Medical Xpress

Haiti cholera mutations could lead to more severe disease: Strain is evolving to be more like virulent 1800s cholera

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The cholera strain that transferred to Haiti in 2010 has multiple toxin gene mutations that may account for the severity of disease and is evolving to be more like an 1800s version of cholera, reports a new Northwestern Medicine study.

The strain, "altered El Tor," which emerged around 2000, is known to be more virulent and to cause more severe diarrhea and dehydration than earlier strains that had been circulating since the 1960s. This study reports the altered El Tor strain has acquired two additional signature mutations during the past decade that may further increase virulence.

In addition, these newly discovered signature mutations documented in the study further link the Haitian cholera epidemic to the strain from Nepal.

The paper will be published April 16 in the journal *mBio*.

The new Northwestern study suggests the strain with multi-signature toxin gene mutations may trigger a unique pattern of infection accounting for the severity of disease noted during the Haiti cholera outbreak.

"The cholera strain from the 1800s epidemic did the same thing," said Karla Satchell, the senior author of the paper and an associate professor

of microbiology-immunology at Northwestern University Feinberg School of Medicine. "That strain also modified its toxin genes and the cholera got worse."

Satchell has spent her career studying a single toxin of the bacterium that causes cholera, MARTX, which helps the bacteria block the body's immune defense so cholera can colonize the gut. She closely followed genomics research conducted to track the Haiti epidemic, curious to see how her toxin was affected. She was shocked to see it had completely mutated out of existence.

"Oh, my!" she recalls thinking. "My toxin has been booted out of this key strain." She postulates that this may have affected the behavior of the mutated strain in disease.

Satchell and colleagues analyzed publicly available genomic sequencing data and found this new cholera strain had accumulated some curious genetic changes during its global spread. First, the main cholera toxin that causes the diarrhea acquired genetic changes that converted the toxin to a form similar to that produced by strains prevalent during the historic cholera epidemics of the 1800s.

Surprisingly, this new strain next acquired a genetic lesion that inactivated the MARTX toxin, previously recognized to be important for evading the immune system. A third as yet uncharacterized genetic mutation in the cholera toxin followed, suggesting a mutation emerged in the cholera toxin to compensate for the loss of MARTX.

These mutations occurring in the same strain indicate that the bacterium interacts differently with the immune system than previous strains.

"Perhaps this results in the bacterium more successfully evading early detection after a person accidently drinks cholera infected fluids,"

Satchell said. "Interestingly, these multiple mutations in important proteins that specifically contribute to disease could explain why this strain is causing more severe disease, although the contribution of each mutation to human infection remains to be studied."

Previously published research on the Haiti cholera strain noted the change in the bacterium's DNA and tracked its origin to Nepal, but scientists didn't ask how the changes affected the bacterium's function. In addition, scientists had believed the bacterial strains responsible for the "new wave" of cholera that engulfed Haiti and first began spreading in 2000 were functionally identical to most other strains prevalent in the environment.

Satchell's finding further confirms the strain infecting Haiti likely originated in Nepal, consistent with the conclusion from the whole genome analysis and public health studies. Strains with this unique signature of a cholera toxin with three genetic changes coupled with loss of MARTX has spread only in a very defined geographical area including India where it was first detected in 2007. It has spread through Bangladesh, Cameroon, Nepal and then into Haiti and the Dominican Republic in 2010. Even though other strains are nearly identical and barely distinguishable at the genetic level, only this very small group of isolates share this unique signature, verifying from a functional viewpoint that the strain that moved to Haiti likely originated in Nepal.

"What we discovered is that the bacterial strains responsible for the 'new wave' of cholera are not all functionally identical with minor modification as previously thought, nor are they similar to most other strains prevalent in the environment, but, in fact, the strain with multi-signature toxin gene mutations may instigate a unique pattern of infection accounting for the severity of disease noted during the Haiti cholera outbreak," Satchell said.