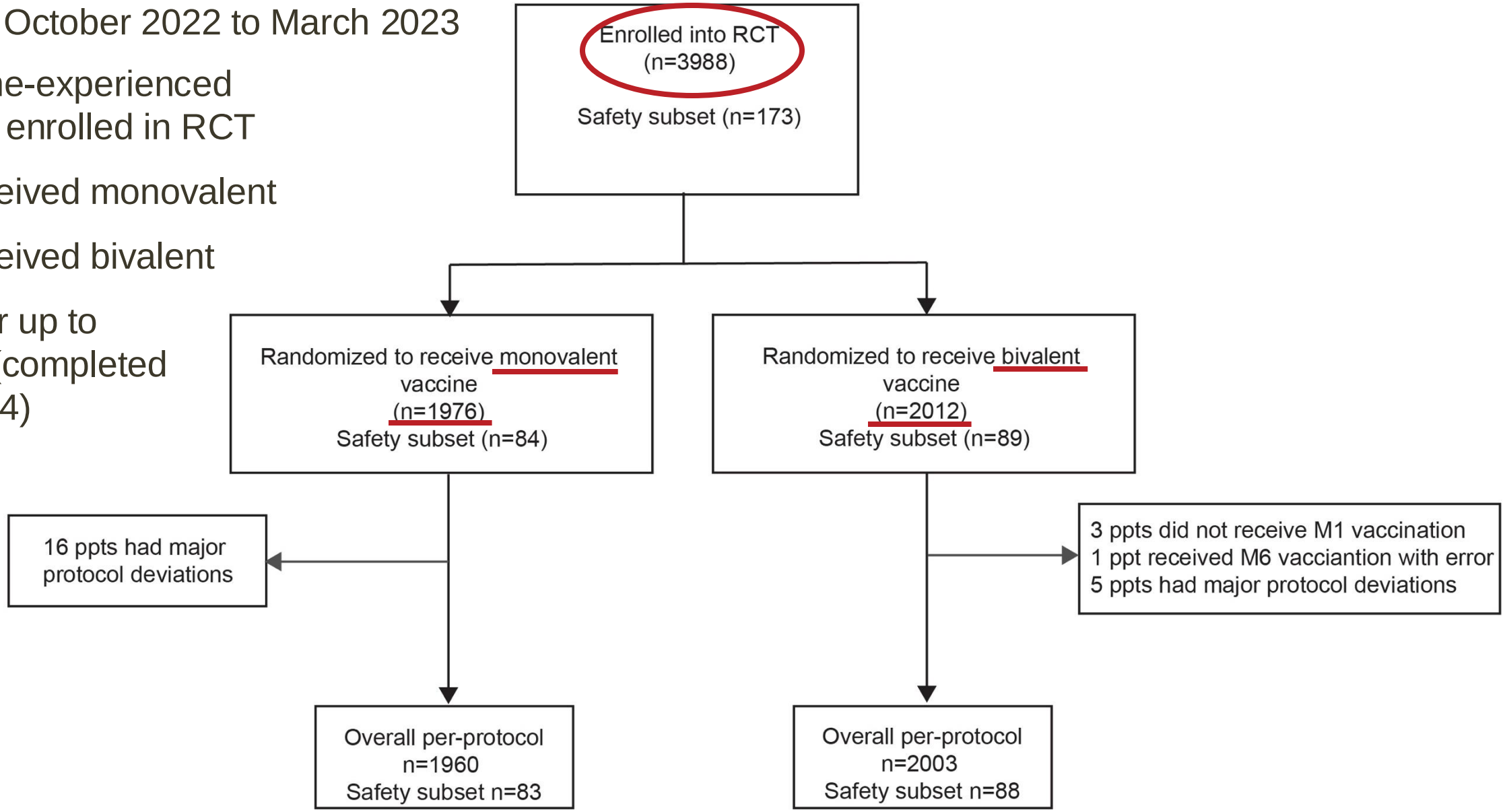
Enrollment: October 2022 to March 2023

3988 vaccine-experienced participants enrolled in RCT

n=1976 received monovalent

n=2012 received bivalent

Followed for up to 12 months (completed by April 2024)



