Background. Previous studies suggest that RSV increases NP bacterial colonization and may facilitate infection. However, the role of NP colonization with potentially pathogenic bacteria (PPB) in the pathogenesis of RSV bronchiolitis is not well understood. We sought to determine the frequency, type, and density of NP PPB detection in infants with RSV infection compared with healthy controls (HC), and its association with clinical outcomes.

Methods. Single-center, prospective study of previously healthy infants with RSV infection and age-matched HC. Inpatients (IP) were enrolled within 24 hours of hospitalization, outpatients (OP) at the ED or primary clinics and HC at well-child visits. RSV infection and the following PPB: [*S. pneumoniae*, *M. catarrhalis*, *H. influenzae*, and *S. aureus*] were detected and quantified by PCR. We compared demographic, clinical characteristics, and outcomes of care according to NP PPB detection.

Results. From 2010 to 2018, we enrolled 815 infants: 664 with RSV infection [IP, 560; OP, 104] and 151 HC. RSV+ OP (6.1 [3.7–10.7] months) and HC (6.9 [3.8–10.8] months) were older than IP (2.5 [1.4–5.4] months; $P < 0.001$). Identification of ≥1 PPB was 89% in RSV+ infants [IP, 88%; OP, 90%] versus 63% of HC ($P < 0.0001$). While *H. influenzae* or >1 PPB detection was higher in RSV infection ($P < 0.001$), *S. aureus* detection predominated in HC ($P < 0.05$; Figure 1). Frequency of *S. pneumoniae* detection was comparable between groups; however, *S. pneumoniae* loads were one log higher in RSV+ infants versus HC ($P = 0.001$) adjusted for antibiotic use. Differences in colonization rates remained different in RSV+ infants versus HC across age ranges (<3, 3–6, >6–12, and >12–24 months; Figure 2). Last, RSV patients (both IP and OP) with *S. pneumoniae* or *H. influenzae* detection had fever more frequently (70%–74% vs. 25%–47%; $P < 0.0001$), higher clinical disease severity scores ($P = 0.01$), and higher blood neutrophil counts (34%–36% vs. 16%–19%; $P < 0.001$), versus those with *M. catarrhalis*, *S. aureus* detection or PCR negative. In addition, NP detection of *H. influenzae* in RSV children was associated with higher frequency of atelectasis/consolidation by chest X-ray ($P < 0.005$).

Conclusion. These data suggest that NP colonization with PPB is high in infants with RSV infection independent of age, and that specific bacteria, namely *S. pneumoniae* and *H. influenzae*, are associated with enhanced clinical disease severity.
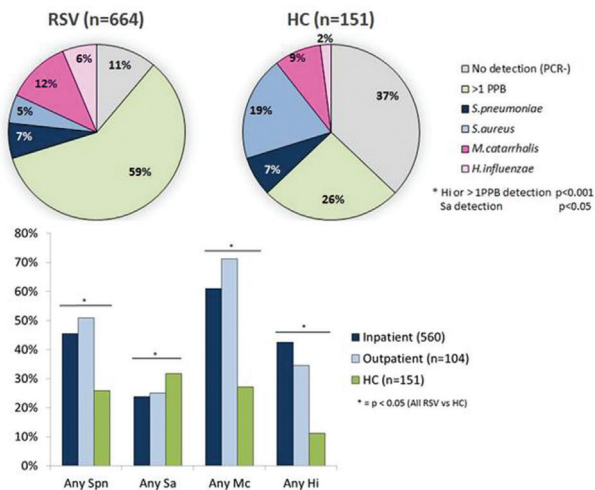

Figure 1. Frequency of NP bacterial detection of potentially pathogenic bacteria (PPB) in infants with RSV (inpatient and outpatient) and healthy controls (HC)
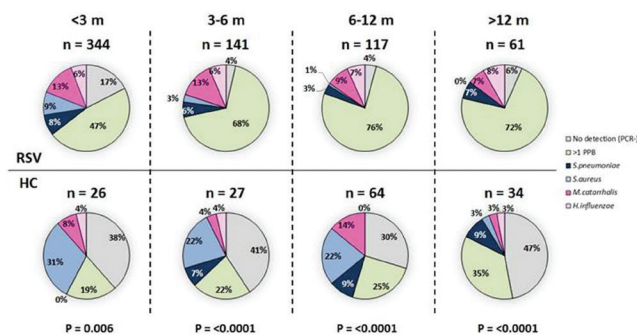

Figure 2. Frequency of NP bacterial detection in infants with RSV and healthy controls stratified by age. HC: Healthy control; PPB: Potentially pathogenic bacteria. Statistical comparisons by Chi-square test.

119. Prospective Validation of a 3-Gene Signature for Tuberculosis Diagnosis, Predicting Progression and Evaluating Treatment Response

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Background. The World Health Organization (WHO) has identified the need for a nonsputum-based triage test for tuberculosis (TB) that can be used to identify those who need further testing to identify active disease. We investigated whether our previously described 3-gene TB score could identify individuals with active tuberculosis (ATB) prior to seeking care ("active case detection") and how the 3-gene TB score correlated with the timing of disease onset, disease severity, and response to treatment.

