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Research Article

Dormant Pathogens and Chronic Diseases: The Hidden Role of Latent Infections in Human Health

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Abstract

Background: Latent infections are a significant yet often overlooked aspect of human health. Some examples include hepatitis B and C viruses, responsible for hepatocellular carcinoma; herpesviruses such as Epstein–Barr virus and cytomegalovirus, responsible for immune dysfunction and malignancies; and Mycobacterium tuberculosis, responsible for latent tuberculosis infection. These infections have substantial clinical significance because they can reactivate under conditions such as stress, immunosuppression, or ageing to cause chronic diseases and permanent health complications.
Aims: To examine the global health impact of latent pathogens, which is another important goal.
Methods: This narrative review synthesises evidence from peer-reviewed literature indexed in PubMed, Scopus, and Google Scholar, with emphasis on studies addressing microbial latency, host–pathogen interactions, immune evasion, associations with chronic disease, and emerging diagnostic and therapeutic approaches.
Results: The comprehensive search suggests that latent infections play an important role in the prevalence of chronic disease worldwide. The findings point to the complexity of interactions between pathogen survival strategies and host immune responses. The latency is dynamically balanced such that the pathogens avoid immune detection but still retain the capability to activate. This highlights a necessity to have better diagnostic tools and novel, effective treatment interventions.
Conclusion: Emerging biomarkers, omics technologies, and computational biology approaches offer promising opportunities for the improved detection and management of latent infections. A deeper understanding of microbial dormancy is essential for developing effective preventive and therapeutic strategies aimed at reducing the global burden of infection-associated chronic diseases.

Keywords: Chronic diseases, Host–pathogen interactions, Immune evasion, Latent infections, Microbial

1. INTRODUCTION

Microbial dormancy, also known as latency, is a unique physiological state in which a pathogen persists in the host with little to no active reproduction, remaining clinically silent yet capable of reactivating and causing illness under the right circumstances (McDonald et al., 2024). This form of persistence is bacteria, fungi, viruses, and protozoa, and involves suppressing overt pathogenic activity and altering gene expression to avoid immune detection (Barry et al., 2009).

Given the increasing awareness of a latent infection as a key cause of chronic disease, this narrative review draws together the latest state-of-the-art knowledge and insights regarding the persistence, reactivation and clinical implications of dormant pathogens. The review emphasizes the molecular mechanisms of latency of microorganisms, such as immune escape, episomal maintenance, metabolic dormancy and the implications of microbial latency for long-term human health. Major pathogens with a latent state (such as *Mycobacterium tuberculosis,* hepatitis virus, herpesviruses, *Helicobacter pylori* and human papillomavirus) are given special attention. Further, new developments in biomarker discovery, applications of omics technologies, and computational biology as a potential tool for enhancing detection, prediction and management of latent infections are also outlined.

1.2 Distinctions among Acute, Chronic, and Latent Infections

Usually characterized by an abrupt onset of symptoms and a brief clinical course, acute infections frequently go away in a matter of days to weeks due to host immune clearance (Gideon & Flynn, 2011). In contrast, chronic infections last for months to years, during which the bacteria may continue to replicate at low levels or remain active, leading to protracted tissue damage and immune stimulation (Nathanson & Tyler, 2013). One specific subset of chronic illnesses is represented by latent infections. In these situations, viruses go into a

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latent stage that is marked by little to no reproduction and no obvious clinical signs.

1.3 Global Health Significance: The Hidden Burden of Latent Infections

A significant but usually underappreciated impact on global health is caused by persistent infections. Latent tuberculosis infection (LTBI) is one of the most important latent infections worldwide, with an estimated one-fourth of the world's population being infected with *Mycobacterium tuberculosis* as a latent infection and a primary reservoir for future development of tuberculosis disease (Cohen et al., 2019).

As shown in **Figure 1,** although the global prevalence of LTBI has somewhat decreased from **30.7% in 1990 to 23.7% in 2019**, according to recent modeling studies, the disease's magnitude is still significant. It presents a significant challenge to meeting the World Health Organization's Tuberculosis elimination targets, which call for faster incidence reductions (Ding et al., 2022). 10.6 million people acquired active Tuberculosis in 2022 alone, underscoring the persistent clinical effects of latent reservoirs (World Health Organization, 2023).In addition to Tuberculosis, several other latent pathogens are becoming more widely known for their links to chronic illnesses, such as cancer, autoimmune dysregulation, and neuropsychiatric disorders (Robert-Gangneux & Dardé, 2012; Flegr, 2013). These include protozoa like Toxoplasma gondii, hepatitis B and C viruses, and herpesviruses like Epstein-Barr virus and cytomegalovirus.

