Recent Developments in Infectious Disease Research

Claire Cummins, MSc

University of Tours, Tours, France
https://orcid.org/0000-0002-4922-3470

https://doi.org/10.57098/SciRevs.Biology.3.3.2
Received September 25, 2024. Revised October 15, 2024. Accepted October 15, 2024

Abstract: The field of infectious disease research is rapidly evolving and advancing, driven by the demand to address both current and emerging threats to global health. The recent COVID-19 pandemic underscored the criticality of infectious disease outbreak preparedness and response, while factors such as climate change, migration, and globalization continue to influence disease transmission dynamics. Innovative approaches to infectious disease research are more essential than ever to prevent future pandemics and the spread of vector-borne diseases.

This comprehensive review article investigates some recent pertinent developments in infectious disease research, including the development of a novel serosurveillance platform, modeled after the one designed during the COVID-19 pandemic, aimed at tackling the growing global threat of arboviruses. Also investigated in this article is the repurposing and application of mRNA vaccine technology, initially developed during the pandemic, to address the complex challenge of tick-borne Lyme disease. Finally, we outline several novel and cutting-edge strategies aimed at tackling the ever-mounting crisis of antimicrobial resistance (AMR).

Each of these innovations marks a significant step forward in global health security and preparedness, offering promising solutions to the challenges of a rapidly evolving world, while drawing on the lessons learned from past outbreaks and epidemics.

Arbovirus Serosurveillance Inspired by the COVID-19 Pandemic

Serosurveillance involves testing blood samples from the general population for the presence of antibodies against a pathogen of interest, allowing estimation of the number of people previously infected and/or vaccinated against the pathogen. Serosurveillance data is extremely important for informing public health policy in aiding outbreak prediction, identifying high-risk groups, estimating the burden of disease, and planning future vaccination programs in a cost-effective manner (Wilson et al., 2012).

As of mid-2024, the COVID-19 pandemic has resulted in more than 770 million confirmed cases and over 6.9 million deaths worldwide, according to the World Health Organization (WHO). The unprecedented and rapidly developing nature of this pandemic required rapid global public health response and intervention, with an example of this being 'SeroTracker', a custom-built online dashboard, fulfilling a worldwide demand for a unified resource for seroprevalence estimates. The platform allows users to visualize seroprevalence data on a world map so as to compare findings between regions, population groups, and different diagnostic testing modalities (Arora et al., 2020).

Building on the success and utilization of the SeroTracker platform, the same approach is now being applied to arboviruses- which include mosquito-borne viruses such as dengue, yellow fever, and Zika, with the development of 'ArboTracker.' This new multi-pathogen dashboard is designed for arbovirus seroprevalence studies. Mosquito-borne viruses pose a significant global health threat, and their transmission is exacerbated by factors such as migration, globalization, and climate change. Yet, many cases remain underreported due to outdated surveillance systems and limited diagnostic resources. ArboTracker is an exciting new tool that could address this gap, allowing researchers and policymakers to explore and visualize seroprevalence estimates via an interactive online map, as well as download datasets for use in predictive disease modeling. Furthermore, the stacking of multiple pathogens within the visualization platform has much potential in future prevalence studies requiring the

grouping of pathogens by family. This will enable the platform to be adapted and customized for quickly assessing and responding to future infectious disease outbreaks (Whelan et al., 2024).

Thinking Outside the Box to Address the Ever-Challenging Lyme Disease

Lyme disease, transmitted by tick-bite from the genus *Ixodes*, is caused by various strains of the spirochete bacteria *Borrelia burgdorferi*. It is one of the most prevalent vector borne diseases in North America and Europe, with its geographical range continuing to expand. The infection, Lyme borreliosis (LB), poses a major challenge due to its biological complexity, person-to-person variation in symptoms, variability of the bacterial genospecies, and diagnostic limitations. In fact, diagnosis of LB is a contentious topic in the scientific community, as it has been subject to much debate and controversy due to its reliance on indirect serological methods. These methods are of low sensitivity, thus making accurate diagnosis, especially in early infection, very challenging.

