Review of: "Phage therapy potentiates second-line antibiotic treatment against pneumonic plague"

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This is a very clear and well-written study exploring the utility of bacteriophage therapy in treating pneumonic plague. Pulmonary infection with *Yersinia pestis* results in pneumonic plague, a severe and rapidly-progressing pneumonia that is almost always fatal. Even in the event of antibiotic delivery, therapy must be initiated within a day after the onset of symptoms to be effective. The authors highlight both the emergence of antibiotic resistant strains of *Y. pestis* as well as fears of intentional misuse of antibiotic resistant strains as a driver for evaluating improved therapeutics. The study is very straightforward and well-designed, and sees the evaluation of delivery of two different phages by both the intraperitoneal (IP) and intranasal (IN) routes. The authors found that intranasal delivery resulted in retention of high level of phage, and thus sought to determine how intranasal delivery of lytic phages might aid in treating pulmonary infection. The authors examine two phages, and found that in general while phage therapy was able to limit bacterial growth in the lung and extend survival, phage therapy did not improve overall mortality. When given in combination, though, with Ceftriaxone, which also sees limited efficacy when used alone, the combinatorial therapy was able to fully rescue mice, seeing 100% survival. This finding was quite dramatic, and is unprecedented in treating this highly lethal infection. Importantly, the authors initiated antibiotic therapy (in phage-treated mice) at 48 hpi, a somewhat late-stage of disease, indicating that dual phage/antibiotic therapy may aid in rescuing mice that have crossed the threshold of time during which antibiotics are typically limited in efficacy. This point is actually underplayed in the discussion and could use mention, and it will be interesting to see how “late” dual therapy can be initiated to mimic real-world exposure scenarios where an individual does not know they are infected until symptoms arise. The studies are well done, nicely controlled, and the writing is clear and concise. The article also highlights an interesting aspect of pneumonic plague that is also not described in the discussion- the fact that it's essentially two different diseases. The authors are able to ameliorate pulmonary infection to a degree, but phage therapy alone is unable to limit the resulting bacteremia and, it is assumed, septic shock. The discussion could use some expounding on why the combined therapy is able to overcome this issue. Overall a nice study of how combinatorial phage/antibiotic therapy can treat a highly lethal infection.