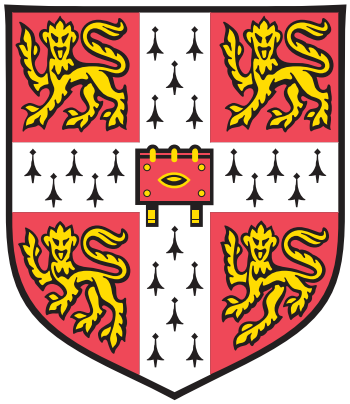
The Origins and Evolution of *Vibrio cholerae* O1 El Tor



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Declaration

This dissertation describes my work undertaken at the Wellcome Trust Sanger Institute between May 2010 and August 2013, under the supervision of Profs. Gordon Dougan, Nicholas Thomson and Julian Parkhill in fulfillment of the requirements for the degree of Doctor of Philosophy, at Corpus Christi College, University of Cambridge.

This thesis is the result of my own work and where the work done in collaboration is presented, it is indicated in the text. The work described here has not been submitted for a degree, diploma or any other qualification at any other university or institution. I confirm that this dissertation does not exceed the page limit specified by the Biology Degree Committee.

Ankur Mutreja

Cambridge, August 2013

Publications

Mutreja, A., Kim, D.W., Thomson, N., *et al*. (2011) Evidence for multiple waves of global transmission within the seventh cholera pandemic, *Nature*, **477(7365)**, 462-465.

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Ali, M., Mutreja, A., *et al.* (2014) Genomic Epidemiology of Vibrio cholerae O1 associated with Floods, Pakistan, 2010, *Emerging Infectious Diseases,* **20(1)**, 13-20.

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Dedicated to

My Parents and Sister

"Always appreciate what you have and what you are getting from life, otherwise you risk losing it. Be very proud of yourself."

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Abstract

The Origins and Evolution of *Vibrio cholerae* O1 El Tor

Cholera, like plague, is an ancient disease of great historical importance, the spread of which was originally believed to be *via* bad air or 'miasma'. In 1854, a London based physician, John Snow, first provided epidemiological evidence for the connection between contaminated drinking water and cholera and approximately 50 years later *Vibrio cholerae*, the etiological agent of cholera was identified by Robert Koch. Cholera is still common in many regions of the world despite having one of the simplest known treatment regimes: oral rehydration. In fact, the increase in the incidence of cholera since 2007 has highlighted the risk our globalized community still faces.

Currently, scientists lack a detailed understanding of how *V. cholerae* transmits and evolves, although water is recognized as a critical factor. This PhD project exploits whole genome sequence data to investigate the evolution of *V. cholerae*, focusing on serogroup O1. Phylogenetic trees based on whole genome sequencing data obtained from over 1000 *V. cholerae* representative of seventh pandemic El Tor, classical and non-O1/O139 isolates collected from across the world where cholera occurs were used to determine evolutionary patterns and relationships. In cases where detailed phenotypic information or meta-data was available, phylogeny was used alongside clinical, phenotypic and geographical information to track and understand the global and regional spread of cholera.

The genotypic basis underpinning the basis of the Ogawa to Inaba serotype change was investigated using *V. cholerae* sampled during a phase III vaccine trial undertaken in Kolkata, India and these mechanisms were defined.

Based on my mining of the phylogeny and whole genome data on which it is based, informative SNPs were selected for the basis of a simple and mobile SNP genotyping scheme. Multiplex ligation-assisted probe amplification (MLPA) was selected as the most suitable laboratory based molecular technique to detect the canonical SNPs and two kits were designed for the use of scientific and public health communities in developing countries.