Methods. This study consisted of a prospective nested case–control trial, Brazil Active Screening Study (BASS; 2016), and re-analysis of data from 2 prospective cohort studies, the Adolescent Cohort Study (ACS; 2005–2007), and the Catalysis Treatment Response Cohort (CTRC; 2010–2013). The BASS case–control subcohort contained 81 adults (ages 20–72 years, 33 ATB, 48 controls). The ACS contained 153 adolescents (ages 12–18 years, 46 ATB, 107 LTBI). The CTRC-contained 138 adults (ages 17–67 years, 100 ATB, 17 other lung disease patients, 21 healthy controls).

Results. The 3-gene TB score diagnosed ATB patients with high accuracy: BASS cohort AUC = 0.87 (95% CI = 0.82–0.91, Figure 1A), ACS cohort AUC = 0.86 (95% CI = 0.76–0.97, Figure 1B), and CTRC AUC = 0.93 (95% CI = 0.88–0.97). In the ACS, the 3-gene TB score predicted progression from LTBI to ATB 6 months prior to positive sputum test (AUC = 0.86; 95% CI = 0.79–0.92, Figure 1B). In the CTRC, the 3-gene TB score correlated with glycolytic activity ratio of PET-CT at baseline (correlation = 0.54, $P = 3.98 \times 10^{-8}$, Figure 1C) and at the end of treatment (correlation = −0.408, $P = 3.72 \times 10^{-5}$). In the CTRC, the 3-gene TB score at baseline predicted the likelihood of prolonged sputum positivity following treatment initiation and treatment response at 6 months ($P = 3.6 \times 10^{-5}$). Collectively, across all cohorts, the 3-gene TB score identified ATB patients with 90% sensitivity and 70% specificity, and had 99% negative predictive value (NPV) at 5% prevalence.

Conclusion. Across 3 independent prospective cohorts, the 3-gene TB score closely approaches the WHO target product profile benchmarks for non-sputum–based triage test at high NPV. These performance characteristics make it a potential test for ruling out ATB and for monitoring disease status.
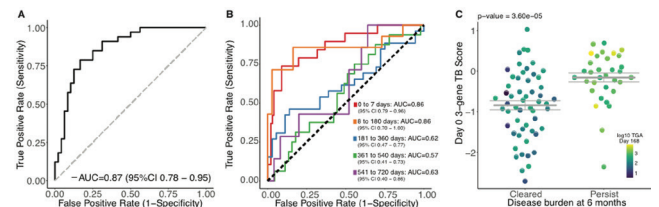
120. A Randomized Double-blind Trial Assessing the Efficacy of M72/AS01_E Vaccine Against Pulmonary Tuberculosis Disease in Adults With Latent *Mycobacterium tuberculosis* Infection

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Background. An effective tuberculosis (TB) vaccine is urgently needed to support the End TB Strategy to reduce the number of new TB cases by 80% by 2030. M72/AS01$_E$ candidate vaccine is an adjuvanted recombinant fusion protein derived from *Mycobacterium tuberculosis* Mtb32A and Mtb39A proteins.

Methods. We conducted a randomized, double-blind, placebo-controlled phase 2b trial (NCT01755598) in Southern and Eastern Africa to assess M72/AS01$_E$'s efficacy against bacteriologically confirmed pulmonary TB disease in HIV-seronegative (HIV−) adults aged 18–50 years infected with Mtb (defined by a positive IFN-γ release assay). Participants were randomized 1:1 to receive M72/AS01$_E$ or placebo at day D0 and D30. Reactogenicity, safety, immunogenicity were assessed, and incident TB disease measured from D30 post-dose 2 up to ≥24 months for this analysis (follow-up ongoing up to 37 months). Efficacy against various TB disease case definitions (Figure 1) was estimated. Primary objective: efficacy against culture- or PCR-confirmed pulmonary TB disease in HIV− adults (case definition 1; success criterion: lower limit of 90% 2-sided CI >0%, power: 80%).

Results. Demographic characteristics were similar between M72/AS01$_E$ (1786) and placebo (1787) recipients. Efficacy against pulmonary TB disease case definition 1 was 54.0% (90% CI: 13.9, 75.4; $P = 0.042$); efficacy against other case definitions and a sensitivity analysis are shown in Figure 1. Leading solicited symptoms were pain, fatigue, and headache (Figure 2). In all recipients, unsolicited symptoms (D0–29) were more frequent after M72/AS01$_E$ (67.4%) than placebo (45.4%), mainly attributable to increased injection site reactions and flu-like symptoms. Serious adverse events (D0–month 7) incidences were similar between groups (M72/AS01$_E$: 1.6%; placebo: 1.8%). During the study, 24 adults died (14 due to traumatic events); all deaths were unrelated to the trial.

Conclusion. M72/AS01$_E$ presents a clinically acceptable safety profile and significantly reduces bacteriologically confirmed pulmonary TB disease incidence in HIV− adults with latent Mtb infection.

