changes in secretion of Tissue Inhibitors of Metalloproteinases. This resulted in collagen degradation as detected by confocal microscopy. In addition, neutrophil and monocyte transmigration increased 60 and 80% respectively. Treatment with Ro32-3555 abolished TB-dependent BBB disruption. The TJPs occludin, claudin-5 and ZO-1 were degraded 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 secretion causes breakdown of tissue and TJPs facilitating leukocyte leucocyte migration. Such MMP-driven BBB breakdown 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-pathogen 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 components, were tested in the zebrafish embryo model of systemic infection.

**Results**: The virulent strain *S. aureus*, SH1000 at high dose (1500 CFU) causes 50% embryo mortality. At low infective dose (150 CFU), *S. aureus* SH1000 is unable to cause significant mortality. Similarly, a high dose of either nonpathogenic bacterium such as *Micrococcus luteus*, attenuated *S. aureus* mutants or separated cell wall component, 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, peptidoglycan, was also able to augment killing of zebrafish embryos. Further analysis of this synergistic interaction may help us unravel mechanisms by which co-operation between 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 interventions to control TB. In order to inform the design and implementation 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 households' TB-related expenses were recorded throughout treatment. Catastrophic costs were defined as the threshold above which total household expenses as a proportion of annual income were most strongly associated with adverse TB outcome.

**Results**: Total costs $\geq$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, implemented, 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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