Results: Baseline Characteristics

	Monovalent		Bivalent	
	PWH n=1529	PWoH n=447	PWH n=1557	PWoH n=455
Country – n (%)				
RSA	1029 (67.3%)	402 (89.9%)	1038 (66.7%)	415 (91.2%)
Non-RSA	500 (32.7%)	45 (10.1%)	519 (33.3%)	40 (8.8%)
Sex - n (%)				
Female	1164 (76.1%)	178 (39.8%)	1176 (75.5%)	191 (42.0%)
Age - n (%)				
Median (range)	39.0 (18.0, 69.0)	33.0 (18.0, 80.0)	39.0 (18.0, 74.0)	31.0 (19.0, 70.0)
History of TB - n (%)	221 (14.5%)	24 (5.4%)	212 (13.6%)	20 (4.4%)
CD4 count (cells/mm^3) - n (%)				
Median (IQR)	656.0 (441.0, 881.0)	-	651.0 (450.0, 891.0)	-
HIV VL* (copies/mL) - n (%)				
>50 copies/mL	1223 (80.0%)	-	1304 (83.8%)	-
Median (IQR)	169.0 (40.0, 5790.3)	-	86.0 (40.0, 6011.0)	-
ART status at month 6 - n (%)				
On ART	1463 (95.7%)	-	1493 (95.9%)	-
SARS-CoV-2 status - n (%)				
Hybrid immunity (+serology or +virology)	1333 (87.2%)	399 (89.3%)	1359 (87.3%)	400 (87.9%)
Vaccine immunity	196 (12.8%)	48 (10.7%)	198 (12.7%)	55 (12.1%)

Major effort by sites: Over 54,000 swabs collected and over 22,000 pulse ox readings.

Results: Relative Efficacy at Month 6

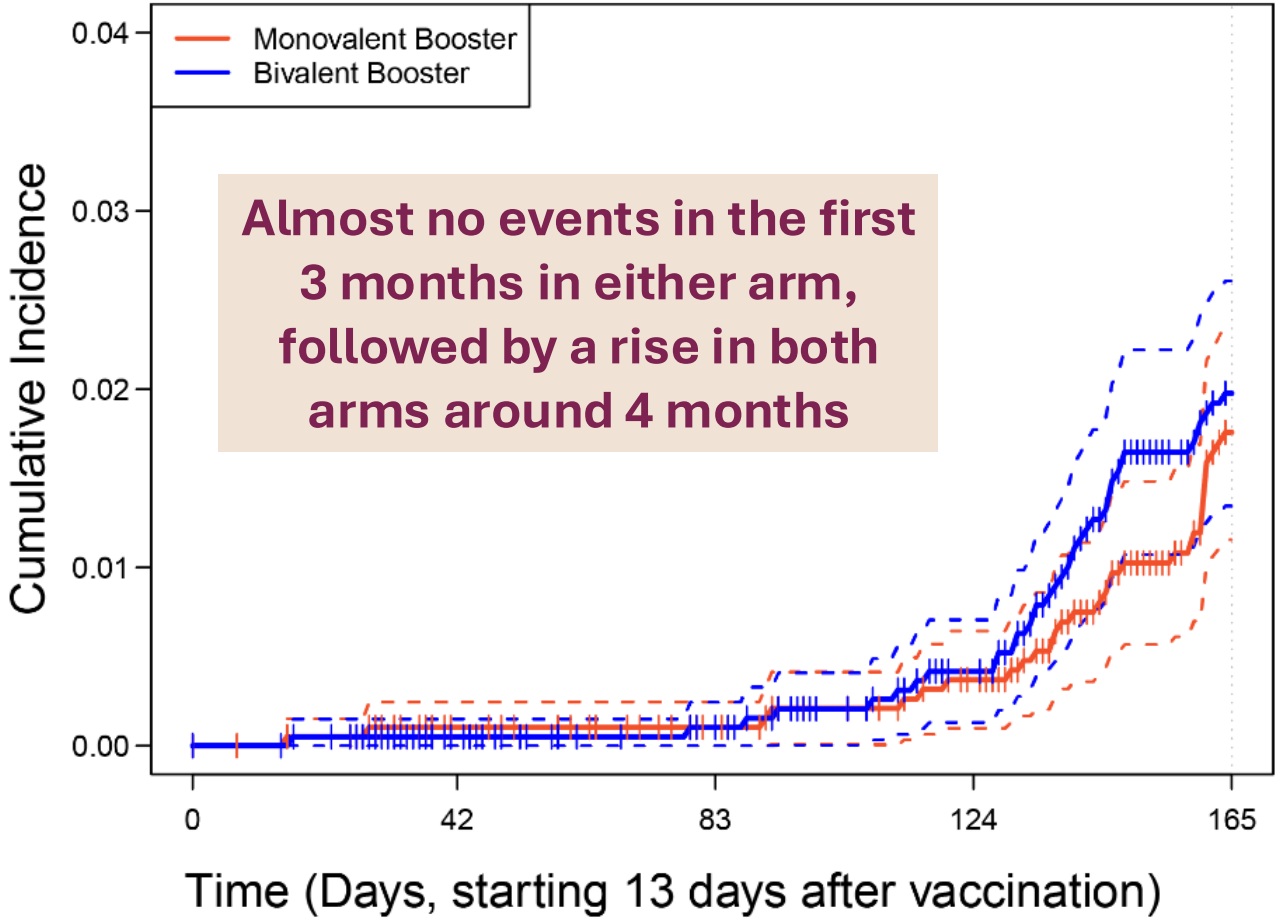
113 total Covid-19 events
56 in monovalent (1 severe)
57 in bivalent (none severe)

