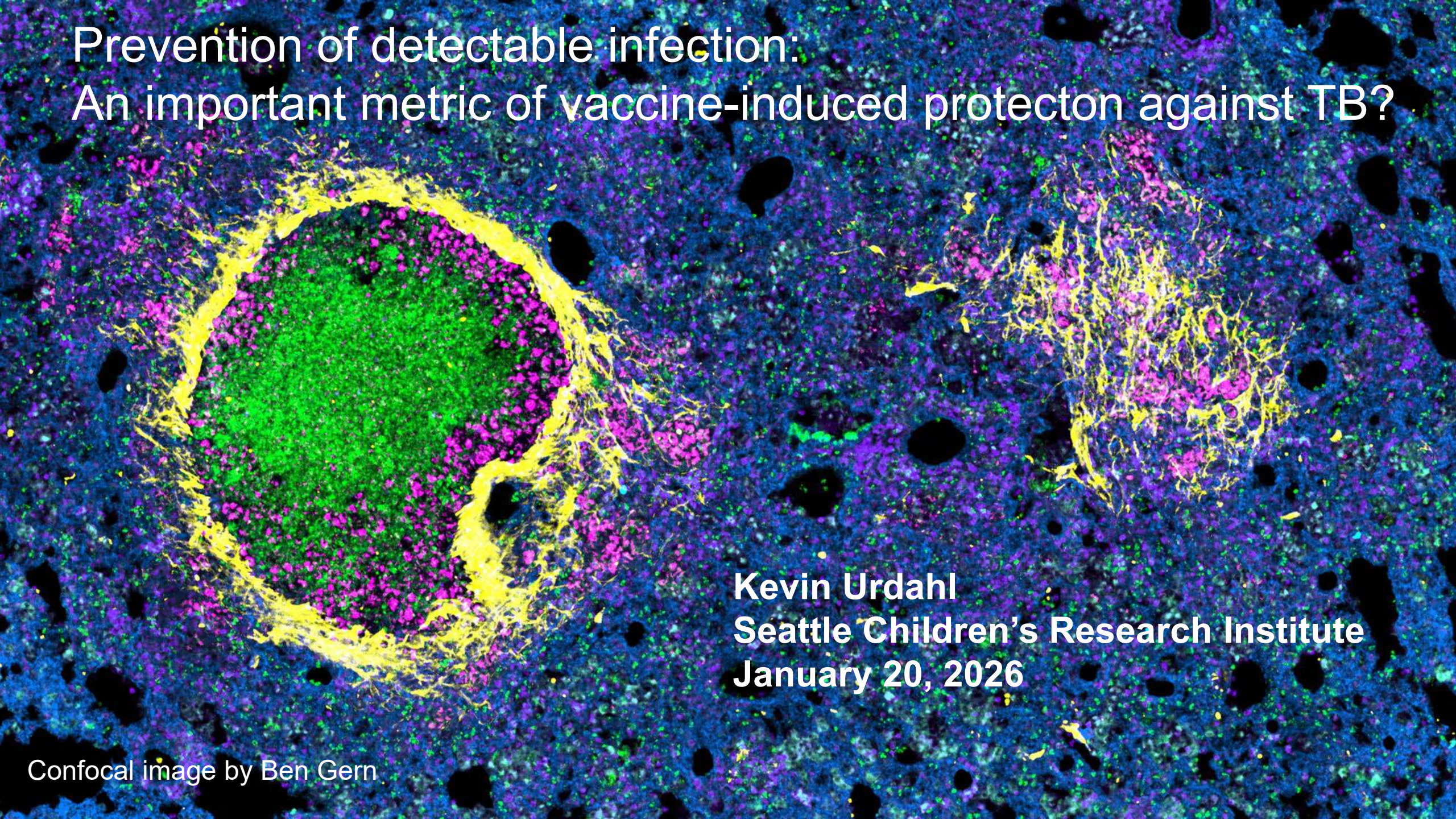
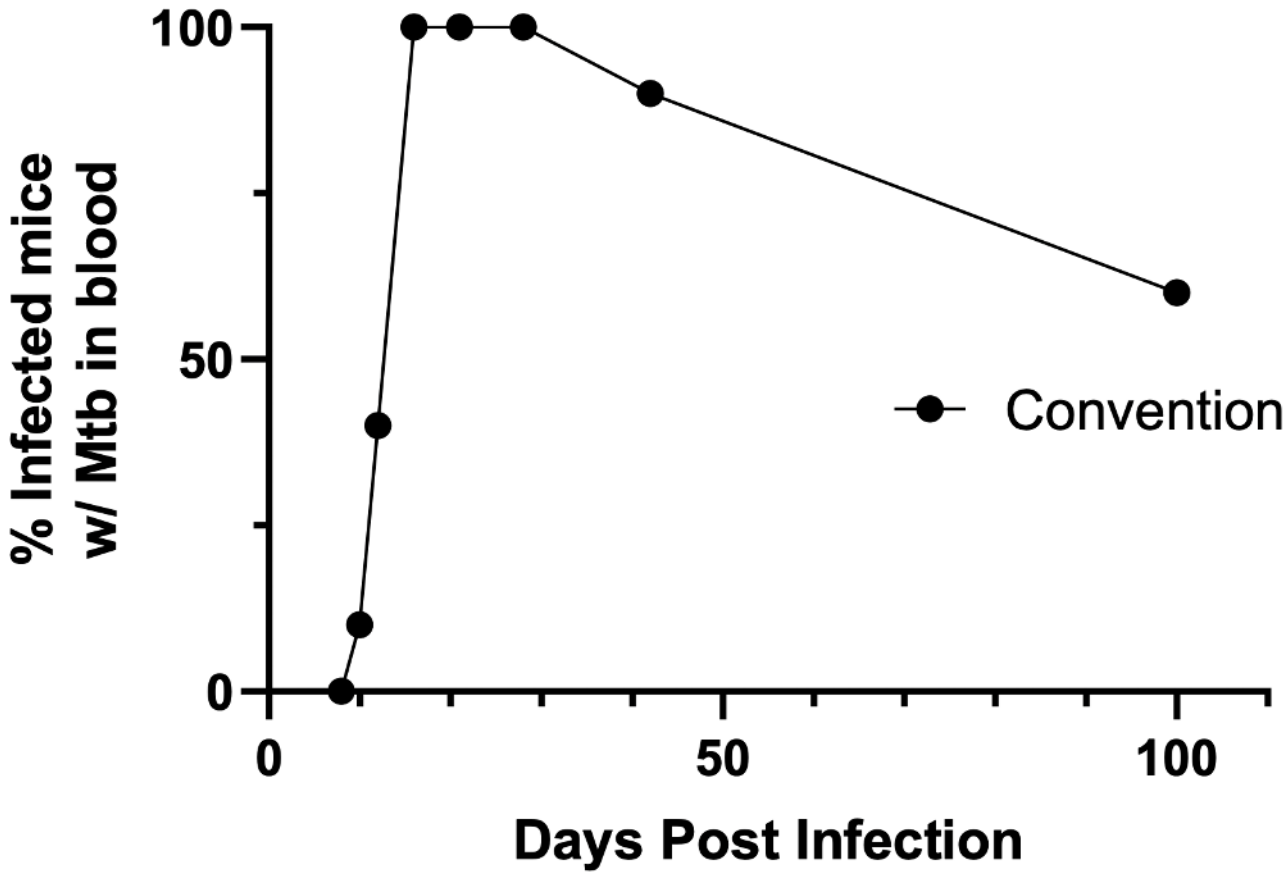
Prevention of detectable infection:
An important metric of vaccine-induced protecton against TB?