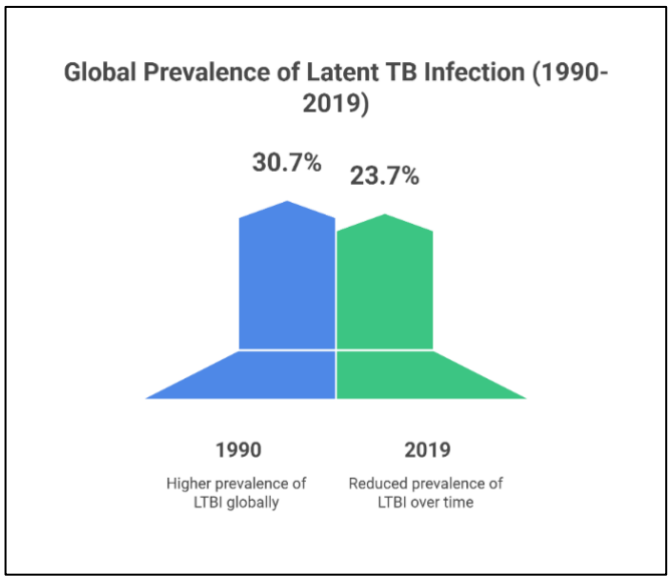


Figure 1. Global prevalence of latent tuberculosis infection (LTBI) in 1990 and 2019. *The prevalence decreased from 30.7% in 1990 to 23.7% in 2019, yet the overall burden remains substantial and continues to challenge WHO's TB elimination targets. (Ding et al., 2022).*

These examples highlight that, Although significant strides have been made in the research of infectious diseases, it remains difficult to identify, track, and get rid of latent infections as many pathogens can enter (and remain in) latent states with mechanisms that can allow them to evade the immune system and survive for years or decades in a clinically silent manner (Barry et al., 2009; Nicoll et al., 2012; McDonald et al., 2024). Latent reservoirs thus continue to impede efforts of disease control and contribute to disease outbreaks and recurring infections, chronic inflammation and long-term morbidity in a wide variety of infectious diseases (Getahun et al., 2015; Cohen et al., 2019). These difficulties arise further in the application of conventional diagnostic and therapeutic procedures – dormant pathogens often are by far more successfully detected or eradicated in specialised cellular reservoirs or tissue microenvironments in which metabolic activity is low (Barry et al., 2009; Nicoll et al., 2012).

The use of emerging technologies, such as multi-omics technologies, host-derived biomarkers, computational modelling and artificial intelligence-based predictive tools for early detection, risk stratification and management of latent infections, is increasingly being sought to accomplish these goals (Argelaguet et al., 2018). Thus, the objective of this review is to provide a comprehensive understanding of microbial dormancy and latency while highlighting its molecular foundations across a broad range of pathogens. In particular, it aims to distinguish latent infections from acute and chronic infections based on the molecular mechanisms at play, as well as their clinical manifestation. Accordingly, this review aims to examine the global health impact of latent pathogens, which is another important goal. Of particular interest is the epidemiological importance of latent tuberculosis infection (LTBI), which remains a significant reservoir for disease reactivation and transmission (Vanni et al., 2020).

Given that latent infections are often silent and difficult to detect, the study also examines the diagnostic, treatment, and public health issues associated with them (Canova et al., 2024). It concludes by highlighting new

methods that could provide fresh approaches to the future detection, forecasting, and treatment of latent infections, including high-throughput omics technologies, biomarker discovery, and computational modelling (Knipe & Cliffe, 2008; Nicoll et al., 2012).

1.4 Novelty and Scope

Much of what has been done on microbial latency has been undertaken with specific pathogens, such as Mycobacterial tuberculosis, herpesviruses, hepatitis viruses or Toxoplasma gondii, studied in isolation (Flynn & Chan, 2001; Nicoll et al., 2012; Münz, 2019; Montoya & Liesenfeld, 2004). Pathogen dormancy remains poorly characterized for most microbial groups and under the umbrella of a cohesive theory. In addition, despite significant advances in our understanding of the molecular mechanisms driving persistence, immune evasion and reactivation, few reviews have synthesized these mechanisms into the development and implications for chronic diseases and global health.

This review aims to fill this gap by drawing a cross-cut to other microbial pathogens, including bacteria, viruses and protozoans and provide an integrated view of microbial dormancy. In addition to analyzing the molecular and immunological mechanisms required to allow for long-term persistence, this paper delves into the possibility that latent infections could play an important role in chronic states of cancer, autoimmunity, neuropsychiatric and chronic inflammation.

Furthermore, it draws attention to new developments in the discovery of biomarkers, multi-omics technologies, and computational biology and modeling that could help with the detection, monitoring and management of latent infections (Argelaguet et al., 2018). The objective of this review is to integrate the data from various systems of microorganisms and to create a wider understanding of the role microbial latency plays in the modulation of long-term human health and disease.

2. MATERIALS AND METHODS

This study was designed to be a narrative review of the literature on the topic of microbial dormancy and latent infections and its focus on persistence, reactivation, host/pathogen interactions, immune evasions, their connection to chronic diseases, and new diagnostic and therapeutic strategies. Peer-reviewed literature was searched using major scientific databases such as PubMed, Scopus, and Google Scholar. Current literature was reviewed for the purpose of synthesizing the current knowledge on the molecular and biological basis of pathogen latency and the human health implications thereof.

Studies covering key issues of microbial latency, such as the processes involved in the establishment and persistence of latent infections, immune-evasion mechanisms of persistent pathogens, immune determinants of latency reactivation, and the nature of the immune reaction to persistent pathogens were reviewed. Special attention was given to pathogens known to have, or be clinically relevant for, persistent states in humans, such as *Mycobacterium tuberculosis*, herpesviruses, hepatitis B and C viruses, human papillomavirus, *Toxoplasma gondii,* and *Helicobacter pylori*. The association between latent or persistent infections and chronic diseases such as tuberculosis, malignancies, immune dysregulation, chronic inflammation, and other potential chronic health outcomes was also reviewed.