Symptoms can vary depending on the person as well as the genotype of the infective bacteria, and include erythema migrans, headaches, arthralgia, and myalgia (Fig. 1). However, especially in cases that go untreated due to inaccurate diagnosis, the strong and chronic antibody response that fails to clear the infection long-term can cause much more serious and chronic symptoms such as arthritis (Fig. 1), profound fatigue, and cognitive impairment (Guérin et al., 2023).

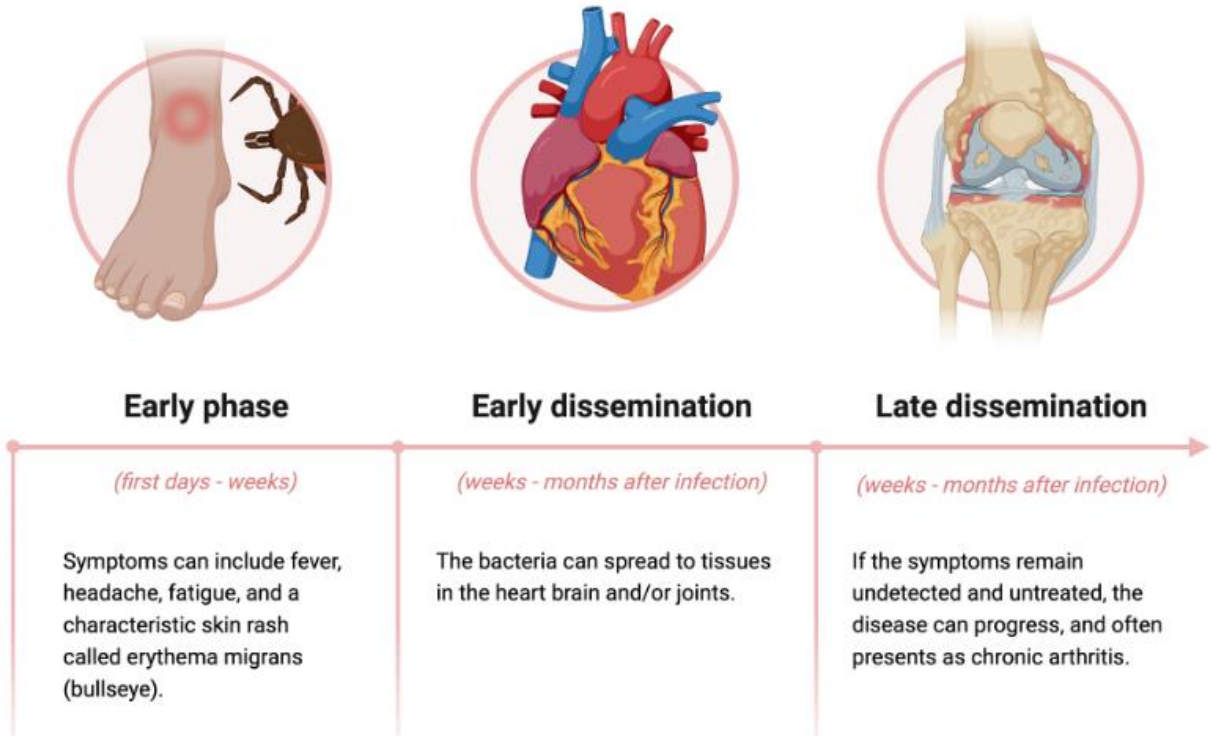

Figure 1: *Phases and symptoms of Lyme Disease. (Created with BioRender.com)*

Suboptimal diagnosis inevitably leads to suboptimal treatment of Lyme disease, with the symptoms often being mistaken for viral infection, leading to unnecessary treatments such as steroids, which can actually worsen the condition, or utilization of inappropriate antibiotics that are ineffective against *Borrelia burgdorferi*. Inadequate treatment of Lyme disease with non-recommended antibiotics can lead to serious complications. Therefore, though effective treatment exists for early stage disease, delayed diagnosis can make treatment more challenging as the bacteria may have disseminated throughout the body before treatment was initiated (Aucott et al., 2009).

