GETAH VIRUS

Swine Health Information Center

The mission of the Swine Health Information Center is to protect and enhance the health of the United States swine herd through coordinated global disease monitoring, targeted research investments that minimize the impact of future disease threats, and analysis of swine health data.

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SUMMARY

Importance

- Getah virus (GETV) is an arbovirus found throughout Eurasia. It has been mostly associated with outbreaks in horses, particularly in Japan. However, GETV is also known to cause disease in neonatal pigs and fetal death in pregnant sows.
- GETV mutates rapidly, and it is transmitted by different mosquito species whose distribution is ever changing. A better understanding of the epidemiology of GETV in pigs is needed to prepare for future outbreaks.

Public Health

- Antibodies to GETV have been identified in humans, and strain M-1 was implicated as a possible cause of febrile disease. However, there are no reports of clinical disease in people.

Infection in Swine

- Most GETV infections are subclinical in adult pigs.
- Piglets may develop anorexia, depression, diarrhea, and neurological signs, with death occurring in several days.
- Fetal death occurs in pregnant sows, especially if viral exposure occurs before 28 days of gestation. Dead fetuses may be stunted, congested, or discolored, but some show no signs of infection.

Treatment

- There are no alphavirus-specific antiviral drugs.

Cleaning and Disinfection

- Alphaviruses are not stable in the environment. They are inactivated by formaldehyde, beta-propiolactone, detergents, and lipid solvents.

Prevention and Control

- GETV prevention in endemic areas centers on mosquito control (i.e., remove standing water where mosquitoes lay eggs, use insecticides to kill both mosquito larvae and adults, house animals indoors/in screened buildings, etc.).

Transmission

- Like Japanese encephalitis virus (JEV), GETV is maintained in a transmission cycle between mosquitoes and vertebrate hosts. Both horses and pigs are amplifiers. The main vectors are *Culex (Cx.) tritaeniorhynchus*, *Aedes vexans nipponii, Cx. gelidus,* and *Cx. fuscocephala* depending on location.
- Vertical transmission is suspected in pigs. Other routes, like direct contact and inhalation, are thought to be unimportant for GETV transmission in pigs, though they occur in horses.

Pathogenesis

- Pathogenesis of GETV infection in pigs is not characterized.

Diagnosis

- Several reverse transcriptase polymerase chain reaction (RT-PCR) assays have been developed for GETV. Targets include nonstructural proteins 1, 2, and 3 (NSP1, 2, and 3).
- Antibodies can be detected via enzyme-linked immunosorbent assay (ELISA), serum neutralization (SN), hemagglutination inhibition (HI), and complement fixation (CF). Recently described ELISAs are based on the E2 glycoprotein.

Epidemiology

- Horses with GETV develop fever, rash, and edema of the limbs. In addition to horses and pigs, illness has been described in blue foxes and cattle. Antibodies to GETV are found in many animals including wild boar.
- Seroprevalence studies show that GETV is common in swine in Asia (up to 100% following outbreaks). In Japan, seropositivity in pigs increased in years where equine outbreaks occurred. Mortality in swine can be high, particularly in neonates.

Etiology

- GETV is a single-stranded RNA virus in the family *Togaviridae*. It is an Old World alphavirus belonging to the Semliki Forest serocomplex, which includes closely-related Sagiyama virus.
- Important components of the virion include the capsid protein (C), envelope ("spike") glycoproteins E1 and E2, and NSPs 1–4.

History in Swine

- Clinical infection was first documented in pigs in Japan in 1985, when newborn piglets that were healthy at birth developed depression, tremors, and diarrhea, and died within two to three days. GETV was circulating in Japan prior to this, but infections were thought to be subclinical.
- Both natural and experimental GETV infections have been confirmed in pregnant sows. Fetal death was described in sows infected early in pregnancy (days 26, 28, experimentally).
- GETV outbreaks in swine have occurred since 2017 in China, affecting both neonates and pregnant sows.

Immunity

- Serum neutralizing antibodies develop by six days post-infection (dpi) in experimentally infected pigs.
- A live-attenuated trivalent vaccine (GETV, JEV, and porcine parvovirus) has been available for swine in Japan since 1993; however, its efficacy is unknown since currently circulating GETVs are different from vaccine strains.

Gaps in Preparedness

- Disease has been identified in swine, but the importance of GETV as a swine pathogen remains unclear. Even in humans, the pathogenesis of alphavirus infection is not clearly understood, and licensed vaccines and targeted anti-viral therapies are lacking.
- More information is needed on potential hosts and local vectors to understand the risk to livestock and provide a targeted response if GETV reaches North America.