Furthermore, the literature was scanned for alternative methods of detecting, documenting, forecasting and controlling latent infections. These ranged from host derived biomarkers through multi-omics technologies (genomics, transcriptomics, proteomics, and metabolomics), computational biology, artificial intelligence-based techniques, precision medicine, immune-directed approaches, and finally synthetic biology. Selected literature was qualitatively synthesized for an integrated overview of microbial dormancy, pathogen persistence, pathogen reactivation, and its connection to human chronic diseases and public health problems.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Mechanisms of Pathogen Latency

In the reversible condition of pathogen latency, microorganisms remain in the host without actively replicating, but they still have the capacity to reactivate. It is an essential survival tactic that promotes long-term persistence, immune evasion, and the emergence of chronic diseases (Alcamí & Heesters, 2023).

3.1.2 Entry into latency

Various pathogens use unique molecular mechanisms to subvert host immune responses and persistently infect the host while under immune surveillance (Alcamí & Heesters., 2023). During dormant infection in Mycobacterium tuberculosis, the activation of the DosR regulon by hypoxia, nutrient limitation and nitric oxide exposure enables the transcription of mycobacterial programs that lead to metabolic adaptation and to the persistence of mycobacteria within granulomas (Park et al., 2003; Barry et al., 2009). Epstein–Barr Virus (EBV) is kept in latency in memory B cells with very limited viral gene expression, allowing low levels of immune recognition, with the viral episome (Münz, 2019).

Herpes simplex virus (HSV) establishes neuronal latency by the expression of latency-associated transcripts (LATs), which downregulate the expression of lytic genes and favour long-term persistence (Thellman & Triezenberg, 2017). Hepatitis B virus (HBV) uses stable covalently closed circular DNA (cccDNA) present within the nucleus of its target cells, hepatocytes, for viral reactivation (Revill et al., 2019). Likewise, HIV enters latency when it enters resting $CD4^+$ T cells, and viral transcription is mostly silent until it is reactivated (Siliciano & Greene, 2011).

3.1.3 Immune Evasion

Elimination requires the recognition and elimination of the pathogen, and success in avoiding or changing host immune recognition is essential for persistence of the pathogen over the long-term. Interestingly, it is found that Mycobacterium tuberculosis prevents subsequent phagosome–lysosome fusion, thereby preventing the killing of the bacteria by the phagocytic cells, and favoring the persistence of the bacteria (Ehrt & Schnappinger, 2009). Alcamí & Heesters (2023) indicated that the herpesviruses escape from recognition by the cytotoxic T cells due to the downregulation of major histocompatibility molecules class I and disruption of antigen presentation pathways.

Hepatitis B virus (HBV) persists in a stable covalently closed circular DNA (cccDNA) in the nucleus, whilst at the same time dampening innate immune activation and maintaining the long-term presence of the virus (Revill et al., 2019). Likewise, HIV advances persistent infection through hindering immune checkpoint (IC) pathways, such as programmed cell death protein-1 (PD-1), that upset functional enemy reaction against the infection (Wherry, 2011; Blank et al., 2019). These immune evasion mechanisms allow pathogens to create stable latent reservoirs, which may appear either clinically inconspicuous or remain hidden for an extended period but are still capable of being revived in the future.

3.1.4 Reactivation triggers

Latent infections may not have symptoms for long time periods but may be reactivated by disruption of the host immune system to cause disease. It is well established that latent Mycobacterium tuberculosis (MTB) infection often reactivates in people who are HIV co-infected, malnourished, elderly, suffering from diabetes or other underlying conditions called immunosuppression (Getahun et al., 2015; Price et al., 2024). Physiological stress, heat, ultraviolet radiation or immune suppression can trigger the reactivation of the virus, leading to clinical disease (Thellman & Triezenberg, 2017).

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) reactivation is also common in people receiving chemotherapy, corticosteroids, biotherapy or other immunosuppressing drugs (Revill et al., 2019; Vutien et al., 2025). Pathogen reactivations reflect, in summary, the coexisting virulence of the pathogen and immune responses to the host. To aid in providing better risk prediction, early diagnosis, and therapeutic strategies in people who have latent infections, it is important to understand these triggers.

3.1.5 Dormant Pathogens and Chronic Diseases

Latent infections play a significant role in the global burden of several chronic diseases by promoting chronic interactions between the host and the pathogen that can last for years or even decades (McDonald et al., 2024; Nicoll et al., 2012). While these infections may not manifest clinically in their latent state, their chronicity may encourage chronic inflammation, immune dysregulation, tissue damage and disease processes. (Barry et al., 2009; Canova et al., 2024). The reactivation can also worsen the clinical signs of the disease and lead to more complications down the road, depending on the pathogen and the protection of the host's immune system (Knipe & Cliffe, 2008; Cohen et al., 2019). Examples of latent pathogens and some of their known connections to chronic human diseases are provided in the following sections, and in **Figure 2**, the general life history of a pathogen from host uptake to latency and eventually reactivation is summarized.