Bivalent arm: cumulative incidence
2.00% (95% CI 1.35 to 2.61)

Monovalent arm: cumulative incidence
1.80% (95% CI 1.15 to 2.36)

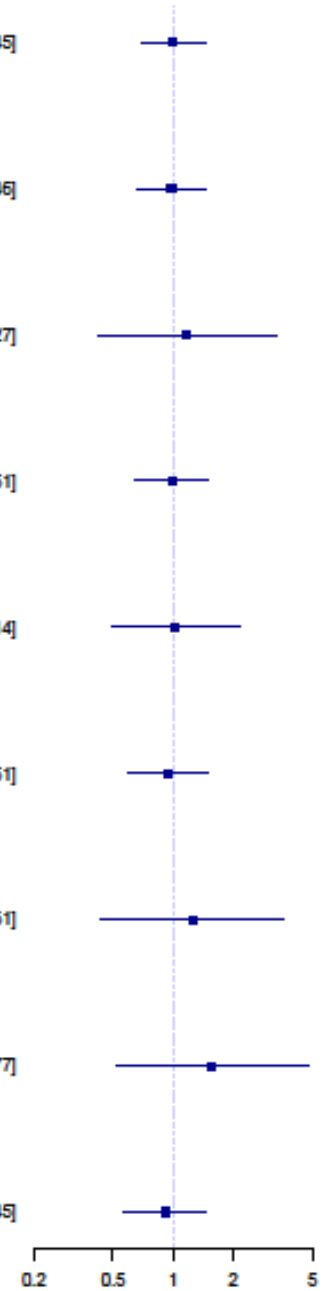
Hazard ratio
1.00 (95% CI 0.69 to 1.45); p=0.99

Relative risk
1.12 (95% CI 0.70 to 1.80); p=0.62



No. at Risk					
Monovalent	1949	1896	1880	1860	1742
Bivalent	1996	1935	1917	1891	1771
Total Events					
Monovalent	0	2	2	7	32
Bivalent	0	1	2	8	37

Analysis Cohort	Subgroup	Arm	No. of Endpoints	No. of Person-Years	Rate per 100 Person-Years	Hazard Ratio (95% CI)	P-value
RM6	All	Bivalent	57	1022	5.58		NA
		Monovalent	56	1004	5.58	1.00 [0.69, 1.45]	0.99
	M6 Hybrid Immunity	Bivalent	49	893	5.49		NA
		Monovalent	49	883	5.55	0.98 [0.66, 1.46]	0.93
	M6 Vaccine Immunity	Bivalent	8	129	6.22		NA
		Monovalent	7	121	5.79	1.17 [0.42, 3.27]	0.76
	PLWH	Bivalent	42	798	5.26		NA
		Monovalent	42	780	5.39	0.99 [0.64, 1.51]	0.95
	PLWoH	Bivalent	15	223	6.71		NA
		Monovalent	14	224	6.24	1.03 [0.50, 2.14]	0.93
	PLWH CD4 ≥350 cells/µl	Bivalent	34	685	4.96		NA
		Monovalent	35	658	5.32	0.94 [0.59, 1.51]	0.81
	PLWH CD4 <350 cells/µl	Bivalent	8	113	7.06		NA
		Monovalent	7	122	5.74	1.25 [0.43, 3.61]	0.68
	PLWH VL ≥50 copies/ml	Bivalent	7	122	5.74		NA
		Monovalent	6	150	3.99	1.57 [0.52, 4.77]	0.42
	PLWH VL <50 copies/ml	Bivalent	35	676	5.18		NA
		Monovalent	36	629	5.72	0.91 [0.57, 1.45]	0.69