LITERATURE REVIEW: GETAH VIRUS

IMPORTANCE

Getah virus (GETV) is an arbovirus found throughout Eurasia. It has been mostly associated with outbreaks in horses, particularly in Japan. However, GETV is also known to cause death in neonatal pigs and fetal death in pregnant sows. GETV antibodies have been found in many different animals. The virus mutates rapidly, and it can be transmitted by many different mosquito species whose distribution is ever changing. A better understanding of the epidemiology of GETV in pigs is needed to prepare for future outbreaks.

PUBLIC HEALTH

Antibodies to GETV have been identified in humans and monkeys.[1] On Hainan Island, China, the GETV strain M-1 was implicated as a possible cause of febrile illness in humans, but there are no reports of clinical disease in people.[2] Furthermore, no signs of illness were reported among horse handlers present during the 1978 GETV epizootic in racehorses in Japan.[1] Ross River virus, a close relative of GETV, is a known zoonosis.[3]

INFECTION IN SWINE

Most GETV infections are subclinical in adults, but potentially fatal in newborn piglets.[4] Naturally infected **newborn piglets** may develop tremors, depression, and yellow- brown diarrhea.[4] Piglets inoculated with GETV at 5 days-of-age became anorexic, and developed red skin discoloration and neurological signs (trembling of the tongue, loss of coordination in the pelvic limbs) at 20 hours post infection (hpi). Some piglets died within 60 to 70 hpi, others were near death within two to three days. A single piglet that did not develop clinical signs recovered.[4]

In **older piglets**, 4 to 5 months-of-age, experimental IM inoculation with GETV did not lead to clinical disease.[4] However, a mixed group of 4-week-old and 8-month-old pigs that were inoculated IV or IM developed fever and anorexia post-infection. Depression and diarrhea were also observed in piglets inoculated with the strain MIP-99.[5] Fetal death can occur in both experimentally and naturally infected **sows**, especially when viral exposure occurs prior to days 26 to 28 of gestation.[6] Dead **fetuses** from infected sows can be stunted, congested, or discolored, but some show no signs of infection.[7]

Grossly, lesions in piglets include renal malformation and spot bleeding on the kidney.[8] Histology has identified multifocal non-suppurative polioencephalomyelitis, a thickened renal cortex with microscopic infarction, hepatic nuclear necrosis, and hemorrhagic splenitis. Perivascular dermatitis, cuffing of cerebral blood vessels, and hyperplastic lymphoid tissue are also seen.[9]

TREATMENT

There are no alphavirus-specific antiviral drugs. Supportive care includes use of analgesics and anti-inflammatory drugs.[10]

CLEANING AND DISINFECTION

SURVIVAL

Alphaviruses are not stable in the environment.[11]

DISINFECTION

Alphaviruses are inactivated within minutes at temperatures of 58˚C or higher, and lose infectivity when exposed to UV light, radiation,[12] and acidic conditions. Their ideal pH range is 7 to 8.[6] Effective denaturing agents include formaldehyde, beta-propiolactone, detergents, and lipid solvents.[12]

PREVENTION AND CONTROL

DISEASE REPORTING

GETV is not an OIE-listed disease. There are no recommendations for importation of horses or swine from countries or zones affected by GETV. Any suspicious clinical or necropsy findings should always be reported to the USDA and your State Animal Health Official.

DISEASE PREVENTION

GETV prevention in endemic areas centers on control of mosquito vectors (see *Transmission*).

- Remove standing water where mosquitoes lay eggs (empty items that hold water like tires, buckets, pools, birdbaths, etc.),
- Kill mosquito larvae with larvicides, and
- Kill adult mosquitoes with adulticides (use in dark, humid areas where mosquitoes rest).[13]

Insecticides can be applied to animals to prevent bites (e.g., "fly spray" for horses). Animals should also be housed indoors at night, and all windows should be screened.

Certain at-risk horse populations in Japan are vaccinated annually, which may limit the number of GETV outbreaks.[14]

DISEASE CONTROL

Standard biosecurity practices should be in place on swine premises. Although GETV is primarily mosquito-borne, pig-to-pig transmission may be possible. Vertical transmission seems to occur in pregnant sows.

TRANSMISSION

Like Japanese encephalitis virus (JEV), GETV is maintained in a transmission cycle between mosquitoes and vertebrate hosts. Both horses and pigs are amplifiers.[15] Other species may act as natural reservoirs or amplifying hosts, though infection in wildlife species is believed to be subclinical. The main vectors are *Culex (Cx.) tritaeniorhynchus*, *Aedes vexans nipponii,*[9] *Cx. gelidus,* and *Cx. fuscocephala* depending on location.[6] Characteristics of these vectors are described in Table 1.[16, 17, 18]