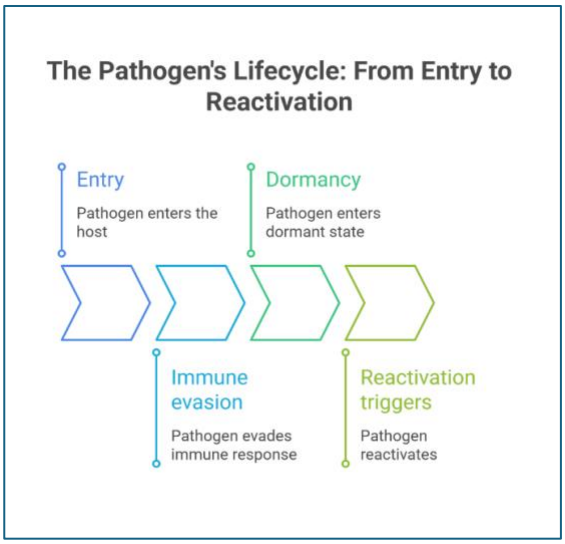


Figure 2. Conceptual overview of the pathogen life cycle during latent infection**.** *The schematic illustrates the sequential stages of host infection, immune evasion, establishment of latency, long-term persistence, and pathogen reactivation under favourable conditions. The figure is a conceptual illustration created by the authors and adapted from published literature, including Barry et al. (2009), Knipe and Cliffe (2008), Nicoll et al. (2012), and McDonald et al. (2024)*

3.1.5.1 Mycobacterium tuberculosis and Tuberculosis

About 25 per cent of the people in the world are thought to have latent *Mycobacterium tuberculosis* infection (LTBI) and thus one of the largest known reservoirs of persistent bacterial infection worldwide (Cohen et al., 2019; World Health Organization, 2023). In granulomas, *Mycobacterium tuberculosis* is able to survive long-term in a metabolically silent state, which allows survival despite nutrient deprivation and hypoxia, and inhibits its clearance by the immune system (Barry et al., 2009). While latent infection is clinically silent, it is correlated with sustained immune activation and low-grade inflammation, representing the dynamic equilibrium between host immune control and the persistence of the bacteria. As the T-cells and macrophages become hyperactive due to persistent exposure to antigen, granuloma maintenance, tissue remodelling and continued pulmonary damage occur (Hwang et al., 2014). Reactivation of the LTBI is most often seen in those with impaired immunity (HIV infection, diabetes mellitus, malnutrition or immunosuppressive therapy), leading to the development of active tuberculosis and increased

morbidity (Getahun et al., 2015; World Health Organization, 2023).

3.1.5.2 Herpesviruses

The members of the herpesvirus family cause persistent latent infections in a physiological subpopulation of host cells, allowing efficient immune control while maintaining latent infection. Latency is mostly asymptomatic but is associated with chronic immune activation and a variety of autoimmune diseases as well as various forms of malignancy and their association with immunosenescence. Epstein–Barr virus (EBV) and cytomegalovirus (CMV) are notable human herpesviruses, since there are clear associations between them and chronic disease, and immune dysregulation over short to long timeframes (Münz, 2019; Griffiths & Reeves, 2021).

a. Epstein–Barr Virus (EBV)

Epstein–Barr virus (EBV) establishes lifelong latency in memory B cells, where viral gene expression is highly restricted, enabling immune evasion while maintaining persistent infection. Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma are among the cancers that have been associated with latency (Münz, 2019). In addition to oncogenesis, accumulating evidence suggests that EBV infection is associated with autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus. when tolerance is lost due to prolonged immunological activation (Longnecker et al., 2013).

b. Cytomegalovirus (CMV)

Human cytomegalovirus contributes to chronic immunological dysregulation by causing myeloid lineage cells to go into latency. Immunosenescence, which is marked by an increase in T cells specific to CMV and a decrease in the diversity of the immunological repertoire, has been linked to chronic CMV infection (Griffiths & Reeves, 2021). CMV load is associated with higher cardiovascular risks, frailty, and all-cause mortality in older and immunocompromised people (Cannon et al., 2010).

3.1.5.3 Hepatitis B and C Viruses

Hepatitis B virus (HBV) is a virus that leads to long-term persistence, with the maintenance of serum covalently closed circular viral DNA (cccDNA); Hepatitis C virus (HCV) usually causes chronic persistent infection by continuing replication in hepatocytes. Although the virus appears to be clinically resolved, HBV cccDNA can be located in the DNA of the hepatocyte nuclei, resulting in the possibility of reactivation at another time (Revill et al., 2019). Hepatocellular carcinoma (HCC), liver failure, and cirrhosis are all significantly influenced by persistent HBV and HCV infections (El-Serag, 2012). Understanding the role of chronic inflammation in hepatocarcinogenesis, which is the continuous process of injured hepatocytes being replaced by new hepatocytes, is due to the creation of a pro-oncogenic microenvironment from repeated cycles of hepatocyte injury and replacement by new hepatocytes (El-Serag, 2012).HBV and HCV are responsible for a significant global burden of virus-associated hepatocellular carcinoma (HCC) and have a major impact on the public health burden (Polaris Observatory Collaborators, 2023b).

