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EVIDENCE BRIEF

Risk Assessment for Langya Henipavirus (LayV) in Ontario

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Key Messages

- Langya henipavirus (LayV) is a newly identified virus in the genus *Henipavirus* (Family *Paramyxoviridae*). Researchers detected LayV through sentinel acute febrile illness surveillance in the Henan and Shandong provinces of eastern China from 2018 through 2021.
- Researchers reported 35 acute LayV infections in humans, with additional detections reported in rodents, shrews, goats and dogs. Based on the limited evidence thus far, LayV is likely a zoonotic pathogen involving white-toothed shrews (*Crocidura* species). Based on current evidence, human-to-human transmission appears unlikely. Further research is needed to confirm potential modes and routes of transmission for LayV.
- Twenty-six out of 35 acute LayV cases had no other co-infection etiology identified after extensive investigations, and these patients presented with a febrile influenza-like illness accompanied by fatigue, cough, myalgia and gastrointestinal symptoms. Hospitalization was required for 14 of the 26 patients.
- No cases have been reported in Ontario or outside eastern China to date. Given the current known distribution of LayV and clinical case outcomes to date, the risk of importation, transmission (human-to-human or zoonotic), and severe disease in Ontario is low with a high degree of uncertainty. The risk of Ontarians acquiring a LayV infection after travel to eastern China is equally low, with a high degree of uncertainty. Due to its recent discovery, clinical laboratories have not yet established specific testing for LayV detection, therefore the impact on laboratory testing is moderate with a moderate degree of uncertainty. The overall risk assessment may change as new evidence emerges.
- The discovery of LayV infection among humans and other animals underscores the importance of monitoring zoonotic agents worldwide to prevent exposure to infected animal hosts, importation of infected animal hosts into new regions, and overall increased burden of disease in the general population.

Issue and Research Question

Langya henipavirus (LayV) is a newly identified virus from eastern China, with infections reported in humans and other animals.[1] To date, there is no reported human-to-human transmission, but our understanding of the current LayV epidemiology and transmission risk remains limited due to the novelty of the discovery and rarity of cases reported thus far.

This evidence brief summarizes available information and evidence on LayV relevant to its potential for impacting the health of Ontarians.

Methods

Public Health Ontario (PHO) performed a rapid search of primary and preprint literature on LayV using the MEDLINE database on August 19, 2022 (search strategy available upon request). Preprints are research papers that have not undergone peer-review but made publicly available to provide the latest data relevant an emerging topic such as LayV. English-language peer-reviewed and preprint records that described LayV were included if identified.

This evidence brief will concentrate on summarizing the data and information reported by Zhang et al. (2022), using background literature on related henipaviruses for context.[2]

Ontario Risk Assessment

Given the current known distribution of LayV (restricted to Henan and Shandong provinces of China with low number of cases) and clinical case outcomes to date, the risk of importation, transmission (human-to-human or zoonotic), and severe disease in Ontario is low with a high degree of uncertainty. The risk of Ontarians acquiring a LayV infection after travel to eastern China is equally low, with a high degree of uncertainty. Due to its recent discovery, clinical laboratories have yet established specific testing for LayV detection, therefore the impact on laboratory testing is moderate with a moderate degree of uncertainty. The overall risk assessment may change as new evidence emerges (see Table 1).

Table 1. Risk assessment for Langya virus in Ontario

Ontario-Specific Issues	Risk Level	Degree of Uncertainty
Importation to province	Low	High
Transmission within province	Low	High
Cases with severe disease	Low	High
Infection following travel to eastern China	Low	High
Impact on laboratory diagnostic testing	Moderate	Moderate

Henipaviruses

Langya henipavirus (LayV) is a newly identified virus in the genus *Henipavirus* and the family *Paramyxoviridae*.[2] Other henipaviruses include Cedar henipavirus (CedV), Ghanaian bat henipavirus (GhV), Hendra henipavirus (HeV), Nipah henipavirus (NiV), Mojiang henipavirus (MojV), and the newly described tentative species Angavokely henipavirus (AngV), Daeryong henipavirus (DARV), Denwin henipavirus (DewV), Gamak henipavirus (GAKV) and Melian henipavirus (MeliV).[3-6] HeV and NiV were the only henipaviruses previously known to cause disease in humans.

The reservoir hosts of CedV (Australia), HeV (Australia and southeastern Asia), GhV (Ghana), NiV (southern and southeastern Asia) and AngV (Madagascar) are fruit bats or flying foxes (*Pteropus* spp.).[3-5,7-9] The host of MojV (China) is the buff-breasted rat (*Rattus flavipectus*), while the hosts of DARV (South Korea), DewV (Belgium), GAKV (South Korea) and MeliV (Guinea) are white-toothed shrews (*Crocidura* spp.).[3,6,10] HeV infects humans through direct contact with the bodily fluids or tissues of infected horses (horses infected through bat saliva, excreta or urine).[8,11] NiV primarily infects humans through direct contact with infected bats, infected pigs/pig tissues (pigs infected through bat excretions), or contaminated fruit or date palm sap (sap contaminated through bat excretions).[11] Human-to-human transmission of NiV can occur through close contact or through respiratory droplets or urine or blood; human-to-human transmission for HeV is not known.[11]

The incubation period for HeV and NiV typically ranges from 5–16 days, causing a flu-like illness with fever, cough, myalgia, headache and dizziness.[4] Encephalitis may develop, leading to confusion, seizures, abnormal reflexes and coma. Among the known HeV human infections (n=7), four died.[4,7,8] The case fatality rate for NiV infections range from 40% to 70% or higher.

