Kaiser Permanente **Research**

Focusing on infectious disease:

Clinical trials and epidemiologic research into Valley fever





ver the years, the Department of Research & Evaluation's Division of Clinical Trials Research has tackled some of the most serious infectious diseases facing Americans. In the 1980s, researchers conducted trials to help patients with HIV/AIDS to survive. In 2011, clinical trials began focusing on hepatitis C.

Recently, clinical trials and R&E epidemiologists targeted a deadly regional disease: Valley fever. Also known as coccidioidomycosis, Valley fever is a respiratory disease caused by inhaling microscopic fungal spores that live in dry desert soil in the southwestern United States.

Most people who breathe in the spores don't get ill, but others can develop fever, chest pain, and coughing, which look like flu or pneumonia. In some cases, the spores spread into the bloodstream, leading to very serious health issues including death.

High number of Valley fever cases prompt inquiry

The number of reported Valley fever cases in California was 5,372 in 2016, a record level and a jump of 71% from the previous year, according to the state's Department of Public Health. In northern Los Angeles County's Antelope Valley, Valley fever cases increased 258% from 2001 to 2016, when nearly 600 cases were reported.

Physicians in Kern County and Antelope Valley said numbers seem to have increased since then.

Investigation required expansion of clinical trials

To develop a clinical trial program focused on determining the best time to treat patients for Valley fever with antifungal treatments, the division implemented clinical trials in endemic areas that had never conducted clinical trials before–the Antelope Valley and Bakersfield in Kern County, California.

"Despite Kaiser Permanente being a very large entity, we can quickly accommodate research needs where they exist," said William Towner, MD, director of the Division of Clinical Trials Research. "The only place we could study Valley fever is in Kern County or Antelope Valley, because that's where the patients are. So, when the opportunity arose for a Valley fever research project, we adapted relatively quickly to establish a research program in these communities."



More than 5,300 cases of Valley fever were reported in California in 2016. Here, Dr. Sara Tartof points to areas most affected in Southern California.

Epidemiological research adds to knowledge of Valley fever

Laying the groundwork for the Valley fever clinical trial, R&E researcher Sara Tartof, PhD, MPH, investigated the disease from an epidemiological perspective. Her first research article on the subject was published in *Emerging Infectious Diseases* in 2018.

The study looked at how many patients with community-acquired pneumonia were screened for Valley fever from 2001 to 2011. A second paper, not yet published in 2018, examined the sequence of events that Valley fever patients encounter as they make their way through the health care system.

The research found that many patients were prescribed multiple rounds of antibiotics before getting a Valley fever diagnosis. It concluded that limited and delayed testing likely leads to underdiagnosis of the condition.

"Unlike pneumonia, cocci (Valley fever) is a fungal disease and antibiotic treatment doesn't work," Dr. Tartof said. "So, after multiple failed rounds, lots of imaging, and health care utilization with patients not getting better, they are finally tested for cocci."

Dr. Tartof's research and the clinical trials work share a joint aim to keep people healthier in the affected areas by finding the most appropriate time to test for

Cover: Dr. Jonathan Truong, the assistant area medical director for infectious disease at Kaiser Permanente Antelope Valley, arrived in Lancaster in 2000 and quickly realized there was an issue with Valley fever. Through research, he's worked to understand why. And he was thrilled to help get a clinical trial study up and running to learn more about the disease that affects hundreds of people a year in the Antelope Valley.

Valley fever and the best treatment for the disease. For instance, should antifungal treatments start before physicians are even sure the patient has Valley fever?

History of clinical trials in infectious disease

The history of infectious disease clinical trials at Kaiser Permanente Southern California began with HIV/AIDS clinical trials starting in the 1980s. At that time, physicians spent their own after-hours time working to find the best treatment for HIV/AIDS.

In 2002, Dr. Towner and Hai Linh Kerrigan, PharmD, developed the infrastructure to support physicians conducting these clinical trials. This provided more consistent care for patients and more support for physicians by taking care of the administrative research requirements and regulations.

