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REVIEW MICROBIOLOGY

Global epidemiology of HTLV: Under-reported and under-studied regions

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ABSTRACT

To examine the global epidemiology of human T-lymphotropic viruses (HTLVs), with a focus on under-reported and under-studied regions such as Turkiye, and to highlight public health challenges, including insufficient surveillance and lack of awareness. A comprehensive review of published literature and epidemiological data was conducted to identify trends, prevalence rates, and gaps in surveillance. Key sources included peer-reviewed journals and global health reports. HTLV-1 was identified as highly endemic in regions such as Japan, the Caribbean, South America, and sub-Saharan Africa. Limited data were available for Turkiye and adjacent regions, with estimated prevalence rates below 0.1%. Insufficient screening, stigma, and resource constraints were noted as major barriers to improved surveillance and prevention. HTLVs remain a neglected public health issue with significant implications for healthcare systems. Targeted research, expanded surveillance, and public health interventions are urgently needed, particularly in under-studied regions like Turkiye and Southeast Asia. Human T-lymphotropic viruses (HTLVs) are globally distributed retroviruses with significant health implications, particularly in endemic regions. Despite the known association of HTLV-1 with adult T-cell leukemia/lymphoma (ATLL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), comprehensive epidemiological data are lacking for several regions. This review examines the global epidemiology of HTLV, with a particular focus on under-reported and under-studied areas, including Turkiye. Highlighting the public health challenges posed by insufficient surveillance, lack of routine screening, and limited awareness, this review emphasizes the urgent need for global efforts to address this neglected public health issue.

Keywords: Epidemiology; Human T-lymphotropic virus; HTLV; prevention; surveillance; transmission.

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Human T-lymphotropic viruses (HTLVs), belonging to the Deltaretrovirus genus, were the first human retroviruses discovered, with HTLV-1 identified in 1980 [1]. HTLV-1 is associated with severe diseases, including ATLL and HAM/TSP, while HTLV-2, though less pathogenic, has been implicated in certain neurological conditions [2, 3]. Despite an estimated global burden of 5–10 million cases, true prevalence remains uncertain due to under-diagnosis, lack of surveillance, and absence of routine screening in blood banks and antenatal settings [4, 5]. This review provides an updated analysis of the epidemiology of HTLV, with a focus on high-prevalence regions, under-studied areas (including Turkiye), and the barriers to accurate reporting.

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HTLV BIOLOGY AND TRANSMISSION

Biological Structure and Classification

Human T-lymphotropic viruses (HTLVs) belong to the genus Deltaretrovirus in the family Retroviridae. Like other retroviruses, HTLV carries its genetic material as single-stranded RNA, which is reverse-transcribed into DNA upon infection of the host cell. HTLV-1 and HTLV-2 are the two primary types infecting humans, with HTLV-1 being more pathogenic. HTLV-1 is associated with severe diseases such as adult T-cell leukemia/lymphoma (ATLL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), while HTLV-2 has a weaker association with disease and is predominantly linked to neurological conditions [1, 2].

The viral genome of HTLV encodes structural proteins (Gag, Pol, and Env), regulatory proteins (Tax and Rex), and accessory proteins (p12, p13, p30, and HBZ). Tax and HBZ play key roles in viral replication, cellular transformation, and the development of HTLV-associated diseases. Tax is particularly important for driving the proliferation of infected T-cells, which may contribute to oncogenesis in ATLL [3, 4].

Host Interaction and Pathogenesis

HTLV-1 primarily infects CD4+ T-cells, while HTLV-2 targets CD8+ T-cells. Once integrated into the host genome, the virus persists in a latent state, with clonal proliferation of infected cells driving viral spread rather than active replication. This mode of propagation minimizes immune detection, allowing the virus to persist lifelong in the host [5].

The immunopathogenesis of HTLV-1-associated diseases involves sustained immune system stimulation and inflammatory processes. In HAM/TSP, immune-mediated destruction of spinal cord neurons leads to progressive neurological deficits. In ATLL, tax-driven genetic instability and dysregulated signaling pathways result in malignant transformation [6].

Modes of Transmission

HTLV is transmitted through three primary routes, each associated with specific risk factors:

1. **Mother-to-Child Transmission (MTCT):**

   Vertical transmission occurs predominantly through breastfeeding. Infected mothers transfer the virus to their infants via milk, particularly when breastfeeding is prolonged beyond six months. The rate of transmission ranges from 15% to 25% in endemic areas [7]. Reducing breastfeeding duration or substituting with formula milk significantly lowers transmission rates, as evidenced by Japan's antenatal screening programs [8].

