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Silkworm-Based Vaccine Production for H5N1: A One Health Approach to Pandemic Preparedness

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Abstract

The persistence of highly pathogenic avian influenza A(H5N1) at the animal–human–environment interface exemplifies the urgent need for a One Health approach to pandemic preparedness. Outbreaks in poultry and wild birds continue to cause severe economic disruption, food insecurity, and sporadic but often fatal human infections, while viral evolution challenges existing vaccine strategies. Conventional platforms, egg- based, mammalian cell culture, microbial expression, and mRNA, face limitation ns in scalability, cost, speed, and deployment in low- and middle-income countries. In this context, silkworm-based biofactories provide a promising alternative for vaccine production. Silkworm larvae can generate complex antigens with mammalian-like post-translational modifications at low cost, with minimal infrastructure, short production cycles, and reduced environmental impact. Their dual-use potential for veterinary and human vaccines aligns with the One Health imperative, enabling simultaneous protection of poultry and people while reducing the risk of zoonotic spillover. Decentralized silkworm-based production in outbreak-prone regions could shorten supply chains, accelerate response, and enhance equitable access. Realizing this potential will require investment in bioprocess optimization, regulatory adaptation, and public–private partnerships. By leveraging silkworm biofactories, global health systems can advance toward sustainable and resilient preparedness against H5N1 and other emerging zoonoses.

Keywords: Influenza A Virus; H5N1; Silkworms; Vaccines; One Health; Pandemic Preparedness

Introduction: One Health and Emerging Zoonoses

In a world where human, animal, and environmental health are inextricably linked, the One Health approach has evolved from a theoretical framework into an urgent, actionable imperative. This perspective recognizes that the health of people is deeply connected to the health of animals and the ecosystems they share, and that disease prevention and control cannot be siloed within a single sector [1]. Nowhere is this interconnectedness more apparent than in the context of zoonotic pathogens, diseases that cross the species barrier from animals to humans, often with devastating consequences for human health, agricultural livelihoods, and regional economies [2].

H5N1 as a Persistent Global Threat

Among these pathogens, the highly pathogenic avian influenza A(H5N1) virus represents a particularly salient case. H5N1 predominantly infects domestic poultry species, including chickens, ducks, and turkeys, which are frequently exposed to wild aquatic birds that serve as the principal natural reservoirs of the virus. Increasing evidence also indicates cross-species transmission to a range of wild and captive mammals, such as seals, otters, and felids, underscoring its capacity for broader host adaptation. Infections in these animals most commonly arise following the ingestion of infected birds, although alternative transmission routes have been documented. Sporadic cases in domestic mammals, including cats, dogs, and cattle, suggest that exposure to infected poultry or contaminated environments constitutes a plausible pathway of infection. These observations highlight the potential for cross-species transmission and the importance of monitoring non-avian hosts as part of H5N1 surveillance [3].

The persistence of H5N1 not only in domestic and wild birds but also in mammals coupled with sporadic but severe human infections underscores the dynamic interface between wildlife, livestock, and people. Human cases are often linked to close contact with infected birds or contaminated environments, highlighting how animal health and environmental conditions directly influence the risk of spillovers [4]. Simultaneously, ecological factors such as migratory bird patterns, climate change, and land-use practices shape the circulation and evolution of the virus, influencing both the scale and timing of outbreaks [5].

Economic and Societal Impacts of Avian Influenza

The impact of H5N1 extends far beyond human and animal health, with profound economic ramifications that reverberate across local, national, and global scales. Outbreaks in North America, for instance, have necessitated the mass culling of millions of poultry, triggering extensive compensation programs for affected farmers while destabilizing supply chains that encompass feed production, transport, processing, and retail distribution [6]. These disruptions not only affect commercial producers but also smallholder farmers and communities dependent on poultry as a primary source of income and nutrition [7].

In Europe, similar outbreaks have generated economic shocks of comparable magnitude. Trade restrictions and export bans imposed to prevent virus spread have led to sudden losses in international markets, while escalating biosecurity measures, ranging from farm-level decontamination protocols to regional surveillance programs, represent significant ongoing costs for governments and the private sector alike. Market volatility, driven by consumer uncertainty and fluctuating poultry prices, compounds these challenges, highlighting the vulnerability of both domestic economies and global supply networks to a single pathogenic threat [8].

The One Health Imperative in Pandemic Preparedness

By embracing a One Health lens, interventions against H5N1 extend beyond human clinical care to include enhanced veterinary surveillance, biosecurity in poultry farming, wildlife monitoring, and environmental management [9,10]. This integrated approach not only improves early detection and containment of outbreaks but also informs vaccination strategies, public health messaging, and risk reduction practices across communities [11]. Ultimately, One Health is not merely an academic principle, it is a practical, evidence-based strategy that strengthens global resilience against H5N1 and other emerging zoonoses, safeguarding human and animal populations alike while preserving the ecosystems that sustain them [12].

Epidemiology and Viral Evolution of H5N1

Since its emergence in the late 1990s, avian influenza A(H5N1) has established itself as a pathogen of global concern, triggering recurrent and often devastating outbreaks among domestic poultry and wild bird populations [13]. Its high pathogenicity in birds has prompted extensive culling campaigns, leading to substantial economic losses, disruption of agricultural supply chains, and threats to food security in affected regions. Although human infections remain relatively rare, they are frequently severe and often fatal, reflecting the virus's zoonotic potential and the fragile interface between animal and human health [14,15].