Langya Henipavirus

Discovery and Epidemiology

A team of researchers (Zhang et al. 2022) conducted a zoonotic infection surveillance program at three sentinel hospitals in eastern China targeting febrile patients with animal exposure (within one month of symptom onset) from April 2018 through August 2021.[2] Two of the sentinel hospitals were in the city of Xinyang (Henan Province) and one was in the city of Qingdao (Shandong Province). Throat swab samples for study participants were analyzed using metagenomic sequencing for pathogen discovery (limited to the index patient and five shrews).

In December 2018, a 53-year-old female farmer who presented with febrile illness to the Qingdao sentinel hospital had a throat swab metagenomic analysis revealing a new virus, named *Langya henipavirus.*[2] Following the discovery, the researchers developed a reverse transcription polymerase chain reaction (RT-PCR), cell culture assay and indirect immunofluorescence (IFA) IgG antibody detection assay targeting LayV. From April 2018 to August 2021, 34 additional patients were identified based on throat swabs and blood samples to have an acute LayV infection (case definition not described). All patient specimens (serum, whole blood, throat swabs) were also tested by PCR and serology for additional zoonotic agents and respiratory pathogens, and nine patients were found to have co-infection (one with influenza virus, two with hantaviruses, six with Dabie bandavirus).

From the patients with acute LayV infection without other identified infectious etiologies (n=26), most were female (62%, 16/26) and most were ≥60 years (54%, 14/26) (median: 60.5 years; range: 9–84).[2] The most commonly reported occupation was farmer (85%, 22/26), followed by factory worker (12%, 3/26) and student (4%, 1/26). Fourteen cases were from Shandong Province and 12 from Henan Province.

The authors do not report the type of farming (e.g., cattle, dairy, orchards, crops) performed by patients nor the type of work performed by the factory workers. It is unknown if specific types of farming practices increase the risks of LayV infection. Understanding specific risks could help in the development and implementation of preventative measures. Considering the targeted geographical focus of the sentinel surveillance, it is currently unknown if LayV is present in other regions.

Genome and Phylogenetics

Langya henipavirus, like other henipaviruses, is an enveloped, single-stranded, negative-sense RNA virus. The genomic structure of LayV is similar to other described henipaviruses and consists of 18,402 nucleotides.[2] The *Henipavirus* genome encodes for six structural proteins (3' end to 5' end): nucleocapsid (N), phosphoprotein (P), matrix protein (M), surface glycoprotein (G), fusion protein (F), and large viral RNA-dependent RNA polymerase (L).[7]

Based on phylogenetic analysis of the six structural proteins, Zhang et al. (2022) showed that LayV was most closely related to MojV (another *Henipavirus* with a rodent reservoir).[2] The *L* gene sequence was further reported to have three common polymorphic sites (at nucleotide positions 13521, 13574, and 13643), although the spatiotemporal distribution of these haplotypes and their potential impact on disease severity have not been described.

Reservoirs and Transmission

To determine potential animal hosts of LayV, Zhang et al. (2022) tested domestic animals (goats, dogs, pigs, cattle; n=459) in the residential villages of infected patients, along with 25 species of wild rodents and shrews (n=3,380).[2] Sera from domestic animals were subjected to LayV IFA IgG antibody detection. A small proportion of domestic goats (1.8%, 3/168) and dogs (5.1%, 4/79) were IgG seropositive. Domestic cattle (n=100) and pigs (n=112) were IgG seronegative for LayV. Wild rodent and shrew samples (tissue, intestine contents, urine) were tested by RT-PCR. The authors so not state why they performed different tests for wild and domestic animal hosts. Twenty-seven percent (71/262) of sampled shrews (Ussuri white-toothed shrew, *Crocidura lasiura*; Asian lesser white-toothed shrew, *Crocidura shantungensis*) were RT-PCR positive. Additional rodents that tested positive for LayV by RT-PCR were the northern red-backed vole (*Myodes rutilus*) (1.3%, 1/79), the striped field mouse (*Apodemus agrarius*) (0.6%, 3/462) and the house mouse (*Mus musculus*) (0.5%, 4/782). The relatively high prevalence of LayV RNA detected in shrews compared to other small rodents led the authors to suggest that shrews are one of the primary animal reservoirs for LayV. The route of acquisition from this potential animal reservoir remains to be established, and could include either direct exposure from shrews or via another intermediate host.

The authors performed contact tracing on nine patients and 15 of their close contact family members, and no transmission was reported in close contacts.[2] In addition, the cases have not been previously exposed to one another and did not cluster genotypically, spatially or temporally (based on haplotype designations and epidemiology). The authors acknowledge that the sample size was too small to rule out human-to-human transmission; however, data from this study suggests it is less likely.