Additional modes of transmission appear to be of lesser importance in **pigs**. Experimentally, gnotobiotic piglets inoculated IM with GETV at 5 days-of-age developed severe disease, while oronasal inoculation lead to only minor signs of illness.[19] Attempts to isolate Sagiyama virus (a closely related virus) from oral or nasal secretions in experimentally infected pigs were unsuccessful, suggesting that transmission by contact or inhalation is unlikely.[20] In China, vertical transmission was suspected during a 2017 outbreak in piglets and pregnant sows.[8] In 2018, GETV was reportedly isolated as a contaminant in commercial PRRS live vaccine.[21]

In **horses**, GETV may be transmitted by direct contact with nasal discharge during outbreaks.[9] Horses experimentally infected with GETV shed virus in their nasal secretions,[14] and aerosol transmission has been achieved experimentally.[1] Horse-to-horse spread was implicated in an epizootic in horses India in 1990.[22] In experimentally infected mice and hamsters, GETV can spread vertically[1] and through milk.[9]

Table 1. Getah Virus Vectors*

Genus	*Characteristics*	*Competent GETV Vectors*	
Culex	Breed during warm weather Lay egg rafts on surface of standing water (stagnant or polluted, permanent or temporary) Bite humans, other domestic animals Feed dusk to dawn	*Cx. bitaeniorhynchus* *Cx. fuscocephala* *Cx. gelidus* *Cx. pipiens pallens*	*Cx. pseudovishnui* *Cx. vishnui* *Cx. tritaeniorhynchus*
Aedes	Breed during warm weather, some species may adapt to colder environments Lay eggs on soil or in containers that catch rainwater (like tree holes, old tires, ditches) Bite humans (preferred), other animals Feed during day in shady or dark areas	*Ae. aegypti* ***Ae. albopictus*** ***Ae. communis*** ***Ae. excrucians***	*Ae. nigripes* ***Ae. japonicus*** ***Ae. vexans nipponii***
Anopheles	Breed during warm weather Lay eggs on surface of standing water like puddles, ponds (clean water preferred) Bite domestic animals (preferred), humans Feed dusk to dawn	*An. amictus amicus* *An. vagus*	

*Other potential vectors include *Armigeres subalbatus, Mansonia indiana, M. bonneae*, and *Tripteroides bambusa*

Bold indicates mosquito species is found in the United States

PATHOGENESIS

Viral attachment occurs via E2 glycoprotein (see *Etiology*), which binds host cell surface receptors (probably including lectins, integrins, and/or laminin). The virus-receptor complex undergoes clathrin-mediated endocytosis, and the coated vesicles are released into the cytoplasm, where replication occurs. Virions are formed by budding of nucleocapsids through patches of plasma membrane that are studded with spike glycoprotein.[11, 23, 24] In New World alphaviruses, the nucleocapsid protein (C) inhibits RNA transcription, while NSP2 inhibits host-cell transcription in Old World strains.[11] No information was found on the pathogenesis of GETV in pigs.

DIAGNOSIS

GETV is associated with fever, anorexia, depression, diarrhea, and death in piglets, as well as fetal death in pregnant sows.

TESTS TO DETECT NUCLEIC ACIDS OR ANTIGEN

Virus isolation can be achieved in rabbit kidney (RK-13), African green monkey kidney (Vero),[6] swine kidney (SK-L), hamster lung (HmLu-1)[19] and pig kidney (CPK) cell lines,[7] or by intracerebral inoculation of suckling mice.[1] Reverse transcription polymerase chain reaction (RT-PCR) assays for detection of viral RNA are also available.[6] Newer assays that have been described include:

- TaqMan probe-based qRT-PCR assay to detect NSP1,[25]
- TaqMan probe-based qRT-PCR assays to detect NSP1 and NSP2,[26]
- Reverse transcription loop-mediated isothermal amplification (RT-LAMP) to detect NSP1 (10^3 and 10^1 times more sensitive than RT-PCR and RT-qPCR),[27] and
- RT-PCR assay to detect NSP3.[28]

A triplex RT-PCR assay has been described for GETV, JEV, and Tahyna virus. While primers and probes were designed for all three viruses, only JEV-positive clinical samples were tested experimentally.[29] Multiplex RT-PCR has also been developed for six major swine RNA viruses – porcine reproductive and respiratory syndrome virus (PRRSV), JEV, porcine epidemic diarrhea virus (PEDV), porcine rotavirus A (PoRV-A), transmissible gastroenteritis virus (TGEV), and GETV. The assay targeted NSP1 and was able to detect GETV propagated in Vero cell culture. Sensitivity of the assay to detect GETV from the mixture of viruses was higher than for GETV alone.[30]

Random amplified polymorphic DNA (RAPD) involves the amplification of random DNA segments and does not require prior knowledge of the target genome. Virus discovery cDNA RAPD (VIDISCR) requires complete isolation of the viral genome without contamination of cellular RNA and DNA, followed by comparison of cloned and sequenced fragments with known viral genomes. This technique allows for rapid detection and identification of unknown or unexpected viruses. A novel GETV was identified by VIDISCR from suckling mice exposed to mosquitoes in Yunnan Province, China.[31]