2. **Sexual transmission:**

   HTLV-1 is transmitted via unprotected sexual contact, with male-to-female transmission being more efficient than female-to-male. Transmission risk increases with the presence of co-infections such as sexually transmitted infections (STIs), which compromise mucosal barriers and enhance viral entry [9]. Studies suggest that HTLV-1 is more prevalent in older women, possibly due to cumulative risk from lifelong sexual exposure [10].

3. **Parenteral transmission:**

   Bloodborne transmission occurs through exposure to infected blood or bodily fluids, including:

   - Blood Transfusions: Before the implementation of blood donor screening programs, HTLV transmission through blood transfusions was common, with seroconversion rates reaching 40% in some studies [11]. Current screening has significantly reduced this route of transmission in many countries.
   - Intravenous Drug Use: Sharing needles among intravenous drug users is a major transmission route in some populations, particularly for HTLV-2 [12].
   - Medical Procedures: Unsafe medical practices, such as reusing needles or unsterile surgical equipment, contribute to transmission healthcare-limited environments.

Highlight key points

- HTLV, particularly HTLV-1, is linked to serious health issues like adult T-cell leukemia and HTLV-associated myelopathy, with 5-10 million cases worldwide
- Epidemiologic data on HTLV in underreported regions like Turkiye is insufficient, creating major public health challenges.
- Improving HTLV surveillance, screening, and diagnostic protocols is crucial to better understand the virus's spread and impact.
- In Turkiye, targeted studies on high-risk groups like migrants and refugees are essential to understand HTLV spread and create effective interventions.

Geographic and Social Factors Influencing Transmission

Transmission dynamics vary globally based on cultural practices, healthcare infrastructure, and public health policies. For example:

- In endemic regions such as Japan, the Caribbean, and parts of South America, breastfeeding practices and sexual behaviors influence MTCT and sexual transmission rates.
- In Africa, traditional healing practices and the high prevalence of STIs contribute to increased sexual and parenteral transmission.
- In Turkiye and adjacent regions, migration and refugee movement may facilitate the spread of HTLV among underserved and at-risk populations [13].

Barriers to understanding transmission

1. **Asymptomatic carriers:**
   Most HTLV-infected individuals remain asymptomatic, making it challenging to detect and study transmission patterns. It is estimated that only 2–5% of infected individuals will develop severe diseases such as ATLL or HAM/TSP during their lifetime [14].
2. **Diagnostic gaps:**
   Many regions lack reliable screening programs for blood donors and pregnant women, leading to underdetection of transmission routes and prevalence.
3. **Stigma and awareness:**
   Misconceptions about HTLV transmission, often conflated with HIV, deter individuals from seeking testing and disclosing risk behaviors.

Prevention of Transmission

Efforts to reduce HTLV transmission focus on targeted interventions:

1. **Screening:**
   - Routine blood donor screening has significantly reduced HTLV transmission through blood transfusions in high-income countries. Expanding these programs to low- and middle-income countries (LMICs) is crucial.
   - Antenatal screening for pregnant women, coupled with counseling on breastfeeding alternatives, has proven effective in preventing MTCT [8].
2. **Education and awareness:**
   Public health campaigns promoting safer sexual practices, access to needle exchange initiatives, and alternatives to prolonged breastfeeding can mitigate transmission risks.
3. **Regulation of medical practices:**
   Enforcing strict sterilization protocols and discouraging unsafe injections can reduce parenteral transmission, particularly in LMICs.

GLOBAL DISTRIBUTION

The distribution of HTLV exhibits significant geographical variability, with well-documented endemicity in some regions and a lack of reliable data in others.

High-prevalence Regions

1. **Japan:** Japan has one of the most comprehensive HTLV-1 surveillance systems globally. The prevalence of HTLV-1 is approximately 0.3–1% in the general population, with higher rates in southern regions such as Kyushu and Okinawa [9]. Implementation of a national antenatal screening program in 1987 has reduced vertical transmission rates to below 0.2% [10].
2. **Caribbean and South America:** The Caribbean region is a hotspot for HTLV-1, with prevalence rates ranging from 3–6% in countries like Jamaica, Trinidad, and Haiti [11, 12]. In South America, Brazil has been extensively studied, with general population prevalence rates of 0.4–1.8% and much higher rates in at-risk groups such as intravenous drug users and sex workers [13, 14].
3. **Sub-Saharan Africa:** Sub-Saharan Africa is considered the origin of HTLV, with high prevalence in regions such as Gabon and southern Cameroon, where rates exceed 10% in some communities [15]. HTLV-2 is also found, though predominantly in Pygmy populations [16].