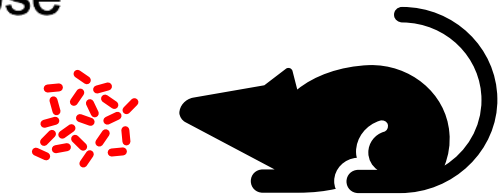


Kevin Urdahl
Seattle Children's Research Institute
January 20, 2026

Confocal image by Ben Gern

Standard TB mouse model is one of systemic infection and failing immunity

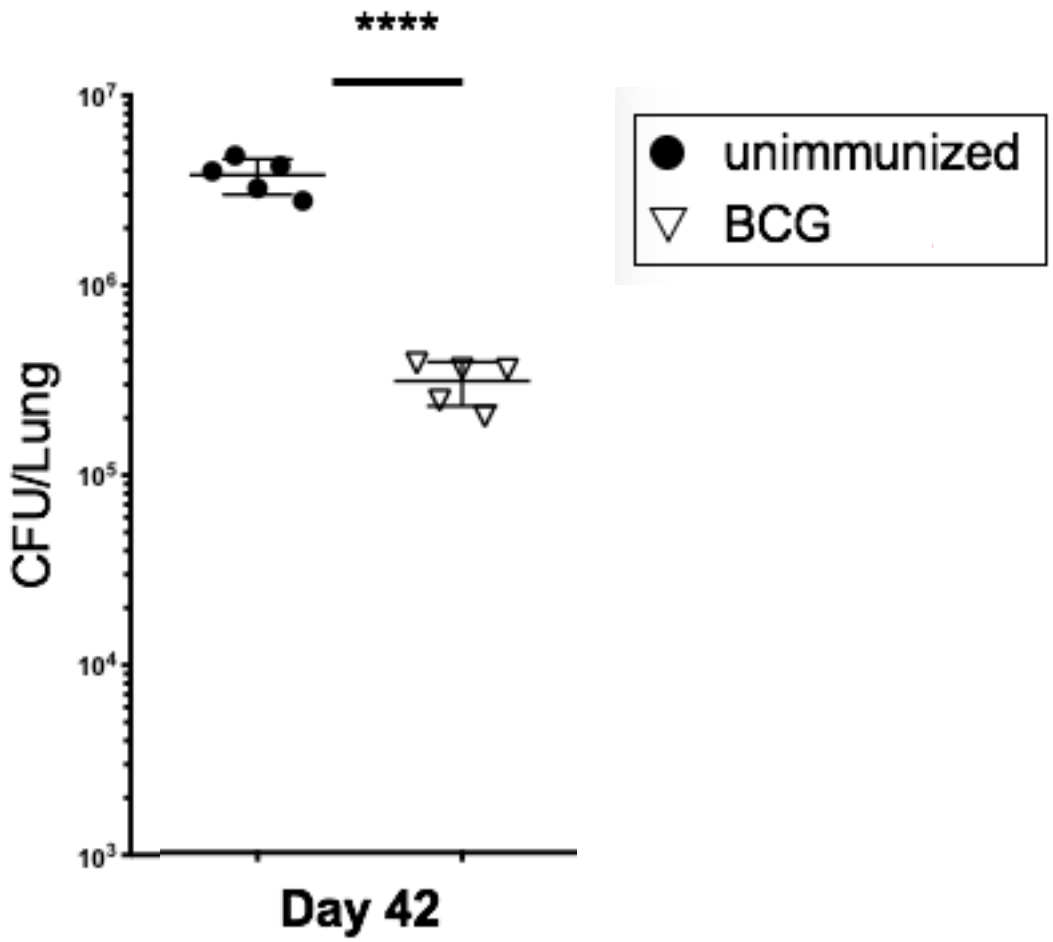




50-100 CFU

Lauren Cross, unpublished

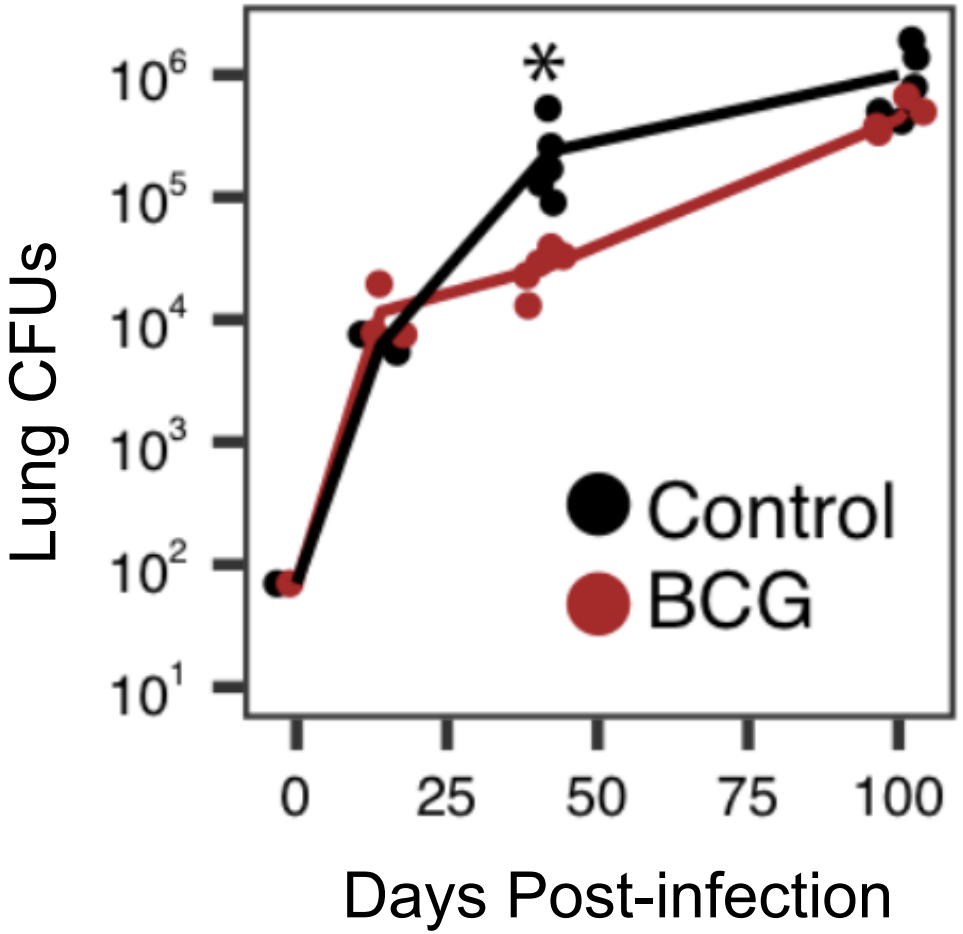
BCG-mediated immunity after conventional dose Mtb challenge (~50 CFU)



