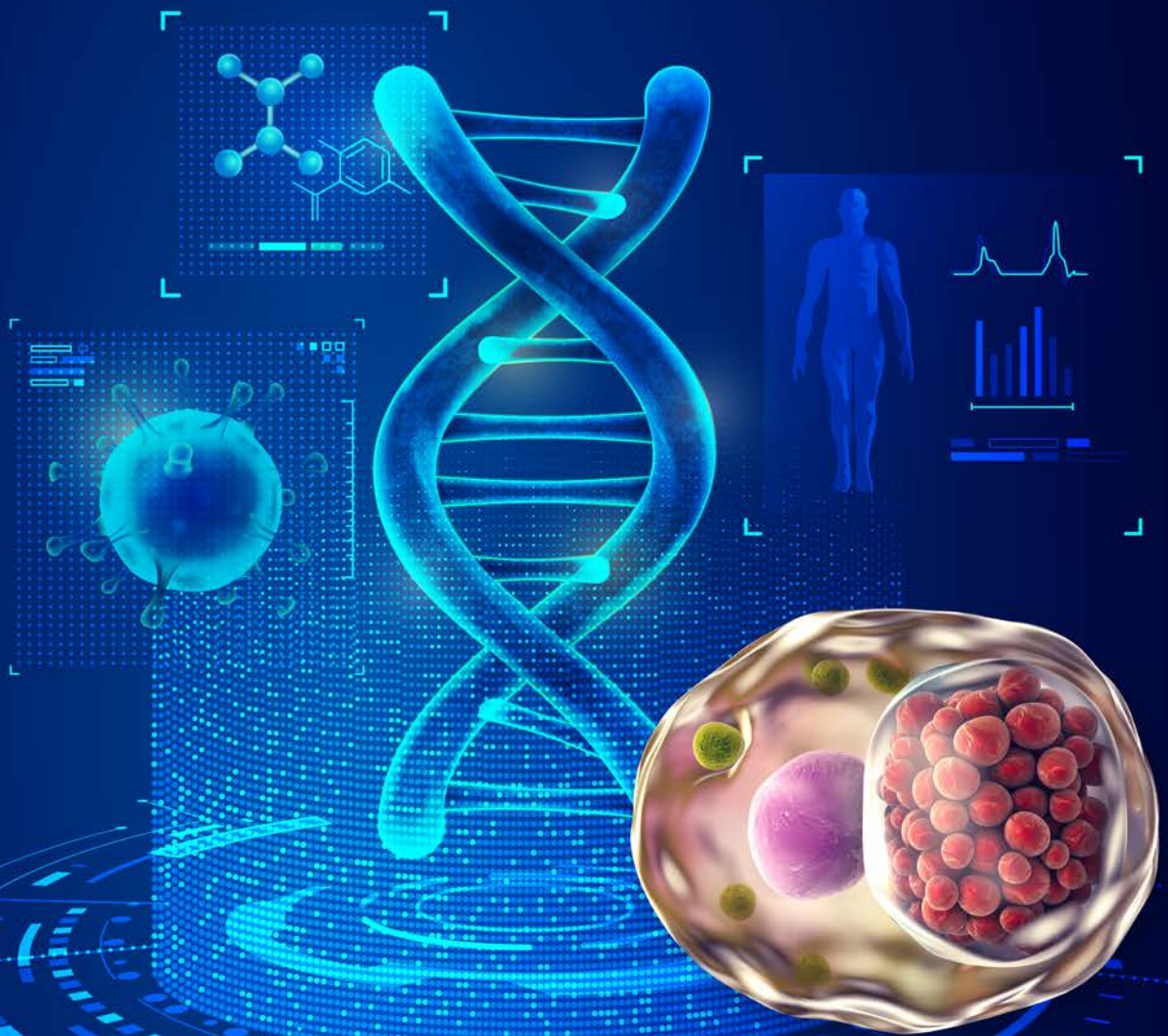


Chlamydia trachomatis
Through the Lens
of Epidemiology,
Immunology, and
Genomics

Professor Robert Brunham



CHLAMYDIA TRACHOMATIS THROUGH THE LENS OF EPIDEMIOLOGY, IMMUNOLOGY, AND GENOMICS

Chlamydia trachomatis is the leading cause of both sexually transmitted bacterial disease and infectious blindness around the world. Professor Robert Brunham from the University of British Columbia and the British Columbia Centre for Disease Control, is an expert in the biology, prevention, and control of infectious diseases. He and his research team are using the epidemiology, immunology, and genomics of *Chlamydia trachomatis* in the context of evolutionary medicine to design and develop an effective vaccine.