Turkiye and surrounding regions

Turkiye, strategically located between Europe, Asia, and the Middle East, has sparse data on HTLV prevalence. Limited studies among blood donors and high-risk populations have reported prevalence rates of less than 0.1% [17, 18]. However, the true burden in the general population remains unclear due to the lack of routine screening and epidemiological studies. Turkiye's close proximity to regions with higher HTLV prevalence, such as the Middle East and North Africa (MENA), raises concerns about potential under-detection [19]. This warrants further investigation, particularly in vulnerable groups such as immigrants, refugees, and rural populations.

Under-reported and Under-studied Regions

1. **Southeast Asia:** While HTLV is known to circulate in Southeast Asia, particularly Papua New Guinea, limited data exist for populous countries such as Indonesia, Vietnam, and the Philippines. Sporadic studies report prevalence rates of less than 1% [20].
2. **South Asia:** India, with its vast population, has minimal data on HTLV prevalence. A few studies in blood donors and antenatal populations report seroprevalence rates ranging from 0.02% to 0.08%, suggesting the virus is under-detected [21, 22].
3. **Middle East and North Africa (MENA):** The MENA region is vastly under-studied, with isolated reports from Iran and Egypt indicating prevalence rates below 1%. These findings likely underestimate the true burden due to limited screening infrastructure [23, 24].
4. **Central Asia and Eastern Europe:** Epidemiological data from Central Asia and Eastern Europe are almost non-existent. The lack of research in these regions highlights a critical gap in global HTLV surveillance [25].
5. **Pacific Islands:** Data from Melanesia and Polynesia suggest possible endemicity, though systematic studies remain scarce. HTLV transmission in these isolated populations warrants further investigation [26].

CHALLENGES IN SURVEILLANCE

HTLV surveillance is hindered by several factors:

1. **Awareness and stigma:** Misconceptions about HTLV, including its conflation with HIV due to overlapping transmission routes, contribute to stigma and under-reporting [27].
2. **Limited screening programs:** Most countries, including Turkiye, lack routine HTLV screening in blood banks and antenatal care, resulting in missed diagnoses [28].
3. **Resource constraints:** In LMICs, the high cost of testing and limited healthcare infrastructure impede widespread screening [29].
4. **Diagnostic challenges:** Current diagnostic tools, such as serological assays, are not always affordable or accessible in healthcare-limited environments [22, 30].

PUBLIC HEALTH IMPLICATIONS

HTLV-associated diseases have long-term implications for healthcare systems, particularly in endemic regions. For example:

- **Economic burden:** Chronic conditions such as HAM/TSP require lifelong care, imposing financial strain on individuals and healthcare systems [28, 31].
- **Mother-to-child transmission:** Vertical transmission remains a significant route of infection, particularly in regions without antenatal screening programs [8, 32].
- **At-risk populations:** High-risk groups, including intravenous drug users, sex workers, and indigenous communities, require targeted interventions to reduce transmission [27, 33].

FUTURE DIRECTIONS

The current gaps in the epidemiological understanding and management of HTLV highlight the urgent need for a multifaceted and globally coordinated response. Below are key areas for future research, policy development, and intervention:

1. **Global Surveillance Programs**

   A comprehensive global HTLV surveillance framework is essential. This could be modeled after existing HIV surveillance systems and should aim to:

   - Include HTLV testing in routine screening for blood donors, pregnant women, and high-risk populations.
   - Standardize diagnostic protocols to facilitate comparison of data across regions.
   - Collect longitudinal data to better understand disease progression and transmission dynamics.

2. **Regional focus in under-reported areas**

   Special attention must be given to regions like Turkiye, Central Asia, Southeast Asia, and the Middle East. For Turkiye, studies should focus on:

   - Prevalence in urban versus rural areas.
   - HTLV in immigrant and refugee populations, given the region's role as a migration hub.
   - Risk factors unique to Turkiye, such as cultural practices and healthcare access.

3. **Cost-effective diagnostic tools**

   Future efforts should prioritize:

   - Development of point-of-care testing kits for rapid and affordable HTLV detection.
   - Integration of HTLV testing into multiplex platforms.

