Leveraging the multi-country Ubuntu COVID-19 vaccine clinical trial as a platform for tuberculosis biomarker research in sub-Saharan Africa

Track E2: Open Science

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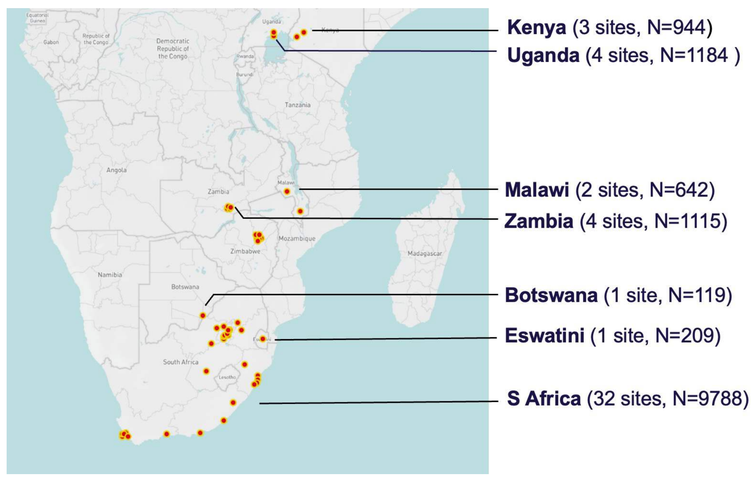
Background

- Vaccine clinical trials offer opportunities for biomarker discovery and validation because they involve well-characterized participants, standardized interventions, and longitudinal sample collections, which are ideal for assessing immune responses and other biological processes.
- Identifying reliable tuberculosis (TB) biomarkers from peripheral blood is a public health priority given the potential to accelerate TB vaccine trials, facilitate diagnosis, improve treatment monitoring, and predict disease progression.
- CoVPN 3008 (Ubuntu), the largest study of COVID-19 mRNA vaccines in Africa, could serve as a platform for investigating TB biomarkers.
- We describe the Ubuntu participant population, sample collection, and next steps for pursuing TB biomarker research.

Methods

- Adults ≥18 years living with HIV or another comorbidity associated with severe COVID-19 were enrolled at 47 sites across seven African countries (Figure 1).

Fig 1. Ubuntu countries and sites

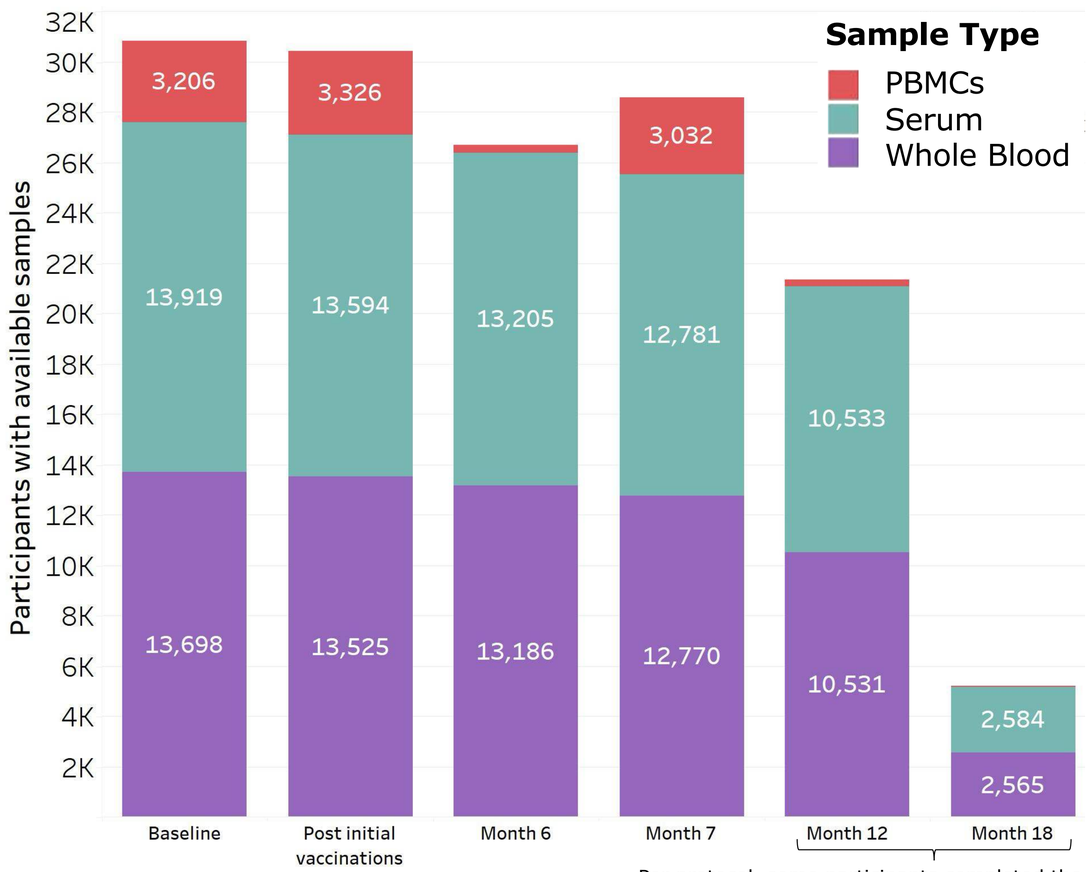


- No exclusions for pregnancy, HIV viraemia, CD4 count, or HIV antiretroviral therapy use.
- Enrolment data included medical history, physical exam, medications, SARS-CoV-2 serology and, for people with HIV (PWH), HIV viral load (VL) and CD4 count.
- Vaccinations were at enrolment and month 6; participants SARS-CoV-2 seronegative were also vaccinated at month 1.
- Serum and stabilised whole blood (in Tempus tubes to preserve RNA) were collected at multiple timepoints. Peripheral blood mononuclear cells (PBMCs) were collected in several subsets of participants.
- Most participants completed 12 months of follow-up; some met exit criteria before month 12; a subcohort continued to 18 months.