Understanding the Origins of Human Health and Disease

Evolutionary medicine seeks to understand the origins of human health and disease by taking an evolutionary perspective to explain certain traits, behaviours, and diseases. It is argued that the traits exhibited by humans, as well as the diseases we suffer from, can be better understood by considering their evolutionary history and how they might have provided adaptive advantages in the past. This perspective can also help guide new and effective medical interventions and treatments. Exciting recent developments in genomics (the study of an organism's complete DNA sequence) are driving the incorporation of evolutionary medicine into clinical practice across medical specialities, including hereditary illness, cancer, and infectious disease.

Professor Robert Brunham is an infectious disease specialist clinician and academic at the University of British Columbia. He is a leader in the

field of evolutionary medicine, and one aspect of his research is dedicated to the epidemiology, immunology, and genomics of *Chlamydia trachomatis* (*C. trachomatis*). By combining these three disciplines, he is providing new insights into the relationship between humans and *C. trachomatis*, and also the development of a vaccine against the pathogen.

Chlamydia trachomatis and Infectious Disease Biology

Chlamydia is a type of bacteria that can only replicate within the cells of other organisms. Examples affecting humans include the pathogens *C. trachomatis* and *C. pneumoniae*. With over 128 million new cases a year, *C. trachomatis* is the most common cause of sexually transmitted bacterial disease worldwide.

Sexually transmitted *C. trachomatis* is a global public health concern, particularly in women. Whilst overt symptoms may not always accompany the infection, it can nonetheless cause



pelvic inflammatory disease, chronic abdominal pain, and long-term reproductive consequences such as reduced fertility and an increased risk of ectopic pregnancy. Infection with *C. trachomatis* increases the risk of HIV infection and is also thought to be a risk factor for cancer caused by human papillomavirus.

More than two-thirds of the global cases of sexually transmitted *C. trachomatis* occur in less economically developed countries with limited diagnostic and treatment services. Infection is much more common in younger people. As well as reproductive tract infections,



certain strains of *C. trachomatis* can cause trachoma – a serious childhood eye infection that can lead to irreversible blindness in adults. Sexually transmitted *C. trachomatis* infections can, in theory, be prevented by practising safe sex and treated with antibiotics. However, there remains an urgent need for a vaccine to protect against and prevent infection, as antibiotics are not always available in resource-limited settings and do not protect against reinfection.

Epidemiology and Public Health Implications

The control of infectious diseases typically focuses on behaviour change, screening, treatment, and vaccines. Due to its significant impact on public health, *C. trachomatis* has been a notifiable disease in British Columbia since the mid-1990s, and a control programme was introduced to limit the spread of the disease across the province. This intervention focused on increased testing and antibiotic treatment to shorten the duration of infection and subsequently reduce the opportunity for transmission. Within a few years, case rates had halved, but by 1998, cases began to rise again. By the early 2000s, cases were even higher than they were before the programme began.

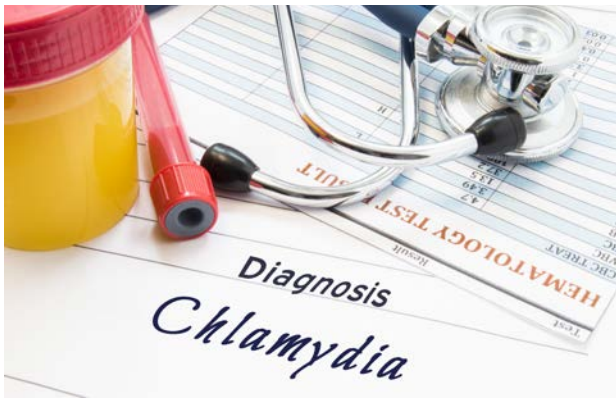
These dramatically increasing rates were associated with rising levels of reinfection – that is, infection with the same or a different strain after a previous infection has been cleared either by treatment or immune action. Resolving this mystery of rising rates under an apparently effective programme required an understanding of the natural history of *C. trachomatis* infection.

At the British Columbia Centre for Disease Control, Professor Brunham proposed that the rise in cases was due to the population becoming increasingly susceptible to reinfection as a result of the *C. trachomatis* control programme. The control

programme detected infection earlier and allowed prompt treatment – but this earlier intervention may have reduced the development of natural immunity. Previous studies have shown that 50% of women with *C. trachomatis* infection not treated with antibiotics will still show detectable levels of bacteria a year after the infection is identified. In other words, natural immunity takes a long time to develop. In a study where all women were treated, those who had spontaneously cleared the infection prior to treatment were four times less likely to become reinfected than those who were not able to naturally clear the infection. Work in mice has also shown that early antibiotic treatment of *Chlamydia* bacteria reduces the development of natural immunity.

To test this intriguing hypothesis, Professor Brunham analysed *Chlamydia* case data from the Greater Vancouver area from between 1989 and 2003, and developed a mathematical model to assess the impact of treatment at different time points after infection. These analyses confirmed that the likelihood of reinfection had increased by 4.6% per year since the beginning of the control programme, with a higher risk of reinfection for younger people and women. Results from the model closely matched the ‘real life’ data and suggest that although early treatment reduces the number of infections in the short-term, reducing the opportunity for immunity to develop increases the number of reinfections, and so, prevalence can reach or even exceed the pre-control programme level.