3.1.5.4 Other Persistent Pathogens

a. Human Papillomavirus (HPV)

The high-risk human papillomavirus (HPV) genotypes—especially HPV-16 and HPV-18—are a significant and powerful contributor to virus-associated carcinogenesis. Although it is usually asymptomatic, persistent infection leads to the viral genome becoming integrated into the host genome, which means the viral oncoproteins E6 and E7 are expressed persistently. These proteins disrupt the activity of the tumour suppressors p53 and retinoblastoma (Rb), causing genome instability, cell-cycle defects and malignant transformation. Thus, chronic HPV infection is tightly linked to oral, anogenital and cervical cancer (Schiffman et al., 2016). The global impact of HPV vaccination has been significantly dampened to date by the fact that it remains underutilised in many parts of the world, but widespread use of prophylaxes has significantly decreased the prevalence of persistent HPV infection and of HPV-associated precancerous lesions (Bernard et al., 2010).

b. Toxoplasma gondii

Toxoplasma gondii is able to reside in the latent form in immunologically competent hosts for the entire life of the host because it enters into cysts in tissue cells, such as neural and muscle tissue. Usually, latent infections are non-clinical, but if the host becomes immunocompromised, clinical symptoms may be seen, including toxoplasmic encephalitis caused by reactivation of infection (Montoya & Liesenfeld, 2004). In addition to its known symptoms, there is emerging evidence regarding neuropsychiatric conditions and chronic *T. gondii* infection, such as schizophrenia and bipolar disorder. The evidence for causality, though, is still too limited to conclude that influenza directly or exclusively causes heart attacks, strokes, and pneumonia, particularly in immunosenescent individuals, and the details of the mechanism remain a work in progress (Robert-Gangneux & Dardé, 2012).

c. Helicobacter pylori

Helicobacter pylori basally colonizes the gastric epithelium by some immune evasion strategies and survival within the toxic gastric milieu. With chronic infection comes chronic gastritis and chronic inflammatory reaction, which, over a long period of time, can cause degeneration of the gastric epithelium. It is established that persistent *H. pylori* infection is associated with gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma, which occurs due to continuous inflammation, injury to epithelial cells and disruptions of host cell signalling pathways (Amieva & Peek, 2016).

Bacterial and viral and protozoan infections are not passive processes that over time shape host immune

responses and tissue homeostasis, but dynamic processes themselves. These infections can substantially lead to the development of chronic diseases, such as cancer, autoimmune diseases, and organ-specific pathologies, due to the sustained inflammation, immune dysregulation, and pathogen-specific mechanisms of persistence in these infections. Hence, a recap of these various mechanisms is crucial for the formulation of measures to prevent pathogen reactivation, detecting people with a worse prognosis of developing disease, and develop targeted therapy.

3.1.6 Role of the Immune System

Regularly, the immune system monitors a latently infected cell to detect and eliminate microbes via coordinated innate and adaptive immune responses, playing a key role in keeping microbes latent (Virgin et al., 2009). The dynamic balance between host immune surveillance and pathogen persistence is crucial for maintaining latency, and disruption of this balance can allow microbial reactivation, chronic inflammation and progression to pathogenesis.

3.1.6.1 Immune surveillance and evasion

NK cells, cytotoxic T lymphocytes (CTLs), macrophages and signalling by cytokines together make up the front line of immune surveillance to prevent microbial reactivation and maintain pathogen latency. These innate and adaptive immune responses work together to constantly identify cells that are infected, inhibit cell proliferation and maintain a balance between the host and the persistent microorganisms (Virgin et al., 2009). Latent pathogens take advantage of the regulatory process in order not to be removed by the immune system when immunity is lost. For instance, Mycobacterium tuberculosis prevents antigen presentation and activation of macrophages, and Herpesviruses decreases expression of major histocompatibility complex (MHC) class I, which in turn diminishes CTL recognition (Alcamí & Heesters, 2023). Furthermore, HIV and chronic Hepatitis viruses alter cytokine signalling and T-cell function, which leads to further immune system impairment and contributes to long-term persistence of the virus (Redeker & Arens, 2016).

3.1.6.2 Chronic inflammation and T-cell exhaustion

Infection with repeated exposure causes chronic low-grade inflammation, which leads to continuous activation of both innate and adaptive immune responses. Continual immunization leads to T-cell exhaustion over time, which leads to T-cell dysfunction with decreased proliferation, cytokine production, and cytotoxicity (Wherry, 2011). Another possible mechanism of T-cell exhaustion is the expression of inhibitory receptors such as programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which together act to inhibit the activation of effector immune cells and promote the persistence of the pathogen in the host (Blank et al., 2019; Wherry, 2011).

3.1.6.3 Impact of immunosuppression

The reactivation of pathogens from latency is one of the main events linked to the dynamic action of the immune system against micro-organisms; thus, the importance of host immunity for microbial latency.HIV infected persons who are CD4+ T-cell-depleted are significantly at higher risk of latent tubercular reactivation because of impaired cell-mediated immune responses (Nathanson & Tyler, 2013). Herpesviruses, hepatitis viruses, and Toxoplasma gondii are also susceptible to reactivation in transplant recipients on immunosuppressive treatment (Razonable, 2020). Immune surveillance is gradually compromised with immunosenescence, making older people more vulnerable to reactivation of latent pathogens, such as cytomegalovirus (CMV), and thus leading to reduced clinical outcomes (McElhaney, 2012).

