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INFECTIOUS DISEASE

The tolerance of superspreaders

'Superspreaders' refer to a minority of infected hosts in a population that is responsible for the majority of pathogen transmission events. Monack and colleagues describe a disease-associated tolerance mechanism that is specific to superspreaders and enables the host to tolerate inflammation associated with oral antibiotic treatment, while continuing pathogen transmission.

An infected host can respond to the pathogen by two types of defence mechanism — resistance (which controls pathogen invasion and replication) and tolerance (which limits the health impact of a given pathogen burden). Using a mouse model of *Salmonella enterica* subsp. *enterica* serovar Typhimurium infection, previous studies by this group have shown that superspreaders shed high levels of the bacteria but remain asymptomatic, which suggests that superspreaders are tolerant to the pathogen.

In this study, the authors found that antibiotic treatment of non-superspreaders rapidly increased their levels of faecal *S.* Typhimurium to the same levels seen in superspreaders, and resulted in increased weight loss and in some cases death. By contrast, superspreaders did not lose weight and remained asymptomatic following treatment with oral antibiotics. Of note, the bacterial burden in systemic tissues was similar between antibiotic-treated superspreaders and non-superspreaders. These data suggest that superspreaders are protected from antibiotic-induced gastrointestinal disruptions.

Further analysis showed that antibiotic-treated moribund non-superspreaders had high levels of the pro-inflammatory cytokines interleukin-1β (IL-1β), IL-6 and tumour necrosis factor (TNF) in their serum and intestines. In addition, the expression of several acute-phase proteins positively correlated with weight loss in antibiotic-treated non-superspreaders. Antibiotic-treated non-superspreaders also had higher numbers of inflammatory monocytes and neutrophils in their spleen, but not intestines, compared with antibiotic-treated superspreaders. Thus, the increased morbidity in antibiotic-treated non-superspreaders is linked to activation of the acute-phase response and high myeloid cell numbers in the spleen.

Finally, neutralization of IL-1β and TNF in antibiotic-treated non-superspreaders prevented significant weight loss and myeloid cell accumulation in the spleen, without affecting systemic or faecal *S.* Typhimurium levels. These data indicate that neutralization of inflammatory cytokines increases tolerance in antibiotic-treated non-superspreaders.

Taken together, these data suggest that superspreaders are uniquely able to tolerate antibiotic-induced intestinal perturbations due to a reduced inflammatory response, although the underlying mechanisms of this reduced response remain to be determined. This study also suggests that, in at least some disease settings, antibiotics could exacerbate disease spread and symptoms.

Olive Leavy

> "superspreaders are protected from antibiotic-induced gastrointestinal disruptions"

ORIGINAL RESEARCH PAPER Gopinath, S. *et al.* Role of disease-associated tolerance in infectious superspreaders. *Proc. Natl Acad. Sci. USA* **111**, 15780–15785 (2014)