When Professor Brunham added a hypothetical vaccine that would provide ten years of immunity to the model, they found that this allowed *C. trachomatis* infection to be entirely eliminated. This critical finding underscores the importance of an effective vaccine to halt the spread of *C. trachomatis*.



Developing an Effective Vaccine

Clearly, vaccination will be key to reducing the burden of *C. trachomatis* infection around the world. Understanding the relationship between bacteria and our immune system is essential to this complex process.

Much of what we know about the immune response to *C. trachomatis* comes from mouse studies using a slightly different Chlamydia species. Nonetheless, studies showing that untreated women are able to clear *C. trachomatis* infections confirm that humans are able to generate an immune response.

Professor Brunham reviewed the data from mouse studies to help guide vaccine research. Mouse studies have shown that, in particular, T-cells (immune cells that directly attack foreign material) and a molecule called interferon-gamma are required to protect against *C. trachomatis* infection and reinfection.

A previous vaccine using an inactivated bacteria was trialed but was not successful, and research is now focussing on subunit vaccines – where proteins from an organism are attached to something that generates a strong immune response. Animal studies showed that a large portion of immune protection from *C. trachomatis* comes from T-cells, so the vaccine needs to include a protein that stimulates this response. A potential target is the MOMP protein – this makes up 60% of the proteins on the outside of the bacteria. However, this protein is not the same across the many types of *C. trachomatis*, so it would not provide broad protection. Additional targets, such as polymorphic membrane proteins, are required for a fully effective vaccine.

There are several challenges to designing a *C. trachomatis* vaccine; the bacteria are good at evading the immune system, and often, when the immune system does react to the bacteria, it results in inflammation – the cause of many of the symptoms. *C. trachomatis* infects the mucosal membrane cells of the female genital tract, and pathogens that target mucosal sites often need different types of vaccines and different vaccine delivery methods compared to pathogens that infect other areas. The immune system of the female genital tract is also uniquely impacted by sex hormones – a vaccine would have to be able to reach the site



and generate a mucosal immune response. Professor Brunham's work highlights the importance of an organism's natural evolutionary history when developing vaccine candidates.

The Impact of Genomics

Progress in genomics is revolutionising the field of microbiology, including our understanding of Chlamydia. Professor Brunham and his collaborators sequenced the DNA of several strains of Chlamydia, knowing that new insight into the organism's genetic makeup would aid the understanding of its traits and potential health implications.

Professor Brunham compared the genetic information from the two strains they sequenced and previously sequenced Chlamydia strains. This allowed them to understand the evolutionary relationships between the bacteria as well as investigate the genetic adaptations and functions of specific genes. They found that the strains they sequenced had very similar genomes to the previous strains. In explanation of this, they suggest that, unlike other bacteria, which tend to coexist with lots of different species as intracellular bacteria, Chlamydia strains exist inside human cells and so are less likely to 'pick up' additional bacterial DNA.

Some differences were found between the two strains, either caused by or causing the different host habitats of the two strains. For example, they found that *C. trachomatis* has a gene coding for a protein that inactivates the protective interferon-gamma molecule produced by T cells and thus increases the length of time that the organism can remain in the infected person. Perhaps most importantly, because the genome encodes all the possible vaccine proteins, this genomic study reinforces the assertion that the Chlamydia genome offers considerable immunological interest.

By combining epidemiology, immunology, and genomics, Professor Brunham highlights the importance of a vaccine to control the Chlamydia pathogen. His important work is also aiding vaccine design and development by shedding new light on the bacteria's genetics and the immune response it generates.



Meet the Researcher

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Professor Robert Brunham received his medical degree from the University of British Columbia. He has since become an expert in infectious disease prevention and control, and uses epidemiology, immunology, and genomics to define the biology of important sexually transmitted and emerging pathogens. He bases his research on the principles of evolutionary medicine and integrates medical practice and science with the humanities and evolutionary biology. He was previously Head of the British Columbia Centre for Disease Control and is now the Head of the Vaccine Research Laboratory at the University of British Columbia Centre for Disease Control. Professor Brunham is a pioneer in the field and has received multiple honours, including the Living Legend Award and the Order of British Columbia.

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KEY COLLABORATORS

Dr Brunham's approach to medical research was inspired by Dr Macfarland Burnet via his book 'The Natural History of Infectious Disease'. Dr Brunham's key collaborators have been Drs Frank Plummer (University of Manitoba and former Scientific Director General of the National Microbiology Laboratory at Winnipeg, Canada), Timothy Read (Emory University School of Medicine, Division of Infectious Diseases & Department of Human Genetics, USA) and Leonard Foster (University of British Columbia, Department of Biochemistry and Molecular Biology, Canada).

FUNDING

National Institutes of Health

FURTHER READING

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