3.1.6.4 Immune checkpoints in chronic infection

In persistent infections, immune checkpoint pathways, including programmed cell death protein-1 (PD-1)/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), are key regulators of T-cell exhaustion and immune homeostasis (Blank et al., 2019). These regulatory mechanisms dampen overactive T-cell effector mechanisms, but may also create conditions for "stealthy" pathogens to avoid immune clearance and exploit checkpoint signalling for long-term persistence (Wherry, 2011). A more emerging possibility is therapeutic modulation of immune checkpoint pathways that may functionally re-establish immune function, which is being explored for the management of chronic bacterial and viral infections (Blank et al., 2019).

3.1.7 Clinical and Public Health Implications

Latent infections may be asymptomatic for many years but can later become clinically apparent and linked to chronic illnesses, which are great clinical and public health challenges. Because of their subclinical presentation, early detection, surveillance, and appropriate management of these infections remain difficult, and the development of sensitive diagnostic tools, specific treatment approaches, and efficient public health interventions are needed (Getahun et al., 2015; Cohen et al., 2019).

3.1.7.1 Diagnostic challenges

Latent infections represent a considerable clinical challenge, since they are characterized by low levels of antigen expression, low metabolic activity and low levels of the replication of the microbe, which makes direct detection difficult. The current tests, including tuberculin skin test (TST) and Interferon γ release assays (IGRA) are useful in determining whether an individual has a latent Mycobacterium tuberculosis infection but are insufficiently predictive of the likelihood for subsequent reactivation (Getahun et al., 2015; Cohen et al., 2019). Likewise, there are latent and actively replicating viruses that are being continuously studied for the development of reliable biomarkers to differentiate them (Wykes & Lewin, 2018). The key diagnostic issues that arise in latent infections can be

summarized as shown in **Figure 3,** such as equipoise of pathogen detection, biomarker uncertainty, and poor prediction of disease reactivation.

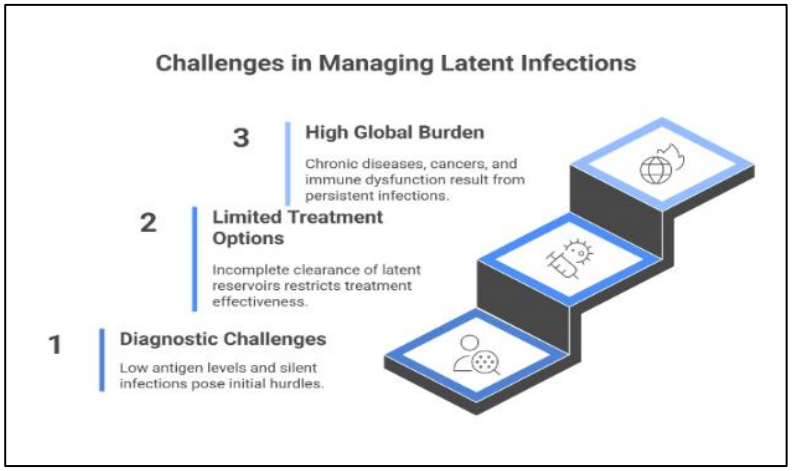


Figure 3. Clinical and public health challenges of latent infections. *Created by the authors based on concepts synthesized from Getahun et al. (2015), Cohen et al. (2019), Dartois (2022), Wykes and Lewin (2018), and GBD 2019 Hepatitis B Collaborators (2022).*

3.1.7.2 Therapeutic strategies

The conventional treatment for latent infections focuses only on interfering with the reproduction of the pathogen or inhibiting its ability to reactivate, but does not try to remove latent reservoirs. Extended treatment durations, drug resistance, and heterogeneity within the bacterial population are still challenges for the successful treatment of latent Mycobacterium tuberculosis infection, for which prolonged antibiotic regimens including isoniazid-containing or rifamycin-containing regimens are still the standard of care (Dartois, 2022). In the same way, antiviral drugs such as acyclovir can inhibit the replication of herpes viruses and decrease the clinical reactivation, but can't destroy dormant viral episomes. Current antiviral treatments can suppress viral replication but cannot eliminate covalently closed circular DNA (cccDNA), which remains a major obstacle to achieving a functional cure for chronic hepatitis B (Revill et al., 2019). Advances in therapeutic approaches include therapeutic vaccination, host-directed therapy, and immune checkpoint modulation, which could help to boost immune control and help better manage persistent bacterial and viral infections in the long-term (Tribolet et al., 2020).

3.1.7.3 Global burden

Despite their high prevalence rates and ability to survive for an entire life, latent infections constitute a major global burden of disease and a potential public health threat if they reappear in an infected organism. The estimated global proportion of the population living with latent *Mycobacterium tuberculosis* infection (MTBI) (about 25% worldwide) is considered a significant reservoir of potential future TB cases (Cohen et al., 2019; Ding et al., 2022).