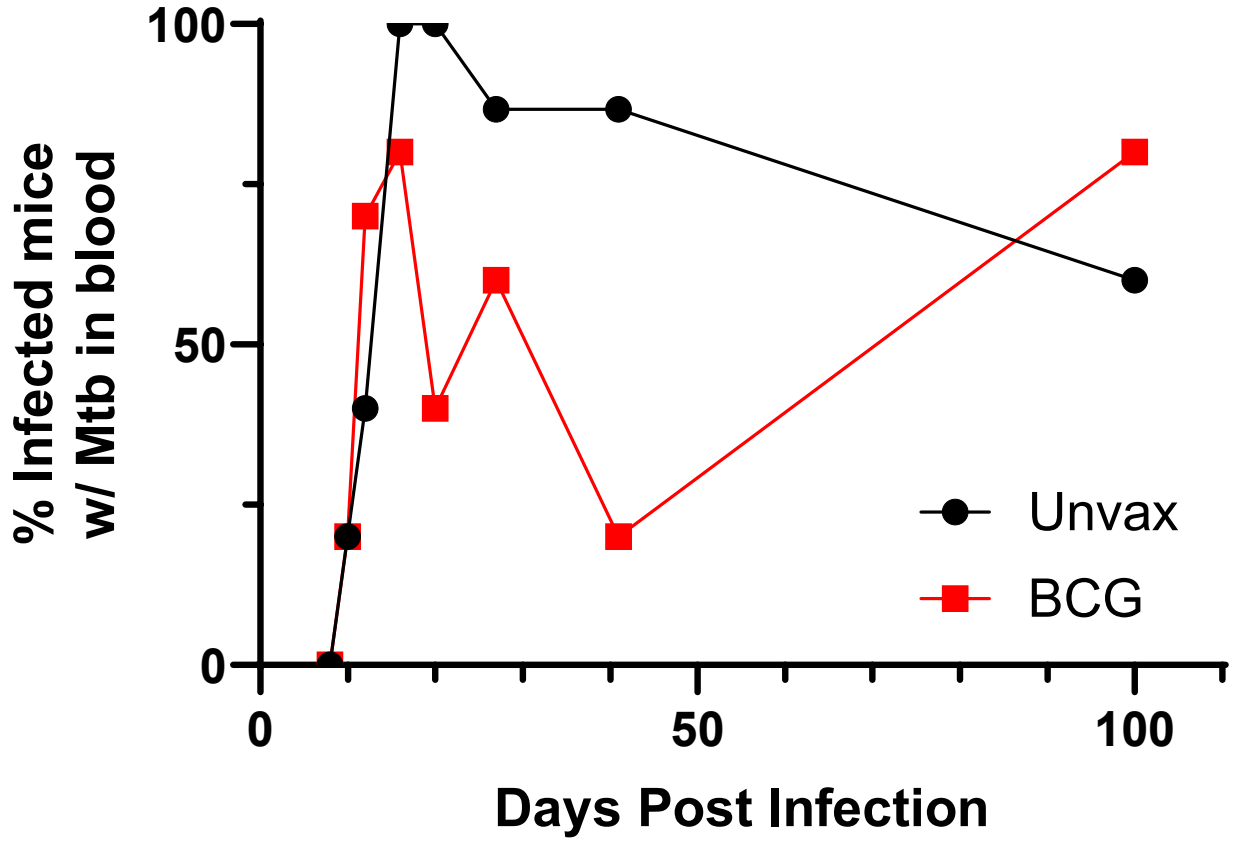
Courtney Plumlee

The ability of BCG to restrict Mtb infection after a 50-100 CFU Mtb challenge dose is transient; mice eventually die of TB

"The Dirty Secret"