The complex challenges that Lyme disease presents have led researchers to explore the alternative of a preventative vaccine, with the first candidate receiving FDA approval in 1998 being

LYMErix, developed by GlaxoSmithKline, a recombinant vaccine targeting the outer surface protein (OspA) of *Borrelia burgdorferi*, which demonstrated 76% efficacy after three doses (Steere et al., 1998). However, only four years later, the vaccine was withdrawn due to low demand and public concerns over the safety of the vaccine (Poland, 2011).

Nevertheless, due to the rising incidence of Lyme disease today, renewed efforts have been made to develop an effective vaccine, with Valneva and Pfizer collaborating to make the VLA15 vaccine, which as of 2024 is in Phase 3 clinical trials with promising results in terms of safety and efficacy. The vaccine, like LYMErix, targets the OspA protein, but trumps LYMErix due to its wider protection, covering the six serotypes of bacteria that are the most common in the US and Europe (Cornstedt et al., 2017).

In 2023, the companies behind the successful mRNA COVID-19 vaccine , Pfizer and BioNTech, announced plans to develop a mRNA-based Lyme disease vaccine, which is in early preclinical stages as of 2024. As was seen during the COVID-19 pandemic, mRNA technology offers excellent flexibility due to quicker design and manufacturing than traditional vaccines. Additionally, production of mRNA vaccines is more efficient, since they are designed to simply encode instructions for the immune system to create the target protein (Fig. 2) and don't require the large-scale production of proteins or inactive pathogens as is the case for conventional vaccines (Pine et al., 2023).

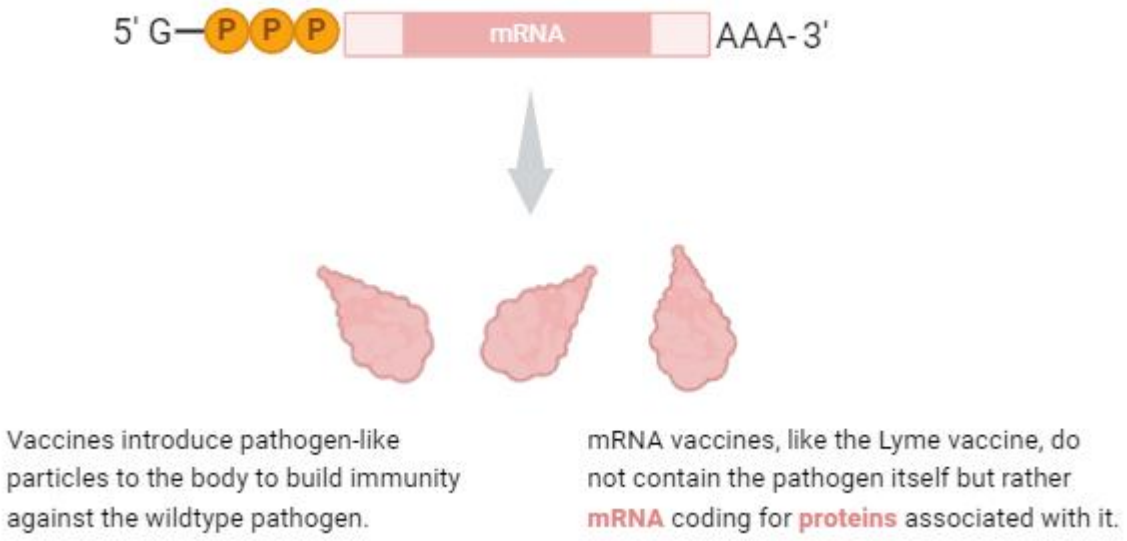

Figure 2: *Schematic overview of the mRNA-based Lyme disease vaccine. (Created with BioRender.com)*

These positive aspects of mRNA vaccines offer much potential for Lyme disease prevention, allowing the targeting of multiple bacterial strains in one vaccine, which can be more easily customized to target different *Borrelia burgdorferi* strains based on regional prevalence.