Chronic infection with hepatitis B virus (HBV) continues to be a major contributor to hepatocellular carcinoma (HCC) mortality and cancer globally, accounting for this burden mostly in high-endemic areas (GBD 2019 Hepatitis B Collaborators, 2022; El-Serag, 2012). Plus, long-term viral infection, particularly cytomegalovirus infection, is associated with higher morbidity in immunocompromised people and older adults and the oncogenic viruses (human papillomavirus) are also responsible for a significant fraction of infection-associated cancers (Griffiths & Reeves, 2021). Taken together, these latent and ongoing infections contribute to a major health system burden the world, especially in LMICs where diagnostic and treatment capacity is limited (GBD 2019 Hepatitis B Collaborators, 2022).

3.1.8 Recent Research and Emerging Insights

Biomedical research over the past few years has significantly advanced knowledge of the mechanisms of pathogen latency at the molecular level and their implications. The identification of hidden reservoirs is evolving, with current developments such as the use of multi-omics approaches, discovery of new biomarkers, artificial intelligence (AI) and computational modelling, to support identification, pathogen reactivation prediction, and the development of more specific diagnostics and therapeutic strategies.

3.1.8.1 Omics methods

The study of pathogen latency has been revolutionized by the development of high-throughput omics technologies, which have allowed genome, transcriptome, proteome, metabolome and epigenome characterisation of host–pathogen interactions. These have uncovered molecular markers that are linked to persistence of the pathogen, immune regulation in host, and disease progression, broadening the knowledge of latent infections in a variety of bacterial and viral pathogens. Multi-omics analysis, involving complementary information in a single study, investigates complex networks in host–pathogen interactions and persistence (Argelaguet et al., 2018) for further enhancing latency research. These multi-

dimensional data aggregated together enable advanced computational analyses and artificial intelligence (AI)-driven predictive models that are being used to diagnose, monitor and control latent infections.

3.1.8.2 Biomarkers of latency

There has also been a great deal of research on the identification of biomarkers that could be used to distinguish between latent infection and active disease and to predict the risk of activation of pathogens. Infectious diseases, for example, have shown promise in terms of identifying circulatory microRNAs as potential, minimally invasive candidates for biomarkers that reflect the pathogen's presence and the host's immune response to it (Tribolet et al., 2020). Likewise, extracellular vesicle-derived proteins and other extracellular vesicle-associated molecules from infected cells offer unprecedented insights into interactions with host and pathogen and are being studied as potential markers for disease monitoring and risk assessment in disease reactivation (Liu et al., 2021). While additional clinical validation is needed, such novel biomarkers offer promise for enhanced diagnosis, personalized risk stratification and precision medicine management for latent infections.

3.1.8.3 AI and computational biology

Emerging techniques and technologies are now leveraging artificial intelligence (AI) and machine learning to model pathogens and their interactions with their hosts, allowing for greater precision in large-scale bio-data analysis. Machine learning algorithms combine host transcriptomic, metabolomic, and clinical data and have demonstrated great promise in predicting tuberculosis treatment outcomes and assisting clinicians in the treatment decision-making process (Fayaz et al., 2024). Besides, computational tools based on artificial intelligence have also accelerated the study of infectious diseases, by enhancing virtual screening approaches and assisting in the identification of new drug targets and therapeutic molecules against intractable infections (Agamah et al., 2020; Xu et al., 2020). The increasing volume of multi-omics data will see next-generation precision medicine, biomarker discovery and disease risk prediction, particularly for latent infections, become enhanced by AI and computational biology.

3.2 Discussion

Pathogen latency is a state of organism which involves persistence of the microorganism in the host with the ability to reactivate, while minimizing immune recognition, as suggested by literature synthesized in this review. In every type of pathogen, whether bacterial, viral or protozoal, persistence can have several pathogen-specific mechanisms such as metabolic adaptation, limited gene expression, immune evasion and maintenance in protected host niches (Barry et al., 2009; Alcamí & Heesters, 2023).

The reviewed data further suggest that latent infection could also play a role in chronic inflammation, immune dys-regulation, tissue damage, and disease course. Reactivation is critical whenever there is a lack of host immune surveillance, which can be associated with factors like immunosuppression, ageing, HIV infection, diabetes, malnutrition, and immunosuppressive therapy (Getahun et al., 2015; Razonable, 2020).

One of the biggest challenges is that the current diagnostic methods are not sensitive enough to differentiate between latent and active infection and to predict reactivation of a latent infection. New biomarkers, multi-omics technologies and computational tools such as artificial intelligence can help identify, monitor and assess the risk of PD, but still need to be validated in patients (Argelaguet et al., 2018; Tribolet et al., 2020; Liu et al., 2021).

Therapeutic management is also complicated because the usual antimicrobial and antiviral treatments might not eradicate the persistent reservoirs. Therapeutic vaccination, host-directed therapy, generation of engineered bacteriophages and immune checkpoint modulation are some of the most promising strategies, especially for persistent infections, that are being investigated (Tribolet et al., 2020; Dartois, 2022; Zahedipour et al., 2024; Łobocka et al., 2021).

In conclusion, the evidence examined shows that the role of pathogen persistence, immune surveillance, reactivation, chronic inflammation and disease progression are all linked and determine the long-term consequences of latent infections.