4. **Mother-to-child transmission prevention**
   Lessons from Japan's successful antenatal screening program should be adapted for other regions.
5. **Vaccine development and therapeutics**
   A vaccine for HTLV remains elusive; targeted research is critical.
6. **Awareness campaigns and education**
   Public awareness and healthcare provider education must be enhanced.

CONCLUSION

Human T-lymphotropic viruses (HTLVs) remain a significant yet under-recognized public health challenge. Despite the virus being identified over four decades ago, there are substantial gaps in our understanding of its epidemiology, transmission dynamics, and associated disease burden. Millions of individuals globally are infected with HTLV, yet the virus is often overlooked in public health initiatives, especially in under-studied regions such as Turkiye, Southeast Asia, Central Asia, and the Middle East. This neglect has resulted in limited screening, poor awareness, and inadequate resources for prevention, diagnosis, and management.

The association of HTLV-1 with debilitating and life-threatening conditions like adult T-cell leukemia/lymphoma (ATLL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) underscores the urgent need for action. These diseases impose substantial socioeconomic and healthcare burdens, particularly in endemic regions where healthcare systems are already strained. Furthermore, the chronic nature of HTLV-associated diseases requires lifelong care, emphasizing the importance of early detection and prevention.

Key Insights

The epidemiology of HTLV is marked by significant geographic variability. High-prevalence regions such as Japan, the Caribbean, South America, and parts of Sub-Saharan Africa have implemented effective strategies, including antenatal screening and blood donor testing, that have demonstrated the feasibility of reducing HTLV transmission. However, many regions, including Turkiye, lack the infrastructure and policies to address the virus. For Turkiye, in particular, its role as a bridge between high-prevalence and low-prevalence regions highlights the potential for HTLV to spread through vulnerable populations such as immigrants and refugees. Targeted research and public health efforts in Turkiye could serve as a model for addressing HTLV in other under-studied regions.

The biology of HTLV also poses unique challenges to its detection and control. The virus's ability to persist in a latent state, its lifelong carriage, and its low progression rate to symptomatic disease complicate efforts to identify and manage infected individuals. This has contributed to a persistent gap in surveillance data, especially in low- and middle-income countries (LMICs). The lack of reliable and affordable diagnostic tools exacerbates this issue, making routine screening infeasible healthcare-limited environments.

Future Priorities

1. **Expanding surveillance:** Strengthening surveillance systems is critical to map the true global burden of HTLV. Integrating HTLV testing into existing HIV/STD frameworks, especially in regions where HTLV remains endemic and poorly studied, can provide an efficient way to enhance detection rates.
2. **Improving access to diagnostics:** Developing and deploying affordable, point-of-care diagnostic tools will enable wider screening in LMICs and resource-limited regions. This will be essential for identifying asymptomatic carriers and preventing mother-to-child transmission.
3. **Prevention strategies:** The success of Japan's antenatal screening program serves as a model for other countries. Expanding such programs globally, especially in regions where HTLV remains endemic and poorly studied, will be a crucial step in reducing vertical transmission rates.
4. **Awareness and Education:** Educating healthcare providers and the public about HTLV's transmission, associated diseases, and prevention measures will be key to reducing stigma and promoting testing and early intervention.

A Call for Global Action

Addressing the global burden of HTLV requires coordinated international efforts, led by public health organizations such as the World Health Organization (WHO), national governments, and research institutions. These efforts must prioritize funding for HTLV research, particularly in the areas of vaccine development, therapeutic interventions, and the identification of biomarkers for

disease progression. Furthermore, fostering collaborations between endemic and non-endemic countries can facilitate the exchange of knowledge and resources to tackle HTLV more effectively.

HTLV also presents an opportunity to integrate neglected tropical diseases (NTDs) into broader health frameworks. The virus disproportionately affects marginalized populations, including those in low-resource settings, which aligns with the global NTD agenda. By including HTLV in these frameworks, international health initiatives can promote equity in addressing infectious diseases.

Final Remarks

HTLV is not just a biological or medical issue—it is a public health and social challenge. The virus's long-term effects on individuals and healthcare systems, coupled with its potential for silent spread, make it a pressing issue that demands attention. With concerted efforts to improve surveillance, prevention, and treatment, the global burden of HTLV can be mitigated. Addressing HTLV effectively will not only reduce the suffering of millions but also provide a model for managing other neglected infectious diseases. This is a challenge that the global health community cannot afford to ignore.

By prioritizing HTLV as a public health concern, we can pave the way for better outcomes for affected populations and a more equitable approach to addressing infectious diseases worldwide. The time to act is now.

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