Figure 1. Incidence rates and vaccine efficacy against TB disease using unadjusted Cox regression model (per-protocol cohort for efficacy)
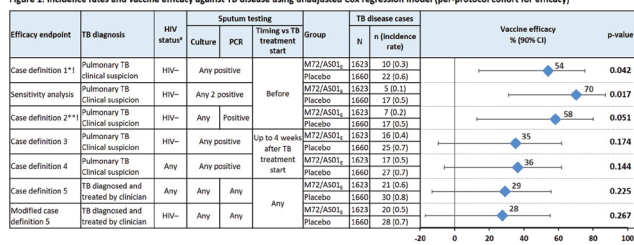
Figure 2. Overall incidence of solicited symptoms (days 0–6, total vaccinated cohort subset)
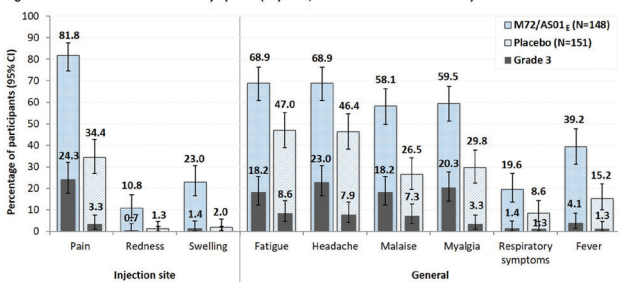
N, number of participants from total vaccinated cohort included in the subset for reactogenicity assessment; CI, confidence interval, represented as error bars; grade 3, significant pain at rest, preventing everyday activity (pain), diameter >100 mm (redness/swelling), symptom preventing everyday activity (fatigue, headache, malaise, myalgia, respiratory symptoms [cough, blood in sputum, purulent sputum, shortness of breath or difficulties breathing, chestwall pain]), axillary temperature >39.5 °C (fever); any fever, axillary temperature ≥37.5 °C.

121. Improving Predictive Value of Phase 2a TB Drug Development Models Through PET/CT Imaging (NexGen EBA)

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Background. Current Phase 2a methods in tuberculosis (TB) drug development are severely limited in capturing a drug candidate's sterilizing activity (ability to prevent TB relapse). We hypothesize that sputum-based measurements of current methods fail to capture drug activity in deep TB lesion compartments, where recalcitrant TB populations are sequestered. In our recent marmoset study, we found complementary 14-day PET/CT delta signatures across different TB lesion compartments that distinguish drugs with long-term sterilizing activity (e.g., rifampin and pyrazinamide) versus drugs with primarily early bactericidal activity (e.g., isoniazid) (Figure 1). We proceeded to evaluate this novel PET/CT Phase 2a approach among TB patients, benchmarked by drugs that are well-characterized clinically and pharmacokinetically.

Methods. HIV-negative patients with smear-positive pulmonary tuberculosis from Cape Town, South Africa were enrolled and randomized to receive a single drug [isoniazid (H), rifampin (R), pyrazinamide (Z), moxifloxacin (M)], a 2-drug regimen (HZ, RZ), or a 4-drug regimen (HRZE, MRZE) for 14 days in an inpatient facility. Primary data points were PET/CT scans evaluated at pretreatment baseline and treatment day 14 (and day 28 in the HRZE arm), and daily overnight sputum for early bactericidal activity measurements.
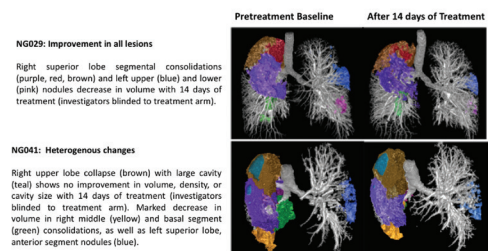
Results. From December 2015 to September 2017, 160 participants completed the study, from whom 340 PET/CT scans and 2,238 overnight sputum samples were collected. PET/CT scans from participants demonstrate diversity of lesion architecture and inter-individual variation in PET/CT changes over 14 days of treatment (Figure 2). A preliminary computational algorithm and first- and second-order PET/CT statistics have been developed for initial segmentation and TB lesion categorization of all study scans. Derivation of radiologic signatures by analysis of 14-day PET/CT changes across each lesion type is ongoing; blinded prediction of each participant's treatment arm based on these signatures is expected by third-quarter 2018.

Conclusion. If successful, these signatures may be applied within a 14-day Phase 2a framework to evaluate new TB drug candidates and construct TB drug regimens with complementary lesion pharmacokinetics.

Figure 1. 14-day PET/CT changes in marmosets necropsied at end of treatment.

Figure 2. Sample variation in PET/CT changes between study participants and TB lesions, reflecting different treatment effects.

Pretreatment Baseline — After 14 days of Treatment

NG029: Improvement in all lesions
Right superior lobe segmental consolidations (purple, red, brown) and left upper (blue) and lower (pink) nodules decrease in volume with 14 days of treatment (investigators blinded to treatment arm).

NG041: Heterogenous changes
Right upper lobe collapse (brown) with large cavity (teal) shows no improvement in volume, density, or cavity size with 14 days of treatment (investigators blinded to treatment arm). Marked decrease in volume in right middle (yellow) and basal segment (green) consolidations, as well as left superior lobe, anterior segment nodules (blue).