3.2.1 Implications

The results of this review have clinical and public health implications as latent infections may not manifest clinical symptoms but still have the potential to re-emerge and cause chronic disease. Better identification of those who may have latent infections and better assessment of their risk for reactivation, therefore, will be important for timely intervention and disease prevention. The current lack of sensitive markers and methods to distinguish latent from active infection are additional driver of the need for more sensitive markers and methods that can distinguish latent infection from active infection (Getahun et al., 2015; Cohen et al., 2019). Further innovative methods such as multi-omics, biomarker discovery, precision medicine, AI and host-directed therapeutic strategies could enhance detection, monitoring and treatment of latent infections. They might complement existing clinical and public health strategies to enable more precise risk assessment and treatment and to help overcome the ongoing challenges of pathogen reservoirs.

3.2.2 Research Contribution

The contribution of this review is a synthesis of the evidence on the functions of latent and persistent infections in chronic human disease from different bacterial, viral, and protozoan pathogens. In contrast to thinking of pathogen-specific mechanisms of latency separately, the review links pathogen persistence, immune evasion, reactivation, chronic inflammation and disease progression in a common framework. The review further identifies novel strategies to study and control latent infections, such as the discovery of

biomarkers, multi-omics technologies, computational biology, AI, precision medicine and host-directed therapeutic strategies. The review highlights and sketches a pathway connecting these advances to the clinical and public health burden of latent infections and underscores the importance of integration for enhancing the detection, risk stratification and management of latent infections.

3.2.3 Limitations

There are a number of limitations to this review. This is a narrative review and aims to provide a qualitative summing up of what has been written rather than a quantitative comparison of the findings in various studies. Also, there are significant differences in the mechanisms of persistence, latency, immune evasion and reactivation of the pathogens reviewed, making it difficult to compare the different infectious diseases. Other significant uncertainties exist with respect to the detection and prediction of latent infections. There are some areas in which existing diagnostic tests may not be accurate enough to differentiate between latent infection and actual infection, and several new biomarkers, multi-omics approaches and computational tests that are emerging for further validation. Several potential therapeutic and synthetic biology methods are still in experimental or developmental stages, and targeting persistent pathogen reservoirs and the feasibility of translating emerging methods into clinical practice are challenges.

3.2.4 Suggestions

Future studies will need to determine how best to develop strategies that will be efficient in targeting latent and persistent pathogen reservoirs without causing too much damage to host tissues. Pathogen resistance to conventional antimicrobial measures is often due to their capacity to enter protected or metabolically altered conditions. Understanding the molecular mechanism of latency and persistence may enable the identification of pathogen-specific vulnerabilities and development of therapy to eliminate or control dormant populations (Dartois, 2022; Tribolet et al., 2020; Zahedipour et al., 2024).

However, the concept of precision medicine should also be considered to take into account variability in the pathogen and host immune responses. The combination of host and pathogen biomarkers along with genome- and transcriptomic-based data might assist in identifying those who are more likely to have a persistent infection or reactivation as well as provide more focused therapeutic approaches (Argelaguet et al., 2018; Liu et al., 2021). Other avenues of therapeutic intervention and synthetic biology are also possible avenues for dealing with long-term infections. New approaches to detection, control or eradication of latent pathogen reservoirs can be developed through continued engineering of biological systems and targeted strategies. These strategies are, however, yet to be tested and validated on a larger clinical sample for wider use (Łobocka et al., 2021; Zahedipour et al., 2024). Finally, increased interdisciplinary scope in order to use advances in the understanding of latent infections in practical diagnostic and therapeutic use will be crucial. Cooperative efforts can facilitate linking molecular mechanisms that enable pathogen persistence to clinical and public health outcomes (Getahun et al., 2015; Cohen et al., 2019).

4. CONCLUSION

Latent infections remain a significant yet often underrecognized contributor to the global burden of chronic diseases. By establishing long-term persistence within the host and reactivating under favorable conditions, these pathogens contribute to a wide spectrum of disorders, including tuberculosis, viral hepatitis, cancer, and immune-mediated diseases. Understanding the molecular mechanisms underlying pathogen latency and host–pathogen interactions is therefore essential for improving disease prevention, diagnosis, and treatment.

Addressing latent infections requires integrated strategies that combine early and accurate diagnosis, effective therapeutic interventions, and coordinated public health efforts. Advances in biomarker discovery, multi-omics technologies, artificial intelligence, precision medicine, and synthetic biology have created new opportunities to improve the detection, monitoring, and targeted management of latent infections while supporting more individualized therapeutic approaches.

Ultimately, overcoming the challenges posed by pathogen latency will require sustained interdisciplinary collaboration among microbiologists, immunologists, clinicians, computational biologists, and public health researchers. Continued investment in translational research and innovative technologies will be critical for transforming our growing understanding of latent infections into effective clinical interventions and public health strategies capable of reducing the long-term burden of chronic infectious diseases.

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AS: Conceptualization, supervision, critical review, manuscript editing, and final approval of the manuscript. **KS:** Conceptualization, literature review, writing—original draft preparation, visualization, manuscript revision, and editing. All authors have read and approved the final version of the manuscript.

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