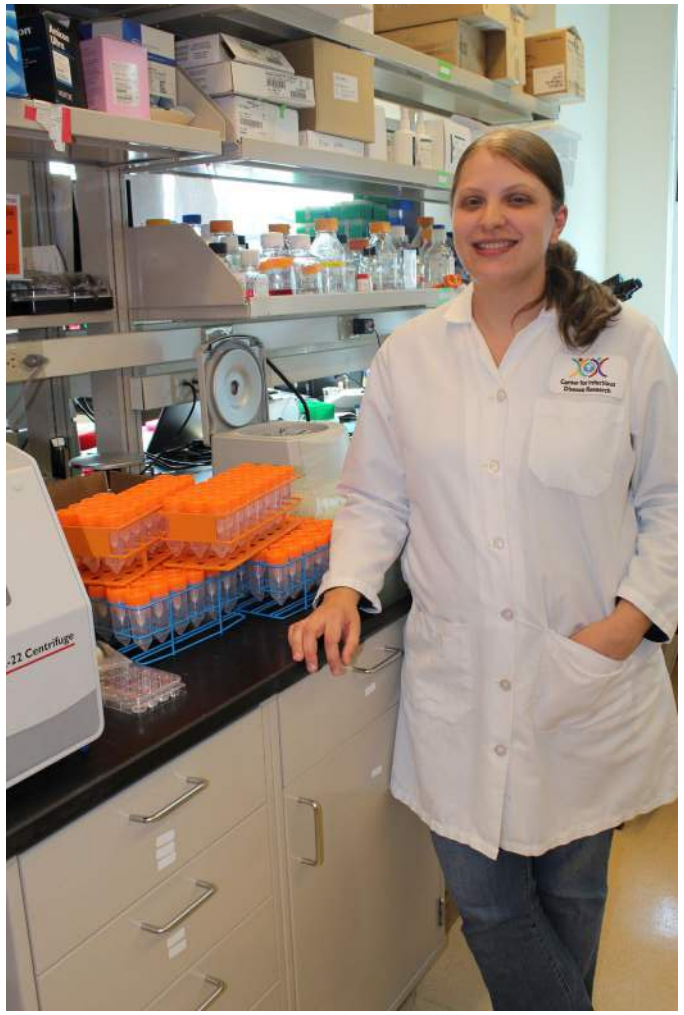


Johannes Nemeth

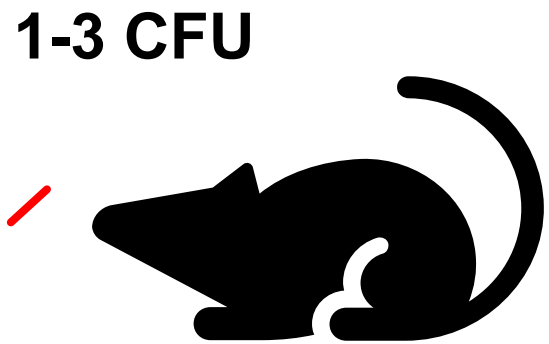


Lauren Cross

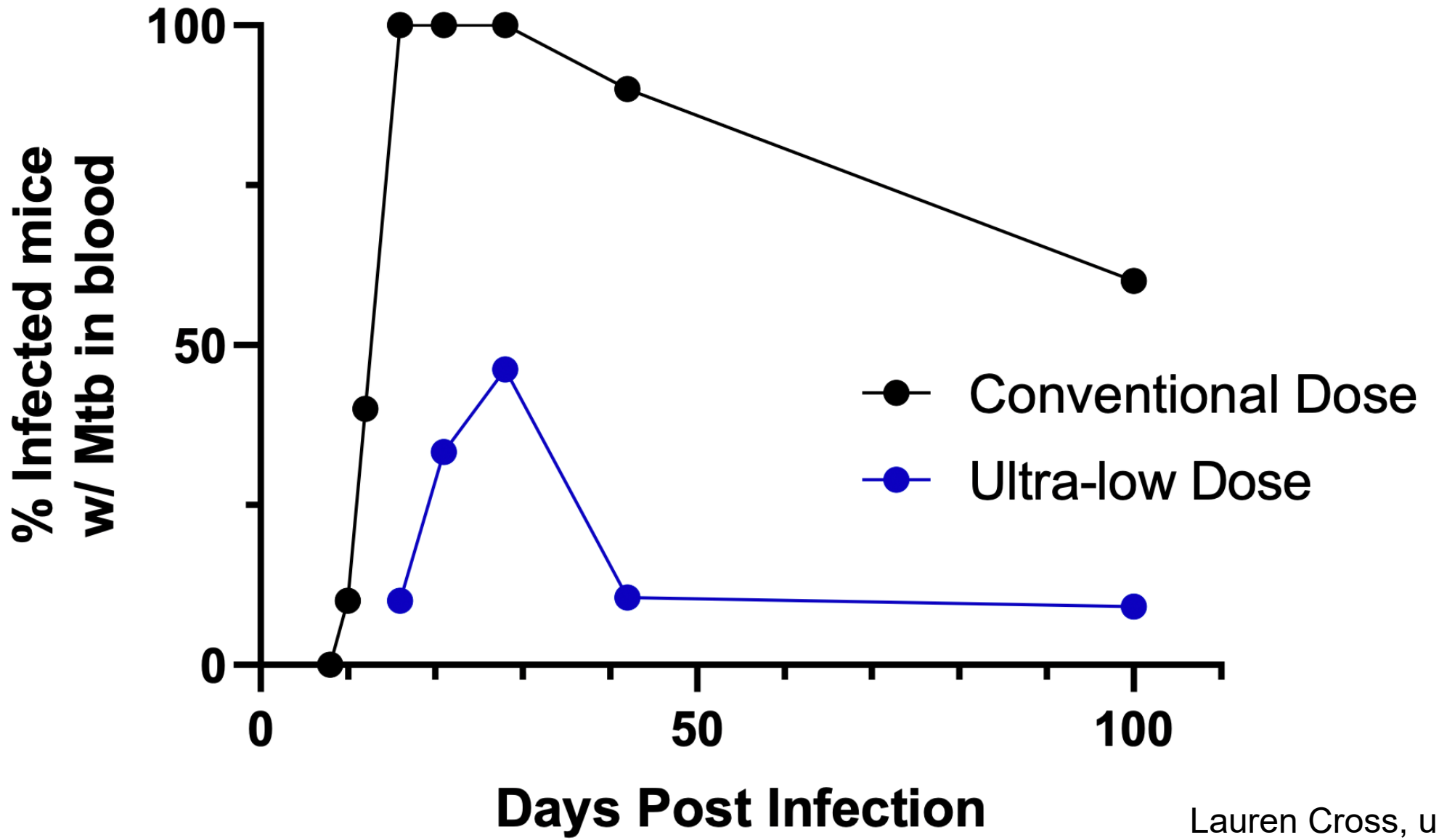