Antimicrobial Resistance: Moving Beyond Antibiotics?

Antimicrobial resistance (AMR) has been a problem plaguing global health security for decades, and in 2024, remains one of the most pressing health challenges facing our population. Over the next 25 years, an estimated 39 million people are expected to die from drug-resistant pathogens alone (Barron, 2024). For decades after AMR first emerged, the problem was remedied by the introduction of newer classes of antibiotics (Martinez, 2014); however, in recent years, this development has slowed down, leading to the exponential growth of resistant organisms.

Additionally, misuse and excessive prescribing of antibiotics in health and agricultural environments has exacerbated the spread. The

mechanisms of how AMR develops are varied and include undergoing genetic mutations in response to environmental pressures or threats either via horizontal gene transfer or spontaneous genomic rearrangement. In this way, bacteria continuously evolve and develop resistance strategies each time new antibiotics are employed (Berger and Loewy, 2024).

With both the continuous rise of AMR and the reduced capacity to develop new antibiotics, the pursuit of novel alternative treatments is a pertinent medical need currently. One approach is to use combination therapy, i.e.: utilizing two or more antibiotics to promote an enhanced response, which is currently used to effectively treat *Mycobacterium tuberculosis* whereby a four-drug regimen targets different pathways for survival, providing more protection if the bacteria gains resistance to one target pathway.

Drug-adjuvant combinations are also being used to combat AMR, because adjuvants enhance the activity of an antibiotic such as Augmentin – a combination of the antimicrobial amoxicillin and the adjuvant clavulanic acid (Konwar et al., 2022).

Antimicrobial peptides (AMPs) are short, positively charged peptides that are involved in the innate immune systems of various prokaryotes, insects, plants, and animals. They have gained traction in recent years as an alternative to traditional antibiotics, as they demonstrate broad-spectrum activities against bacteria, viruses, and fungi. Their positive charge allows them to target the negatively charged components in the bacterial cell membranes (Fig. 3), which means they are effective against both Gram-positive and Gram-negative bacteria. Some AMPs have already been FDA-approved, and they offer much potential as they are predicted to have a low risk for resistance development due to their diverse mechanisms of action (Berger and Loewy, 2024).

