changes in secretion of Tissue Inhibitors of Metalloprotei-
nases. This resulted in collagen degradation as detected
by confocal microscopy. In addition, neutrophil and mono-
cyte transmigration increased 60 and 80% respectively.
Treatment with Ro32-3555 abolished TB-dependent BBB
breakdown. The TJPs occludin, claudin-5 and ZO-1 were
upregulated by CoMtb stimulation and this too was inhibited
by MMP blockade. Leucocyte migration reverted to control
levels with addition of Ro32-3555.

In summary, TB-dependent upregulation of MMP secre-
tion causes breakdown of tissue and TJPs facilitating
leucocyte leucocyte migration. Such MMP-driven BBB break-
down may have a key role in driving CNS inflammation in TB.

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CO-OPERATION DURING STAPHYLOCOCCUS
AUREUS PATHOGENESIS

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Abstract

Introduction: Staphylococcus aureus is an invasive human
pathogen associated with significant mortality. Host-path-
ogen dynamics during infection are poorly understood but
recent work demonstrates that with high dose inocula, an
immunological bottleneck allows clonal expansion of only
a few bacteria, which go on to cause host damage.

Methods: To interrogate this clonal phenomenon further, mixed strain inocula including varying ratios of
virulent and either avirulent bacteria or bacterial cell com-
ponents, were tested in the zebrafish embryo model of sys-
temic infection.

Results: The virulent strain S. aureus, SH1000 at high
dose (1500 CFU) causes 50% embryo mortality. At low infec-
tive dose (150 CFU), S. aureus SH1000 is unable to cause sig-
nificant mortality. Similarly, a high dose of either nonpathogenic bacterium such as Micrococcus luteus,
attenuated S. aureus mutants or separated cell wall compo-
nent, peptidoglycan, were unable to kill. However, when
each of these was co-injected with the low infective dose
of virulent S. aureus SH1000, significant mortality was
observed.

Discussion: Avirulent bacteria do not proliferate within
the host, yet these so-called ‘bystanders’ permit low-dose
S. aureus SH1000 to undergo clonal expansion and kill the
host, far in excess of that seen when low dose is injected
alone. Moreover, the essential cell wall component, pepti-
doglycan, was also able to augment killing of zebrafish em-
bryos. Further analysis of this synergistic interaction may
help us unravel mechanisms by which co-operation be-
tween bacteria affects pathogenesis. This has important
clinical significance as a polymicrobial presence is likely
to occur during human infection.

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IN TB PATIENTS FROM PERUVIAN SHANTYTOWNS,
CATASTROPHIC COSTS EXPLAIN AS MANY
ADVERSE TB OUTCOMES AS MDR TB

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Abstract

Introduction: Poverty is the principal determinant of TB
disease worldwide. However, global funding predominantly
focuses on biomedical rather than socioeconomic interven-
tions to control TB. In order to inform the design and imple-
mentation of a complex social protection intervention to
control TB, we measured catastrophic costs of “free” TB
 treatment and their impact on TB outcome.

Methods: 876 TB patients (11% MDR) were prospectively
recruited in 16 shantytowns in Lima, Peru. Patient house-
holds’ TB-related expenses were recorded throughout
 treatment. Catastrophic costs were defined as the threshold above which total household expenses as a propor-
tion of annual income were most strongly associated
with adverse TB outcome.

Results: Total costs ≥20% of household annual income
were defined as catastrophic and incurred by 345 households
(39%). Catastrophic costs were independently associated
with adverse outcome (OR = 1.7, all p < 0.01) and explained
as many adverse outcomes as MDR TB (PAF 18% versus 20%).

Conclusions: Despite free TB care, having TB disease
was expensive for impoverished TB patients in Peru.
Removing catastrophic costs could have potentially avoided
as many adverse TB outcomes as eradicating MDR TB in this
cohort. These findings have informed the WHO’s post-2015
global TB strategy which explicitly identifies mitigation of
catastrophic costs as a key pillar of the future global
response to TB. Consequently, we have since designed, im-
plemented, and refined one of the world’s first TB-specific
social protection interventions incorporating conditional
cash transfers: the Community Randomized Evaluation of
a Socioeconomic Intervention to Prevent TB (CRESIPT),
which is now ready for further impact evaluation.

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MONOCYTE DEACTIVATION IS ASSOCIATED WITH
MORTALITY IN HIV-ASSOCIATED CRYPTOCOCCAL
MENINGITIS

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