Ultra-low dose infection (ULD)



Courtney Plumlee



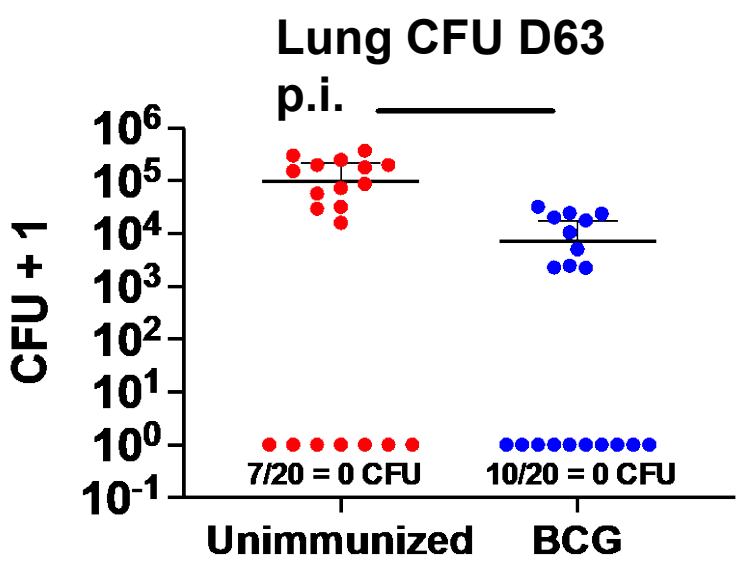
Bacteremia is usually transient in ULD-infected mice