Results

- Among 14,237 participants enrolled from December 2021 to September 2022, data was analysed from 14,001 participants.
- Median age 39 years, 72% assigned female sex at birth, 83% PWH, 12% with prior TB.
- Among 11,681 PWH, baseline median CD4 count was 635 cells/mm^3 (IQR 423-866), 17% had a CD4 count <350 cells/mm3, and 18.5% had HIV viraemia.
- Multiple vials of serial serum and whole blood samples were stored for >12,700 participants through month 7, for >10,500 through month 12, and for >2500 through month 18 (Figure 2).
- Serial PBMC samples were stored for >3000 participants at multiple timepoints.

Fig 2. PBMCs, serum, and whole blood collected at key timepoints during the Ubuntu study period.



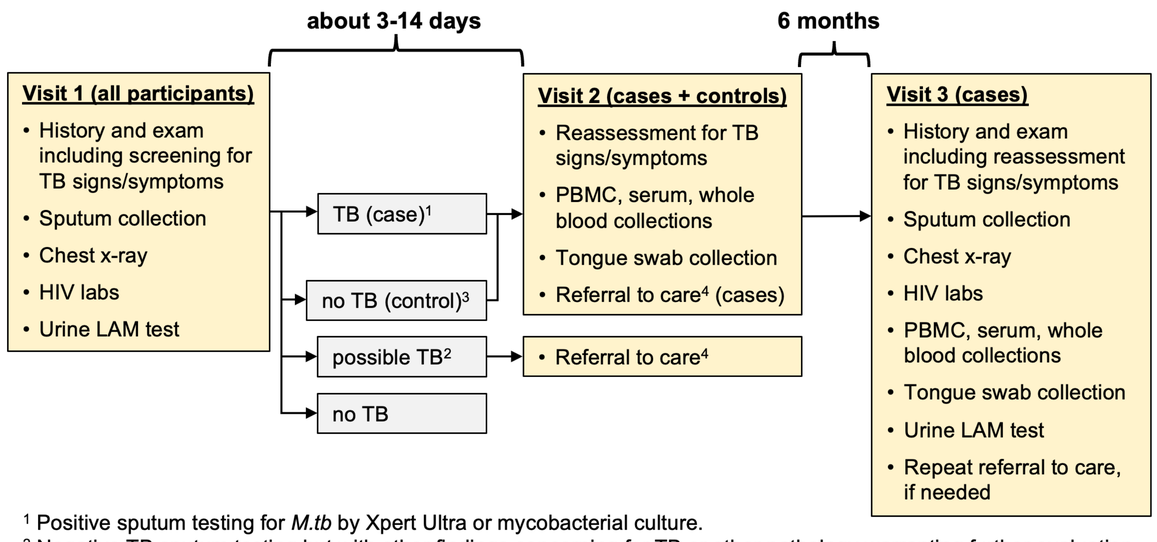
Per protocol, some participants completed the study before month 12 and most completed it before month 18

Figure 2. Serum (in Serum Separator tubes) and whole blood (in Tempus tubes) were scheduled to be collected at baseline, one month after the initial vaccinations (either at month 1 or 2, depending on the study group), month 6, and month 7. Additionally, PBMCs (in Acid Citrate Dextrose tubes) were collected from three participant subsets: ~300 participants had PBMCs collected at all timepoints; ~3000 participants had PBMCs collected at baseline, one month after the initial vaccinations, and month 7; and all COVID-19 cases had PBMCs collected near diagnosis and at day 28.

Discussion

Ubuntu offers a unique opportunity to leverage a large, diverse, well-described, externally monitored cohort in a high TB- and HIV-burden setting with prospectively collected and stored blood samples to research TB biomarkers. **Accurate predictive biomarkers of TB could reduce the size, duration, and cost of TB vaccine trials.**

Fig 3. Ubuntu TB substudy design



[1] Positive sputum testing for *M.tb* by Xpert Ultra or mycobacterial culture.
[2] Negative TB sputum testing but with other findings concerning for TB or other pathology warranting further evaluation.
[3] Controls selected among those with negative TB sputum testing, no prior TB, and no finding suggestive of TB on exam, chest X-ray, symptom review, or other evaluations, per PI assessment. Matched to cases by sex and HIV status.
[4] Referral for further clinical assessment and consideration of TB treatment unless already on TB treatment.

Next Steps

The **Ubuntu TB substudy** will bring back participants to assess them for subclinical or clinical TB, refer those with positive test results to care, and use stored samples, new samples, and information from clinical assessments to investigate peripheral blood transcriptomic biomarkers associated with TB (Figure 3).

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