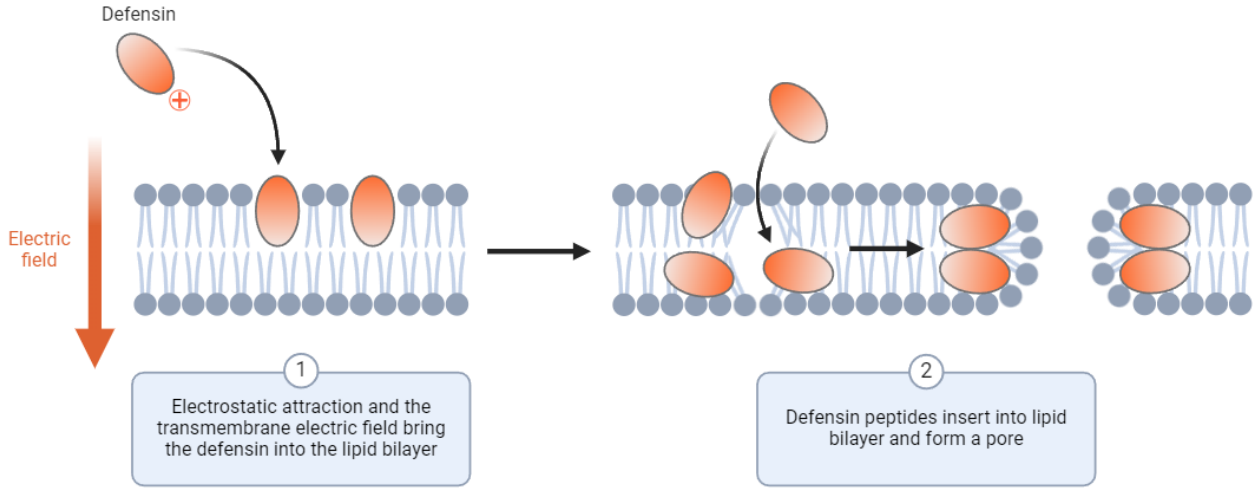

Figure 3: *Antimicrobial peptides disrupt bacterial membrane integrity. (Created with BioRender.com)*

Monoclonal antibodies (MABs) that selectively target antigens have been an area of interest for AMR alternative treatments due to their high specificity and favorable side effect profile (Lu et al., 2020), with only three currently approved by the FDA for the treatment of bacterial infections. These MABs work by neutralizing bacterial secretory toxins (Berger and Loewy, 2024), which again may pose a low risk for resistance development as the treatment targets external mechanisms of the bacteria.

Bacteriophages are naturally-occurring viruses that specifically target and invade bacteria and were researched and used in the clinical setting in the 20th century, however, with the advent of antibiotics, their use declined. However, due to the challenge that AMR poses today, bacteriophage research is of renewed interest with ongoing global

studies aimed at developing optimized phage therapies for clinical use (Konwar et al., 2022). Some bacteriophages produce endolysins, which can destroy bacteria by breaking down their cell walls. An example of this is the endolysin that has been developed into the drug SAL200, which is effective against methicillin-susceptible (MSSA) and methicillin resistant *Staphylococcus aureus* (MRSA). It is also effective against destroying difficult biofilms, which is a huge challenge for conventional antimicrobials (Jun et al., 2017).

Another alternative route from traditional antibiotics is the use of nanomaterials to treat drug-resistant infections, which act as carriers to deliver antibiotics directly to bacterial cells. This innovative mechanism allows the precise targeting of antibiotics to infection sites, reducing the required dosing and thus reducing the capacity for the bacteria to develop resistance. Studies show the effectiveness of nanoparticles against a wide range of problematic multidrug resistant bacteria, including *Staphylococcus aureus, Escherichia coli,* carbapenem-resistant *Acinetobacter baumannii,* and *Pseudomonas aeruginosa* (Berger and Loewy, 2024).

Conclusion

In conclusion, the rapidly evolving landscape of infectious disease research reflects the growing need for innovative solutions to address global health threats. The examples of ArboTracker for arbovirus surveillance, the repurposing of mRNA vaccine technology for complex diseases like Lyme, and the pursuit of alternative treatments to combat antimicrobial resistance, display this innovation. These developments are a testament to how science is rising to meet the challenges of a world increasingly shaped by factors like climate change, migration, and globalization.

Each of these breakthroughs represents a step forward in global health security, providing us with tools not only to address current issues, but also to prepare for future infectious disease threats.

By leveraging new technologies and interdisciplinary approaches to global health, we can better predict, prevent, and respond to infectious diseases, ultimately improving health outcomes and strengthening our preparedness for pandemics yet to come.

References

1. Arora, R. K., Joseph, A., Wyk, J. V., Rocco, S., Atmaja, A., May, E., Yan, T., Bobrovitz, N., Chevrier, J., Cheng, M. P., Williamson, T., & Buckeridge, D. L. (2020). SeroTracker: a global SARS-CoV-2 seroprevalence dashboard. The Lancet Infectious Diseases, 0(0). https://doi.org/10.1016/S1473-3099(20)30631-9

2. Aucott, J., Morrison, C., Munoz, B. et al. Diagnostic challenges of early Lyme disease: Lessons from a community case series. BMC Infect Dis 9, 79 (2009). https://doi.org/10.1186/1471-2334-9-79