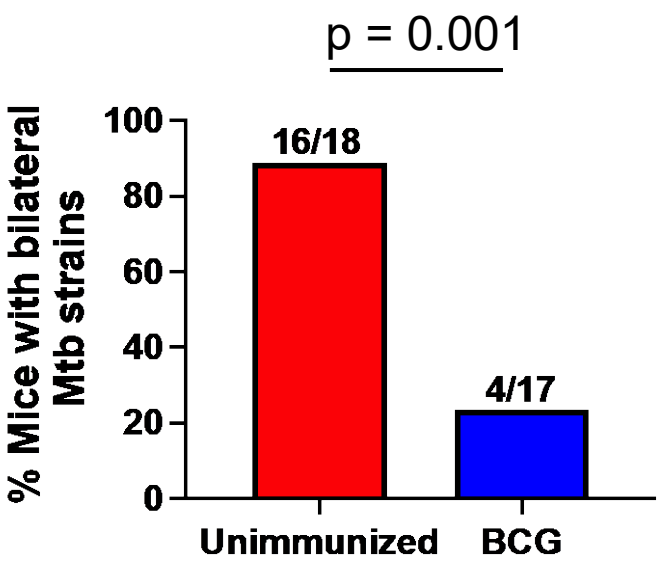
Lauren Cross, unpublished

Three metrics of vaccine-mediated protection can be assessed in the ULD model

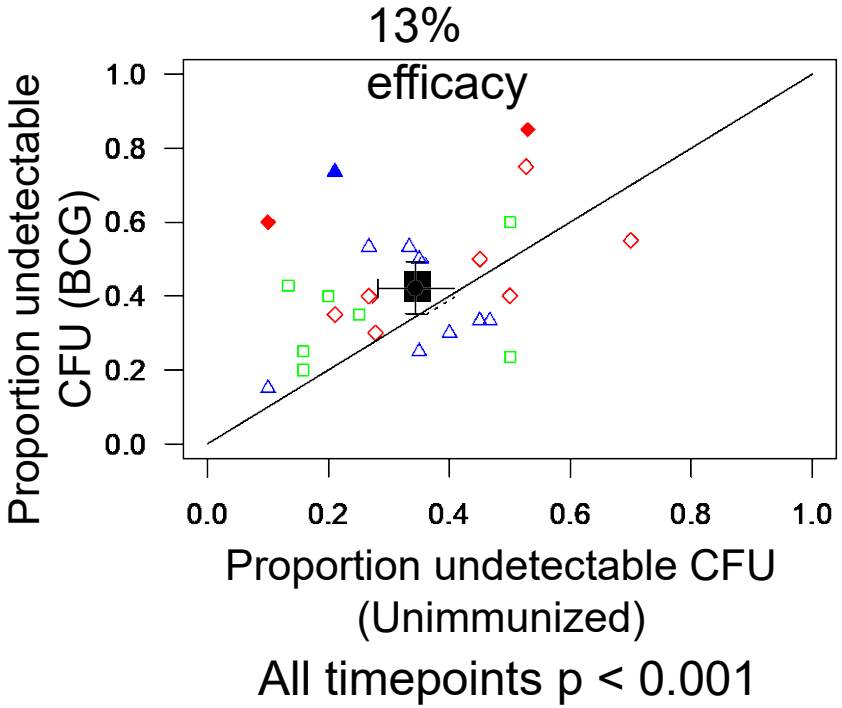
Reduction in overall lung burden



Prevention of dissemination to the contralateral lung



Prevention of detectable infection*



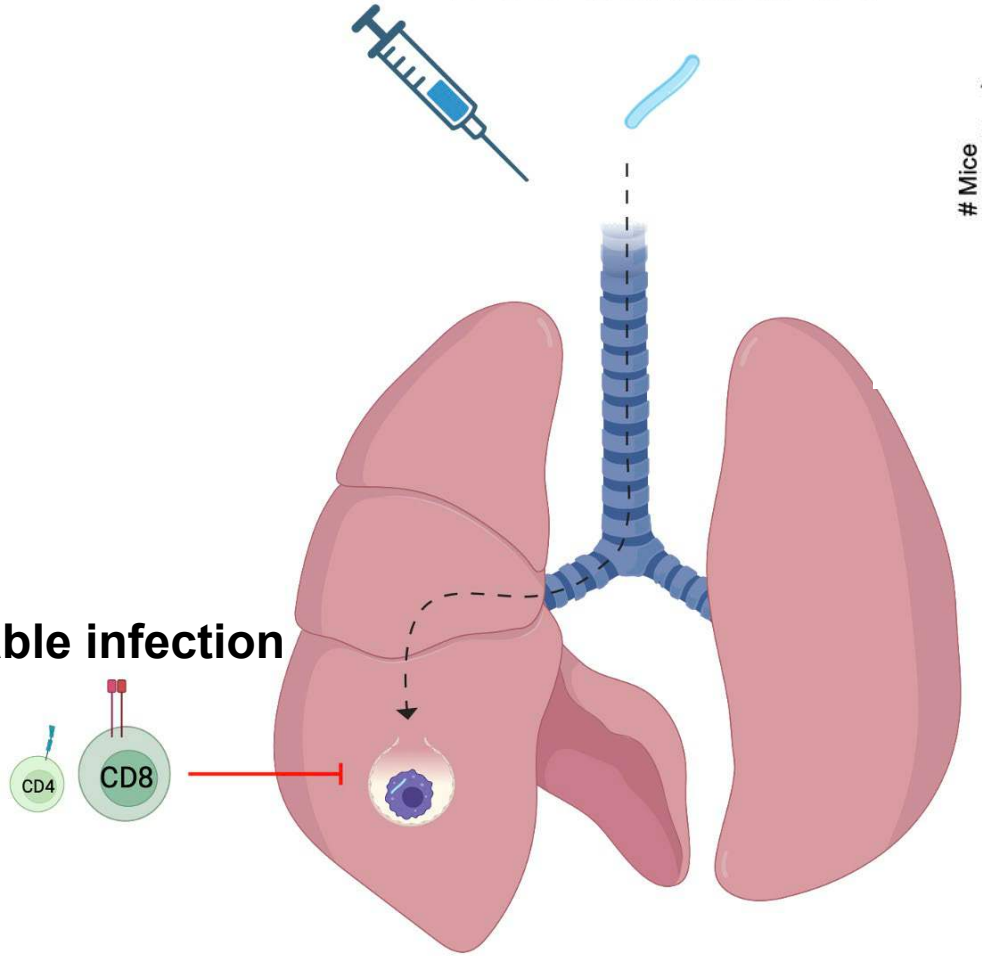
All timepoints $p < 0.001$

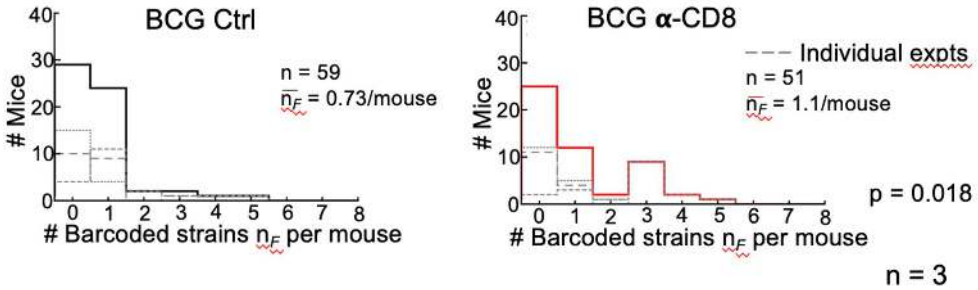
Plumlee, C.R., Barrett, H.W., et al, 2023, PLoS Pathogens. PMID: 38011264; PMCID: PMC10703413.