Cambodia provides a stark illustration of this ongoing risk: since 2023, the country has reported 27 confirmed human cases of H5N1 infection, with a mortality rate approaching 44% [16]. Similar patterns have been observed in neighboring Southeast Asian nations, highlighting both the regional persistence of the virus and the continued vulnerability of exposed populations [17]. Genetic analyses reveal that circulating H5N1 strains belong predominantly to clade 2.3.4.4b, a lineage characterized by rapid evolution, extensive geographic spread, and periodic reassortment with other avian influenza viruses [18]. These evolutionary dynamics not only complicate disease surveillance but also pose a challenge for the development of effective vaccines and antiviral strategies.

Limitations of Conventional Vaccine Platforms

Traditional vaccine strategies have struggled to keep pace with these demands. Egg-based inactivated vaccines, while safe and familiar, rely on embryonated eggs, a constraint when outbreaks surge. Mammalian cell culture systems offer consistency but come with high infrastructure costs, limiting scalability [19,20]. Microbial expression platforms, such as yeast or bacteria, can produce antigens quickly but often fail to replicate the complex structures required for effective immune responses against influenza [21]. mRNA vaccines, recently proven transformative, allow rapid adaptation to emerging strains yet demand sophisticated manufacturing and cold chain logistics that are difficult to deploy broadly, particularly in low- and middle-income countries (LMICs) [22].

Silkworm Biofactories: A Novel Vaccine Platform

Amid the limitations of conventional vaccine production, insect-based platforms, and silkworm larvae biofactories in particular, emerge as a compelling alternative [23]. Silkworms possess the remarkable ability to produce complex proteins with post-translational modifications closely resembling those of mammalian systems, yet they do so at a fraction of the cost and with a scalability that mammalian cell cultures struggle to match [24]. Influenza virus-like particles (VLPs) have already been successfully expressed in silkworm pupae [25], and other vaccine antigens, including those for Japanese encephalitis virus, SARS-CoV-2 spike protein, and Ebola glycoprotein, have also been produced in silkworms with promising immunogenicity [26-28]. These examples underscore not only the technical feasibility of this approach but also its potential to enable rapid, high-volume vaccine production, laying the groundwork for a true One Health vaccine strategy: protecting animals to reduce viral circulation, while concurrently preventing spillover into human populations.

Advantages of Silkworm-Based Production

The promise of silkworm biofactories extends beyond cost-efficiency and scale. Their minimal infrastructure requirements, fast production cycles, and low environmental footprint make them particularly well-suited to low- and middle-income countries, where conventional vaccine production is often constrained by resources and logistical challenges [29]. Moreover, the dual-use capacity of this platform, producing vaccines for both veterinary and human applications, directly addresses the One Health imperative of mitigating zoonotic threats at their source. By bridging the gap between animal and human health interventions, silkworm-based vaccine production represents not only an innovative technological solution but also a strategic approach to sustainable, equitable pandemic preparedness.

Decentralization and Equity in Vaccine Manufacturing

Integrating silkworm larvae vaccine platforms into pandemic preparedness strategies could fundamentally reshape how we respond to H5N1 and other rapidly emerging pathogens [30]. Unlike centralized mammalian cell culture facilities, which require extensive infrastructure and logistics, silkworm-based production can be decentralized and deployed in high-risk regions. Such facilities could dramatically shorten supply chains, mitigate the delays that currently hamper outbreak response, and reduce dependence on cold-chain transport [31]. This distributed approach also enables rapid adaptation: silkworm biofactories can swiftly produce vaccine antigens matched to the genetic makeup of circulating strains, an essential capability given the pace of influenza virus evolution [32]. Moreover, by enabling simultaneous immunization of animal and human populations, this approach addresses both sides of the One Health equation, reducing viral amplification in poultry while protecting human communities from spillovers [33].

Challenges and Pathways to Implementation

Realizing this vision will require sustained investment, technological refinement, and cross-sector collaboration. Research and development must focus on optimizing silkworm rearing conditions, improving baculovirus vector engineering for higher yield and antigen fidelity, and rigorously testing immunogenicity and safety in preclinical and clinical settings [34]. Infrastructure for rearing and processing silkworm larvae must be established or adapted in outbreak-prone regions, allowing vaccine production to take place closer to where it is needed most. Regulatory frameworks, both national and international, will need to evolve to accommodate novel production systems, harmonizing quality and safety standards across borders [35]. Public–private partnerships will be vital to transfer technology, build local manufacturing capacity, and integrate silkworm-based production into national and regional preparedness plans [36].

Conclusion: H5N1 as a Warning and an Opportunity

H5N1 is both a warning and an opportunity. Its persistence in avian populations, sporadic but severe human infections, and the economic shocks it generates underscore the cost of fragmented, reactive approaches [37]. Yet the same virus highlights the potential impact of innovative production platforms such as silkworm biofactories. By embracing this technology, the global health community can not only safeguard human populations and strengthen animal health systems but also stabilize poultry-dependent economies. This is the essence of One Health in action: aligning preparedness, prevention, and sustainability to create a resilient future.

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