3. Barron M. The Antimicrobial Resistance Pandemic: Breaking the Silence | ASM.org. ASM.org. Published 2024. Accessed October 8, 2024. https://asm.org/Articles/2024/October/Antimicrobial-Resistance-Pandemic-Breaking-Silence

4. Berger I, Loewy ZG. Antimicrobial Resistance and Novel Alternative Approaches to Conventional Antibiotics. Bacteria. 2024;3(3):171-182. https://doi.org/10.3390/bacteria3030012

5. Comstedt, P., Schüler, W., Meinke, A., & Lundberg, U. (2017). The novel Lyme borreliosis vaccine VLA15 shows broad protection against Borrelia species expressing six different OspA serotypes. PloS one, 12(9), e0184357. https://doi.org/10.1371/journal.pone.0184357

6. Guérin, M., Shawky, M., Zedan, A. et al. Lyme borreliosis diagnosis: state of the art of improvements and innovations. BMC Microbiol 23, 204 (2023). https://doi.org/10.1186/s12866-023-02935-5

7. Jun, S. Y., Jang, I. J., Yoon, S., Jang, K., Yu, K. S., Cho, J. Y., Seong, M. W., Jung, G. M., Yoon, S. J., & Kang, S. H. (2017). Pharmacokinetics and Tolerance of the Phage Endolysin-Based Candidate Drug SAL200 after a Single Intravenous Administration among Healthy Volunteers. Antimicrobial agents and chemotherapy, 61(6), e02629-16. https://doi.org/10.1128/AAC.02629-16

8. Konwar, A. N., Hazarika, S. N., Bharadwaj, P., & Thakur, D. (2022). Emerging non-traditional approaches to combat antibiotic resistance. Current Microbiology, 79(11), 330.

9. Lu RM, Hwang YC, Liu I-Ju, et al. Development of Therapeutic Antibodies for the Treatment of Diseases. Journal of Biomedical Science. 2020;27(1):1-30. doi:https://doi.org/10.1186/s12929-019-0592-z

10. Martinez JL. General Principles of Antibiotic Resistance in Bacteria. Drug Discovery Today: Technologies. 2014;11(1740-6749):33-39. doi:https://doi.org/10.1016/j.ddtec.2014.02.001

11. Pine M, Arora G, Hart TM, Bettini E, Gaudette BT, Muramatsu H, Tombácz I, Kambayashi T, Tam YK, Brisson D, Allman D, Locci M, Weissman D, Fikrig E, Pardi N. Development of an mRNA-lipid nanoparticle vaccine against Lyme disease. Mol Ther. 2023 Sep 6;31(9):2702-2714. doi: 10.1016/j.ymthe.2023.07.022.

12. Poland GA. Vaccines against Lyme Disease: What Happened and What Lessons Can We Learn? Clinical Infectious Diseases. 2011;52(suppl_3):s253-s258. doi:https://doi.org/10.1093/cid/ciq116

13. Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme Disease with RecombinantBorrelia burgdorferiOuter-Surface Lipoprotein A with Adjuvant. *New England Journal of Medicine*. 1998;339(4):209-215. doi:https://doi.org/10.1056/nejm199807233390401

14. Whelan, M. G., Ware, H., Himanshu Ranka, Kenny, S., Shaikh, S., Roell, Y., Akter, S., Selemon, A., Toews, E., Chu, M., Niklas Bobrovitz, Arora, R. K., & Jaenisch, T. (2024). ArboTracker: a multipathogen dashboard and data platform for arbovirus seroprevalence studies. The Lancet Infectious Diseases. https://doi.org/10.1016/s1473-3099(24)00585-1

15. Wilson, S. E., Deeks, S. L., Hatchette, T. F., & Crowcroft, N. S. (2012). The role of seroepidemiology in the comprehensive surveillance of vaccine-preventable diseases. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 184(1), E70–E76. https://doi.org/10.1503/cmaj.110506