The program tested new HIV/AIDS drugs and drug regimens that were on the path to FDA approval. With access to new drugs, some of which turned out to be effective, many patients survived who may have otherwise died, Dr. Towner said.

Dr. Kerrigan said that "the clinical trials work we are doing in the area of infectious disease really started with HIV, and as soon as that disease started stabilizing, we examined the drug pipeline to see what other needs existed."

Clinical trials in hepatitis C became their next big push

"New novel therapies were coming out that had the potential to significantly improve treatment for hep C, so we had to get our hands on them in the hopes it would help our patients," Dr. Kerrigan said.



Valley fever symptoms often mimic pneumonia. Here, Dr. Jonathan Truong discusses a lung X-ray with colleague Dennis Edora at the Antelope Valley Medical Offices.

Like with HIV/AIDS, the clinical trials allowed patients with hepatitis C to get new medications with higher cure rates sooner. Also, the trials provided these new expensive drugs to patients at no cost.

Kaiser Permanente asked to conduct clinical trials

The issue of Valley fever came to Kaiser Permanente Southern California after U.S. Rep. Kevin McCarthy, whose district includes Bakersfield and much of the Antelope Valley, secured \$5 million in federal funding to launch a 5-year clinical trial of a drug to treat Valley fever. Initial efforts to enroll patients were poor. The National Institutes of Health asked Kaiser Permanente to join.



Over the years, Dr. William Towner has conducted clinical trials for several infectious diseases including HIV/AIDS and hepatitis C. Recently, he and his team focused on a regional disease: Valley fever.

But the timeline to get the program going was much quicker than with HIV/AIDS or hepatitis C, Dr. Towner said.

"Without the willingness and enthusiasm of the administration at Kaiser Permanente's facilities in Bakersfield and Antelope Valley, it would have been impossible to get these clinical trials up and running," Dr. Towner said.

Physicians power clinical trials with commitment

Jonathan Truong, MD, has been chief of infectious disease at Kaiser Permanente Antelope Valley since 2000. He has also served as assistant medical director for medical subspecialty services since 2010.

"When I came out here, I said, 'this place has totally too much cocci," he said. He began to work to understand why.

Inquiry. Investigation. Implementation.



Dr. Jonathan Truong looks at fungal spores that cause Valley fever under a microscope at the Antelope Valley Medical Offices.

Dr. Truong published research on meningitis caused by the Valley fever pathogen *Coccidioides immitis* in 2010 and has been a co-author on Dr. Tartof's Valley fever studies. After becoming a physician lead on the trial, he recruited other physicians to work on the project as well.

As patients come in to the emergency department or urgent care or for general appointments with pneumonia-like symptoms, the physicians ask them if they would like to be part of the study. If they agree, physicians follow them for 2 years and learn what



Scientifically known as coccidioidomycosis, Valley fever is a respiratory disease caused by inhaling microscopic fungal spores that live in dry desert soil in the southwestern United States.



In Bakersfield, Kelly Rappaport and Dr. Aung Htoo discuss the recent cases of Valley fever they have seen. Physicians in the area say the numbers seem to have been rising the past few years.

percentage of them are ultimately diagnosed with Valley fever, how well they respond to antifungal treatments, and in what percentage did the fungal infection spread to the brain and other parts of the body.

"Together, we committed ourselves and changed our work flow to make sure the study would be successful at Kaiser Permanente," Dr. Truong said. "And we aggressively worked hard to enroll patients into the study and to manage them because we felt it was an important study."

Implementation: Clinical trials expected to lead to new protocols

One of the first physicians that joined Dr. Truong in the study was Aung Kyaw Htoo, MD, in Bakersfield.

"Right now, Valley fever is affecting a lot of people in this area, and all the doctors are treating it based on their own experience and intuition," Dr. Htoo said. "There is no proper set protocol. And we want a proper protocol for how to treat patients, how to do the proper follow-up, how to determine the indicators for the disease process. That's what we are trying to achieve with the new study."

Dr. Towner is pleased that the infectious disease work done by clinical trials has progressed to the point it can specifically target the health of KPSC members.

"It is truly satisfying to be able to make a difference like this for our members and the community," Dr. Towner said.