Could mechanisms of protective immunity differ after a physiologic vs. supra-physiologic dose challenge?

A role for CD8-mediated immunity in preventing detectable infection

BCG-immunized



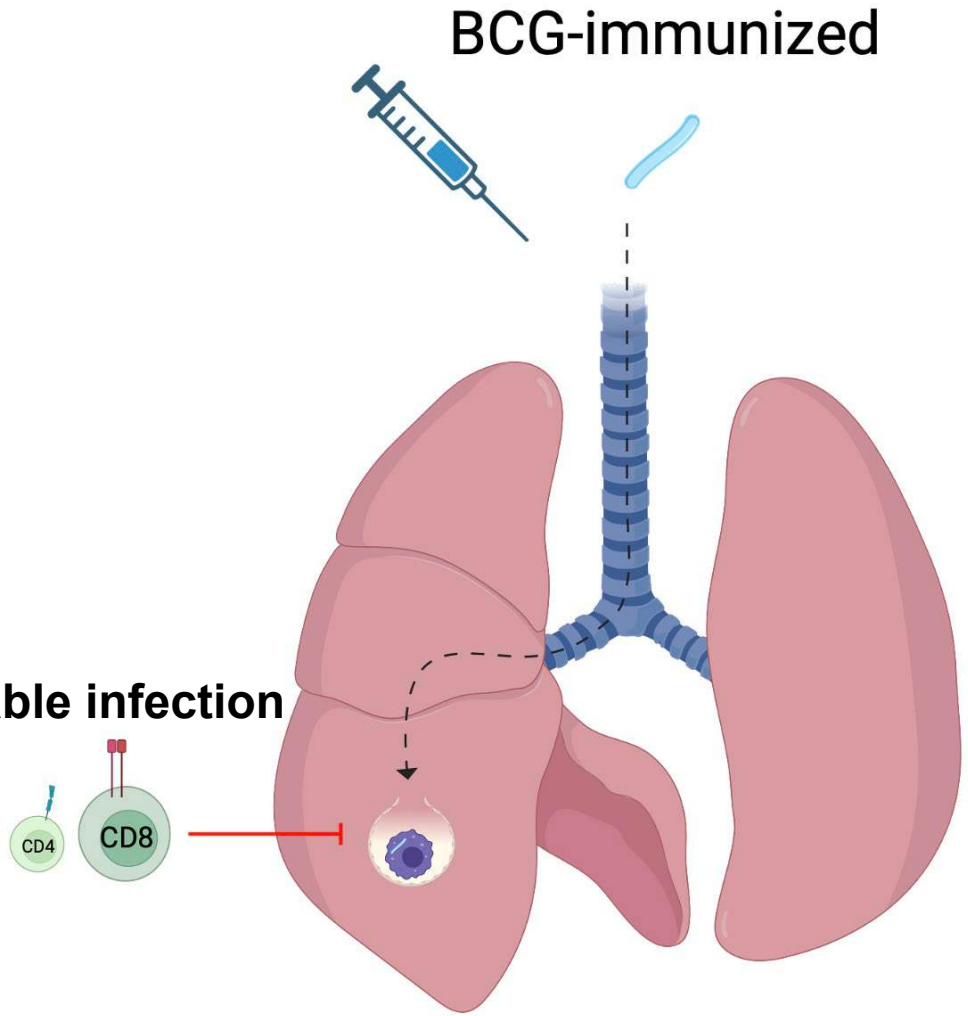


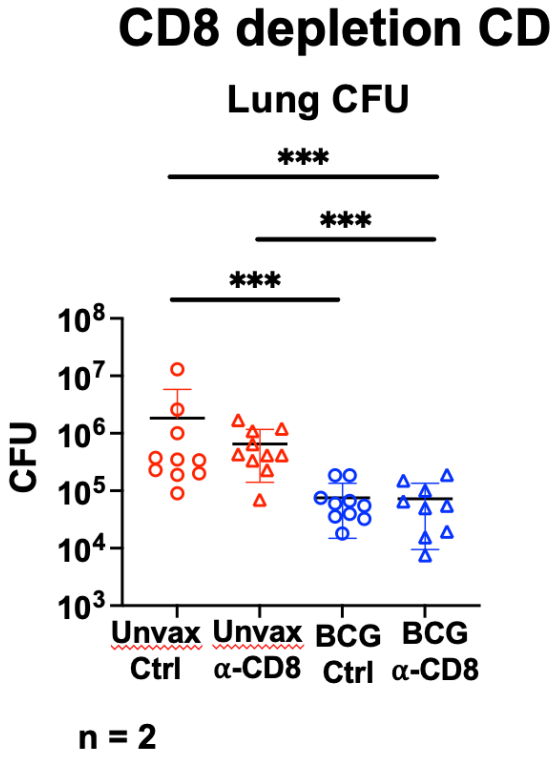
Holly Barrett, unpublished

1. Prevention of detectable infection

A role for CD8-mediated immunity is revealed only with ULD challenge

1. Prevention of detectable infection

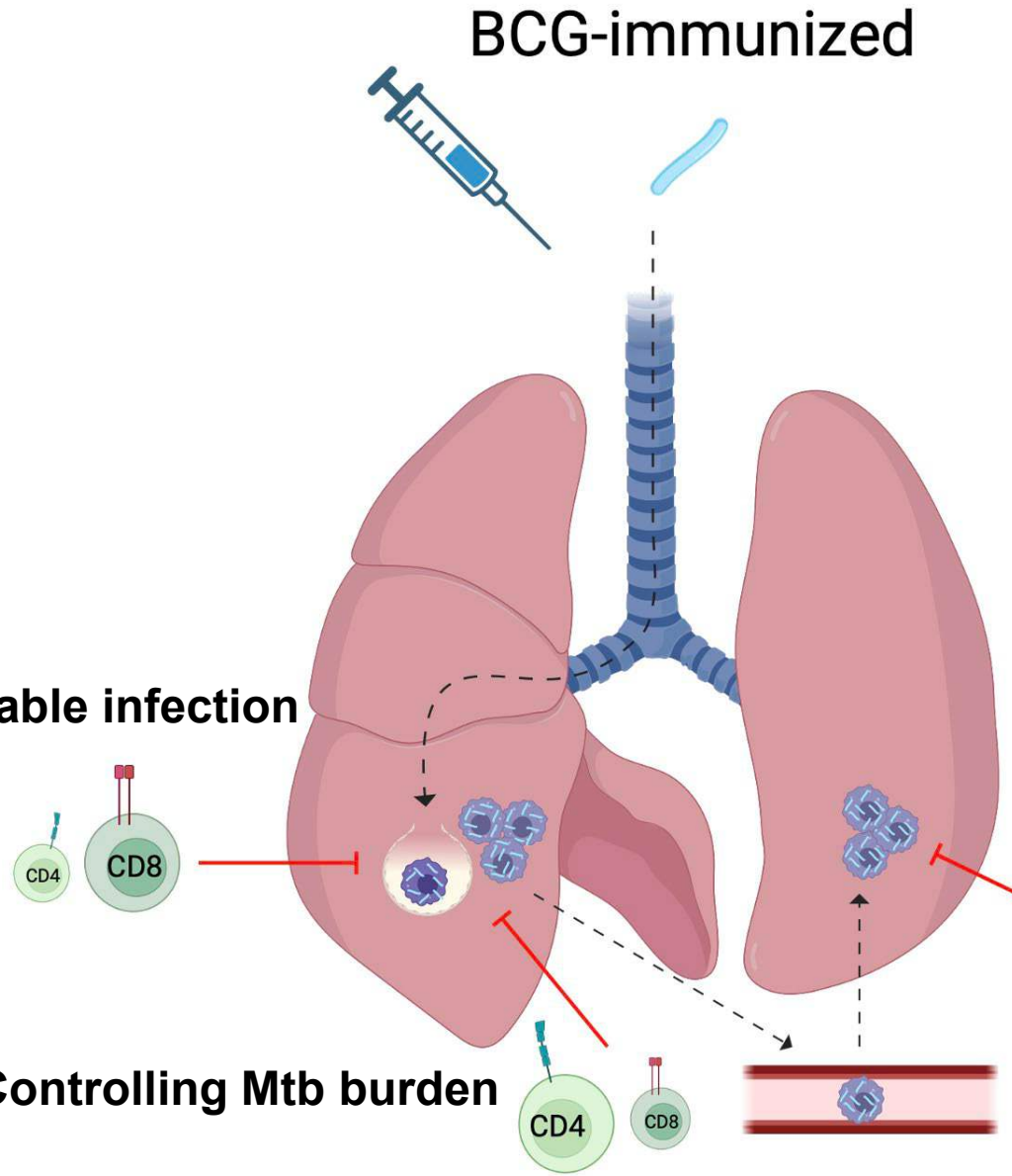




n = 2

Holly Barrett, unpublished

BCG induced CD4 and CD8 T cells play distinct protective roles



Holly Barrett, unpublished

1. Prevention of detectable infection

2. Controlling Mtb burden

3. Prevention of dissemination

Prevention of detectable infection is a distinct metric from reduction of bacterial burden

Lung bacterial burdens

Prevention of detectable infection

(Compiled data from 3 experiments,
20 mice/group/experiment)

Vaccine X

Vaccine X

Sara Cohen and Courtney Plumlee, unpublished

Prevention of detectable infection is a distinct metric from reduction of bacterial burden

Lung Bacterial Burden
vs
Percent Detectable Infection

Comparison of BCG,
3 mRNA vaccines,
1 adjuvanted protein vaccine,
and 1 attenuated adenoviral vaccine.

(all vaccines tested at least 3 times).

Not correlated.

May even be anti-correlated!

Sara Cohen and Courtney Plumlee, unpublished

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- One approach - Test immunogenicity in a handful of strains (e.g., B6, Balb/c, and C3H), then use F1s for protection studies.

Comparing advantages: 1 CFU vs. 100 CFU challenge dose

1 CFU	100 CFU
More physiologic	Less expensive
Reveals protection mediated by aspects of immunity that cannot be assessed with 100 CFU challenge (e.g., role of CD8 T cells)	Requires fewer mice
Can measure **prevention of detectable infection**, a metric that often does not correlate with reduction in bacterial burdens	More labs currently able to perform; more accessible to vaccine developers
Bigger window to discern efficacy differences between vaccine candidates	More feasible for use with diversity outbred mice, or for testing multiple genetic backgrounds

Prevention of infection cannot be measured in humans.

Most TB disease in TB endemic regions likely due to new infection. Thus, prevention of new infection may be best way to prevent disease.

Yet may be an important metric of vaccine-induced protection in animal models.