Forbes

Jan 22, 2022, 10:39am EST | 589 views

Salt In My Soul: Poignant Film Calls Attention To The Need For Phages For Antibiotic Resistance



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Mallory with her mom, Diane Shader Smith DIANE SHADER SMITH

Mallory Smith was diagnosed with cystic fibrosis when she was only 3-years old. Despite daily life interrupted by intensive treatments and more than 70 hospitalizations, she went on to become an excellent athlete and Phi Beta Kappa graduate of Stanford, as well as an environmental journalist. Most of all, Mallory had a remarkable spirit and resilience. She lived life more fully than most of us ever do, knowing that she might die at any moment. She poured out her soul in her 2500 page diary. Before undergoing a lung transplant, she gave her parents the password to her journal and phone in case she "didn't make it to the other side."

Mallory died soon after the transplant, at age 25. She did not die of cystic fibrosis. A completely antibiotic-resistant infection with the bacteria *Burkholderia cepacia* is what killed Mallory. In a desperate, final attempt to save his daughter's life, Mark Smith furiously researched phage therapy, which uses viruses to kill the invasive bacteria. The first phages arrived—too late to save Mallory, who died the next day.

Reading Mallory's diary, her mother, Diane Shader Smith, discovered she "didn't know the depth of her daughter's suffering, which she hid behind a happy facade." She excerpted Mallory's diary posthumously in "Salt in My Soul: An Unfinished Life," first as a book and now in a documentary by the same name. The film was just released in theaters and will be available for streaming on-demand on January 25th. All proceeds from the book and documentary are being donated to phage research and antimicrobial resistance.



Phage background

Bacteriophages (phages), Greek for "bacteria eater," are viruses that infect bacteria. They were discovered in 1915 and were initially used to control cholera outbreaks. Phages fell out of favor for several reasons. First, researchers hadn't convinced people that it was entirely safe. Perhaps more importantly, penicillin and other antibiotics were discovered and found to be easier to administer. There was a rapid period of antibiotic development in the 1940-60 period. Interest in phage therapy was largely confined to the former Soviet Union, notably at the Eliava Institute in Georgia. But that led to it being viewed as un-American, tainted "commie science."

Interest in phage therapy is now growing. This renaissance began with Steffanie Strathdee's remarkable story of saving her husband Tom Patterson's life with phages. He was the first person in the US to receive intravenous phages. After four months in a coma, he woke up two days after receiving the "Hail Mary" treatment and made a full recovery. Strathdee tells their story compellingly in her talk at TEDX-Nashville and in their memoir, "The Perfect Predator." Strathdee is now the Associate Dean of Global Health Sciences, UCSD, and Co-Director, Center for Innovative Phage Applications and Therapeutics (iPATH), the first phage treatment center in the US.

A global community comes together

As Mallory was worsening, her desperate father searched out researchers. Just as Strathdee had physicians from across the country looking to help her, she reached out to support the Smiths. She tweeted,



Jon Dennis, PhD, at the University of Alberta, was one of the researchers who responded. One of the big problems with phages is that they are very particular. They home in on not only one type of bacteria, but also one that has a specific target it can attach to, such as a particular protein on its surface. In contrast, antibiotics can treat a whole type of bacteria, such as all *Strep pneumoniae*, unless the bacteria have developed resistance to penicillin, for example.

Dennis described the painful process of frantically trying to find a phage for Mallory, saying, The University of Michigan's "John LiPuma reached out to all the (phage) labs in North America. He asked them if anybody had phages that would attack the bacteria that Mallory harbored in her lungs. This was our first real opportunity to try and save a patient's life."

"We had a couple that had activity good activity against her strain. We knew her health was deteriorating. We had a crazy rushed weekend screening, purifying the phages getting them shipped. It was a holiday and so we were having trouble finding a courier. We sent them to Adaptive Phage Therapeutics, and they purified them and rushed them to the hospital...It was too late; she'd gone too far. I mean, we did this all right. We got the strains from the states and ID'd two potential candidates and then shipped them back, and to get all this done within a week was amazing. And I think we did it in six days from the time we received the strains to the time Mallory died. So it just wasn't enough time...It was crushing," Dennis said, tearing up.

An autopsy showed that the phages had already begun to work effectively, killing the target *B cepacia* bacteria, Mallory's mother said.

Antibiotic resistance

The World Health Organization has now declared antimicrobial resistance (AMR) one of the top 10 global public health threats. Antibiotic resistance is growing—now, more than 2.8 million antibiotic-resistant infections occur in the US each year, with 35,000 deaths. Surprisingly, deaths are down 18% compared to the 2013 report, which the CDC attributes to better infection control efforts. Unsurprisingly, healthcare-associated infection rates went up again in 2020 due to the overwhelming number of COVID-19 patients and the diversion of staff and (limited) resources to their needs.

At the same time as many bacteria are developing increasing resistance to antibiotics, the development of new classes of antibiotics has stagnated since 1987. Pharmaceutical companies have abandoned antibiotic development for more lucrative drugs that would need to be taken for a lifetime. Most antibiotics are only taken for a brief course of days to weeks.

Phage future

Since Mallory's death, her mother has become a "phage therapy evangelist." Diane has traveled around the country speaking incessantly about the growing problem of antibiotic resistance and the need for innovative phage therapy. She has also been quite a force, seeking to bring meaning and hope for others from her daughter's death. Thus far, she has raised \$5.7 million for research. Mallory's Legacy Fund made the inaugural grant to UCSD's iPATH.

Some good things are coming with this resurgence of interest in phages. NIH has committed \$2.5 million to phage therapy research. The Cystic Fibrosis Foundation is funding several phage therapy trials, including grants to BiomX Inc., Armata Pharmaceuticals, and Yale for *Pseudomonas aeruginosa*, iPATH for *Stenotrophomonas*.

Progress is being made on other fronts and in treatments of a variety of infections, which I'll explore in upcoming posts.



Mallory Smith in her "Live Happy" shirt. DIANE SHADER SMITH

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