A conservatively-estimated one million people contract leptospirosis annually. Of these, more than 60,000 will die. These minimum estimates will rise in coming years as we achieve better measurements of disease burden due to improved diagnostics and better global estimates. The economic cost of human leptospirosis is likely more than $30 billion annually, with an untold economic loss of even greater magnitude, predominantly in low- and middle-income countries where the impact of leptospirosis is the greatest. Climate change, with increased temperatures and flooding throughout the world, will inevitably further expand the human and economic cost of leptospirosis.

Although the routes of transmission are known, it is not fully understood how the disease manifests, and how our immune system protects us from infection. With this knowledge, better diagnostics and treatments could be developed. Addressing this is Professor Joseph Vinetz of Yale University, USA, and collaborators in Peru and Sri Lanka. The researchers focus on bacteria genomics in a mission to translate basic science into diagnostics tests and treatments. Their recent breakthrough brings us a step closer to vaccine development.

Leptospirosis, a neglected tropical disease caused by spiral-shaped bacteria called *Leptospira*, is a global health burden. At the forefront of leptospirosis research, Professor Joseph Vinetz and colleagues at Yale University, USA, discovered virulence genes coding for proteins that enable the bacteria to cause tissue damage. Uncovering the protein structure and function of these novel virulence factors, their work reveals mechanisms of disease that is leading to translation from fundamental research into diagnostics and treatments. The team’s recent findings mark the crucial beginning for long-awaited pan-leptospirosis vaccine development.

Pathogenic types evolved to acquire virulence factors that are exotoxins. Only certain species of *Leptospira* evolved to become infectious and pathogenic. Pathogenic types evolved to acquire virulence factors or exotoxins – ‘weapons’ that enable their survival by invading cells and hijacking cellular machinery in a quest to replicate. Previously, no one knew how *Leptospira* caused disease; little had been known of leptospiral toxins and how they cause disease. What are the virulence factors and the genes that code for them? If these can be identified, described, and understood, we have a far better chance of understanding the mechanisms of disease. Vinetz and colleagues discovered what appears to be the central mediator of severe leptospirosis disease. The power of genomics

Adding to the challenges of understanding how *Leptospira* cause disease is the fact that this spiral-shaped microbe is one of the most complex of all pathogenic bacteria. The researchers’ first step in the long road to understanding how *Leptospira* cause disease is the identification of virulence factors and the genes that code for them. This knowledge will enable the development of vaccines and treatments that can prevent and treat leptospirosis.

**Neglected but not forgotten**

Although a global disease, leptospirosis is more prevalent in areas of poverty and poor sanitation, where it is transmitted from animals to humans through infected tissue, urine, or water sources. Some animals colonised with the bacteria don’t display symptoms, but function as ‘reservoirs’ for the disease while other animals exhibit symptoms following infection. Because the disease can be contracted through flooding and contaminated fresh water, tropical and subtropical areas prone to flooding or storms are especially vulnerable and experience epidemics.

Clinical symptoms of the disease range from asymptomatic to mild to very severe. In severe disease, patients experience fever, kidney failure, jaundice, and bleeding – which may lead to death in up to a quarter of those admitted to hospital. The reason for this varied presentation is unknown, as is much of the disease pathogenesis.

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pathogenic proteins. Additionally, the fact that the strains of (VM) proteins were identified.

Importantly, these findings lay the foundation for further vaccine exploration. Optimisation of vaccine doses and techniques are needed, as well as experiments to confirm these findings and whether immunity is due to antibodies against VM proteins. The researchers' global efforts provide valuable contributions to this field, with the aim of one day making vaccination against leptospirosis a reality.

Vaccination protected mice from clinical symptoms of disease and significantly reduced the quantity of bacteria in the kidney and liver of these animals.

The researchers recently used artificial intelligence and computational modeling to describe the structure of these toxins and how they work. These VM proteins belong to the group known as lectins, meaning they bind to carbohydrates. Computational modeling can predict the parts of the protein that help toxins attach and enter the cell, where they destroy DNA and lead to cell death. By detailing each part of the structure, the team aim to build a comprehensive picture of the complexity of this protein. This is just the beginning, however, and more research is needed to understand how the protein binds to its target, the strength of this binding, and how accurately it does this.

The road to vaccination

Building on their work showing bacterial VM proteins coded by PF07598 cause cell toxicity, the researchers hypothesised that these proteins mediate disease in live animals. The researchers immunised mice with recombinant VM proteins – manipulated versions of the original protein. Encouraging results published in Frontiers in Cellular and Infection Microbiology showed vaccination protected mice from clinical symptoms of disease and significantly reduced the quantity of bacteria in the kidney and liver of these animals.

One such culprit is a novel gene family, called PF07598, which is upregulated in infected hamsters. Interestingly, the most virulent strains of Leptospira have the most copies of this gene suggesting it codes for virulent proteins. Additionally, the fact that the PF07598 gene family is found only in group 1 pathogenic Leptospira further supports a role in virulence. Although the mechanism of its virulence was unknown, this discovery was a turning point, sparking further research to explain the disease pathogenesis.

Building on their previous work, the team then compared genes between pathogenic and non-pathogenic Leptospira – shedding light on what genes cause the disease, the mechanisms by which they do this, and measurable antigens useful to diagnose disease. Identification of the genes and antigens causing pathology opened the door for research to develop diagnostic tests, therapeutics, and vaccines.

Identify, describe, understand! Now that a family of genes coding for VM proteins had been identified, the researchers wanted to describe their structure and function – to unpick the mechanisms of disease. More importantly, they wanted to identify the targets for therapeutic development such as small molecules, antibodies, and vaccines.

What do you think are the advantages and challenges of working globally?

Working in diverse settings throughout the world enables us to understand the burdens of the disease and the importance of discovering ways to intervene against them. People will tell you what they are concerned about and that you can answer their concerns. People at risk for various infectious diseases, including leptospirosis, often ask me about how to prevent them so that they and their families can live healthier lives. This happens to me very regularly as I work in the field setting, leptospirosis is very difficult to diagnose in a timely manner.

Why has leptospirosis been a neglected tropical disease and why has it been so difficult to study?

Leptospirosis has historically been difficult to diagnose in a timely manner because serology is inefficient and culture is difficult for these fastidious bacteria. Even today, when molecular diagnostics potentially could lead to a rapid diagnosis, the technology is too expensive and complex to deploy in the endemic setting. With the lack of diagnosis there’s a lack of understanding and realisation of the impact of this important neglected tropical disease. Furthermore, it is difficult to study because the organisms are difficult to isolate in culture from infected humans and animals, and the organism grows slowly in the laboratory. We have been able to overcome these challenges, which led to the genome project and the enablement of using genomics to more efficiently identify the Achilles heel of Leptospira and open up possible interventions.

What's next in the road to vaccination?

The next steps in the road to vaccination are validating the vaccine candidates in a target animal species such as dogs or cattle, and at the same time building the business argument for investment. Once we finalise an ideal vaccine formulation based on a human compatible adjuvant plus an optimised set of recombinant antigens that we identify from animal studies, we are on the road to GMP manufacture and preclinical studies of vaccine candidates for early clinical development.