Currently, we do not know if LayV can infect rodents or shrews in Ontario (e.g., through spillback human-to-animal acquisition or accidental importation of infected animal hosts). The proposed primary reservoirs of LayV are shrews in the genus *Crocidura*; however, this genus of shrew is not present in North America. It is important to note that authors detected LayV, albeit at a low prevalence, in rodent species also found in Ontario, namely the northern red-backed vole and house mouse. We are not aware of any risks of LayV entering Ontario through imported food, laboratory animals or pets.

Disease Severity

In 26 patients with acute LayV infection with no other pathogens identified using a targeted RT-PCR panel, 14 required hospitalization and 12 were treated as outpatients.[2] The authors did not report any associated deaths and there were no mention of patients requiring intensive care.

Patients presented with fever (100%, 26/26), fatigue (54%, 14/26), cough (50%, 13/26), anorexia (50%, 13/26), myalgia (46%, 12/26), nausea (38%, 10/26), headache (35%, 9/26) and vomiting (35%, 9/26).[2] Inpatients presented with fever (100%, 14/14), myalgia (64%, 9/14), anorexia (64%, 9/14), fatigue (57%, 8/14), cough (57%, 8/14), nausea (50%, 7/14) and vomiting (50%, 7/14). Laboratory abnormalities for all patients included leukopenia (54%, 14/26), thrombocytopenia (35%, 9/26) and impaired liver function (35%, 9/26).

Viral loads were higher in those with pneumonia (n=4) compared to those without pneumonia (n=22). The viral loads in those with pneumonia differed between throat swabs (mean ± standard deviation: 7.6 ± 0.98 $\log_{10}$ copies/ml; n=4) and sera (4.5 ± 1.13 $\log_{10}$ copies/ml; n=4). The number of patients with pneumonia in the study was small, limiting what conclusions can be drawn from viral load data.

The authors did not mention any specific treatment used for the patients with acute LayV infection. There are currently no approved treatments for LayV infections, nor for NiV or HeV infections. The standard of care for those infected with a *Henipavirus* is supportive therapy for respiratory and neurological complications.[4,11] A veterinary vaccine exists for the prevention of HeV infection in horses, and antivirals, monoclonal antibodies and vaccines are under evaluation for the management of HeV and NiV infections in humans.[9]

Laboratory Diagnostics

Zhang et al. (2022) developed a research-use LayV *L* gene RNA real-time RT-PCR assay for throat swabs and serum samples for their study.[2] This real-time RT-PCR was accompanied by a nested RT-PCR and Sanger sequencing of the amplified *L* gene fragment for confirmation of LayV RNA detection. For 14 patients, the authors developed and performed IgG serology by IFA on paired sera from acute and convalescent samples (20 days after illness onset), with a four-fold increase in IgG titers reported in 86% (12/14) of convalescing patients. The authors attempted LayV isolation by inoculating human alveolar basal epithelial (A549), African green monkey kidney (Vero) and baby hamster kidney (BHK-21) cell lines with throat swabs and sera, then incubating and observing for cytopathic effect (followed by real-time RT-PCR of culture supernatant). Vero cell line culture supernatant was used to provide antigenic material for the IFA. The authors did not describe the performance characteristics and clinical validation of the RT-PCR, serology and isolation assays used in the study. Further research is needed to determine if there is serological cross-reactivity among henipaviruses.

Currently, Ontario does not have validated molecular (e.g., RT-PCR), serological or isolation assays specifically for LayV. If LayV infection is clinically suspected in a patient with compatible exposure history, please contact the PHO laboratory customer service prior to testing for consultation with the microbiologist on call.

In general, *Henipavirus* testing for HeV or NiV requires approval and coordination through the emergency response assistance plan (ERAP). To do so, please refer to PHO's *Specimens Requiring Emergency Response Assistance Plan (ERAP) for Transport within Canada*.[10] Specimens for HeV or NiV testing are forwarded to the National Microbiology Laboratory (NML, Public Health Agency of Canada) for testing by virus-specific PCR and/or serology and/or isolation of virus in culture. Available specimen types include serum, plasma, whole blood, cerebrospinal fluid and fresh/frozen/fixed/embedded tissues.[11]

Implications for Practice

Preventative measures to address zoonotic agents, including henipaviruses, require a robust knowledge of transmission routes, pathology, reservoir hosts, susceptible hosts, viral surface survival and stability, quick diagnostic capabilities, and effective treatments.[9] Further research and surveillance into LayV is warranted, especially considering our knowledge gaps in the topics listed above and the potential public health implications of zoonotic infections.

The discovery of LayV in eastern China merits continuous monitoring of local epidemiology and surveillance, both in humans and non-human hosts. It's detection in humans and multiple animal species, as well as the limited number of infected patients reported thus, requires further studies into current and future transmission dynamics. Overall, these newly reported LayV infections underscore the importance of global zoonotic surveillance to identify the introduction and/or spread of new zoonotic agents in the human population.

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