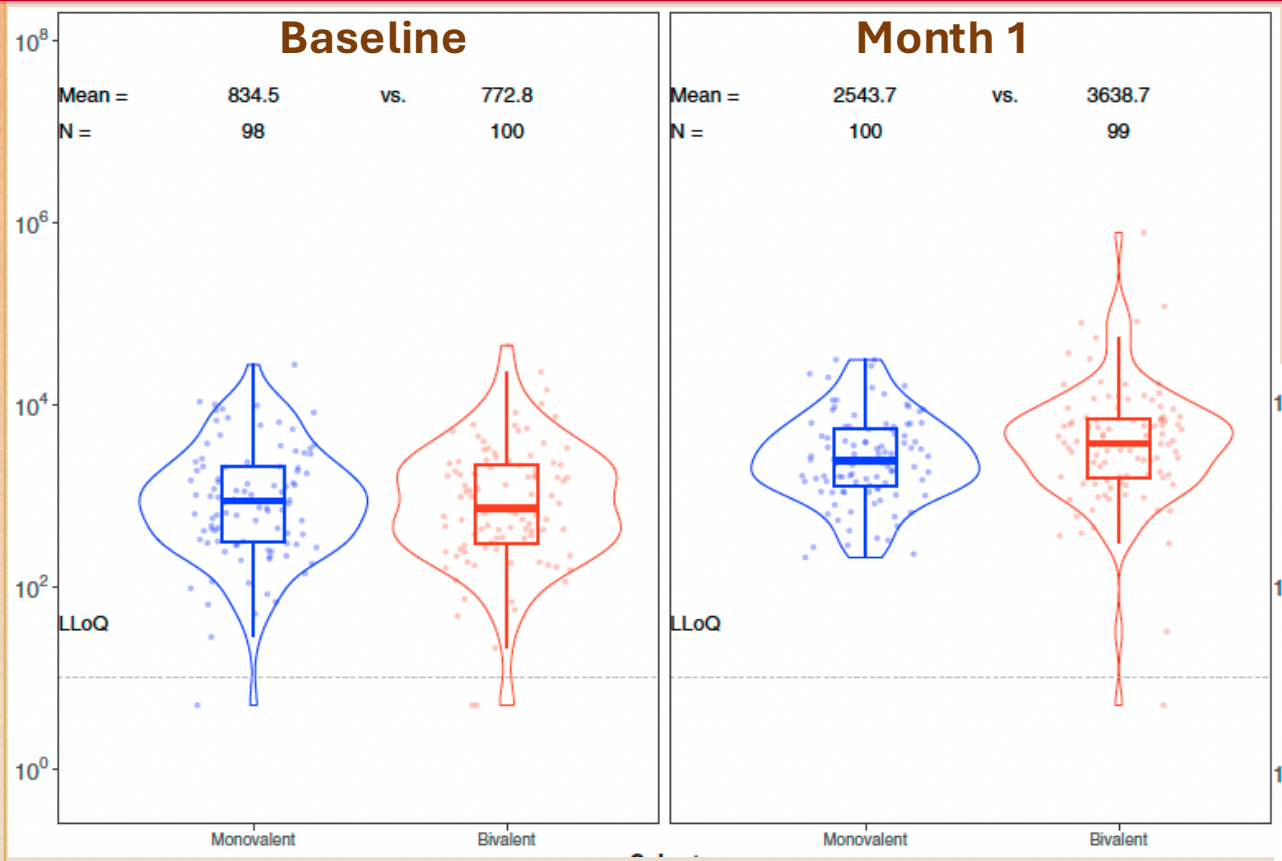
Month 6 results

No observed differences by

- HIV status
- SARS-CoV-2 serostatus
- HIV viral load
- CD4 cell count

Similar results at month 12

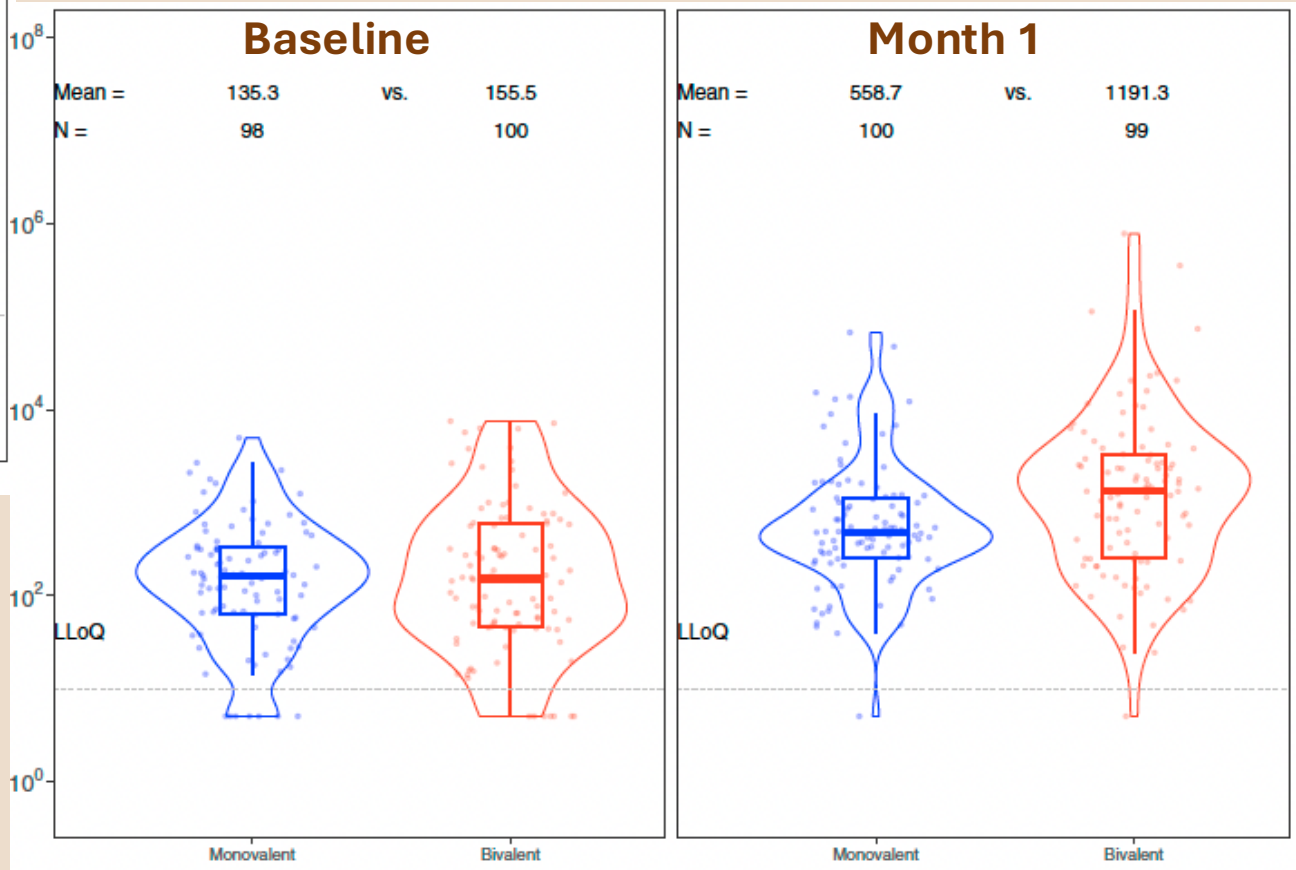
Results: Neutralizing Antibody Titers



ID50 nAb titers to <u>BA.4/5</u>
p=0.026

Blue violin plot = monovalent
Red violin plot = bivalent

ID50 nAb titers to <u>XBB.1.5</u>
p=0.002



Take Home Messages

1. **Both mRNA boosters were equally effective.** Only one severe case of Covid-19 observed, based on daily O_2, temperatures, and symptom screening. **no placebo arm*

2. **Reassuringly, results were similar between booster types by HIV status, HIV viral load, and CD4 cell count.**

3. **Bivalent booster elicited higher levels of nAbs than monovalent booster but did not confer additional clinical protection against symptomatic or severe Covid-19.**

4. **The immune response included variants not directly targeted by the booster vaccines.**

5. **Covid-19 case rates increased for both boost types 4 months after boost, likely due to both waning immunity and variant evolution.**

Thank you

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