TESTS TO DETECT ANTIBODY

Serological tests include enzyme-linked immunosorbent assay (ELISA) and hemagglutination inhibition (HI) using paired sera.[6] Recently described ELISAs have used a recombinant E2 glycoprotein[32] and a 20-mer synthetic peptide for E2 glycoprotein[33] as antigens. There is good correlation between ELISA and HI, though ELISA values may begin to rise several days before HI titers.[34]

Anti-GETV antibodies can also be detected by complement fixation (CF) and serum neutralization (SN). The SN test is thought to be more specific,[1, 14] however, only CF can differentiate GETV from Sagiyama virus.[35] This is due to variations in the capsid amino acid sequences (the capsid protein is a major CF antigen in some arboviruses).[35, 36] HI and SN tests recognize envelope proteins.[35] In horses, serological testing may be affected by previous vaccination.[11]

SAMPLES

There are no specific recommendations for GETV sampling. The virus can be recovered from oral swabs of experimentally inoculated piglets at two days post-infection (dpi),[4] but there is no data available on oral sampling from naturally infected pigs. Sagiyama virus was not isolated from oral or nasal swabs from experimentally infected pigs. Nasal swabs and saliva have been used for diagnosis in horses with varying degrees of success.[14]

EPIDEMIOLOGY

SPECIES AFFECTED

Clinical disease is sporadic and mostly seen in **horses** and **pigs** (see *History in Swine*). Horses develop fever, rash, and edema of the limbs. The first known outbreak in horses occurred in 1978, at two training centers for racehorses in eastern Japan.[37, 38] Additional outbreaks were documented in racehorses in Japan during the 1970s and 80s,[39] and in India in 1990.[22] A vaccination program largely controlled GETV in Japan until 2014, when an outbreak occurred at the same facility affected in 1978.[40] The new isolate differed somewhat from the vaccine strain, but the structural proteins were highly conserved.[41] Reasons for the outbreak were unclear,[40] and GETV was documented again, at the same site, in 2015[42] and 2016.[43] A report linked the GETV strain from horses to an isolate found in Japanese pigs around the same time, indicating simultaneous circulation in these species.[44] Further, sequencing of a GETV isolate from mosquitoes showed that the outbreak strain was circulating in Japan as early as 2012, and that it was closely related to Chinese and South Korean strains.[45] The first equine GETV in China was isolated from febrile racehorses in 2018.[45]

GETV has been isolated from other species with symptomatic illness. An outbreak of GETV in 5-month-old **blue foxes** occurred in Shandong Province, China, in 2017. Fever, anorexia, and depression were seen in 25 animals; six developed neurological signs and died on the third day of illness. The foxes were reportedly fed organs from symptomatic pigs, and the isolated strain was highly similar to the porcine GETV HuN1.[46] GETV was also detected in serum from pigs and mosquitoes from the same geographic region.[46]

In 2018, GETV was isolated from forest-grazing beef **cattle** in Jilin Province, China. Of febrile animals, about 6% were positive for GETV by qRT-PCR. The isolated strain was very similar to the porcine strain HuN1. Seroprevalence of GETV in this group of cattle (n=48) was about 83%.[47]

Anti-GETV antibodies have been discovered in a wide range of animals including chickens, ducks, dairy cattle, beef cattle, pigs,[48] reptiles, marsupials,[9] water buffaloes,[1, 2] and goats.[2] Mice, hamsters, guinea pigs, and rabbits have been infected experimentally.[9] In addition to domestic pigs, wild boar are capable hosts.[49]

GEOGRAPHIC DISTRIBUTION

GETV was first isolated from mosquitoes (*Culex gelidus)* in Malaysia in 1955.[50] It exists in a diverse variety of ecosystems from tropical climates to northern tundra.[16, 51 52] GETV reportedly occurs from Eurasia to Australasia. However, a recent report cast doubt of the presence of GETV in Australia. Australian isolates from the 1960s were found to be virtually identical to the 1955 strain MM2021 from Malaysia.[53] Additionally, high levels of cross-reactivity and cross-protection were seen in mice infected with GETV and Ross River virus, complicating the interpretation of early reports of GETV antibodies in Australian cattle and pigs.[53]

GETV has not been reported in the Americas or the Caribbean. Still, the distribution of alphaviruses like GETV continues to grow due to expanding mosquito populations, adaptation to new mosquito vectors, and increased international travel (as cited by Brown *et al*.).[23] Since transmission is seasonal, and vectors disappear in cold regions during winter, the virus may be reintroduced to temperate climates from southern regions each year.[35]

MORBIDITY AND MORTALITY

High seroprevalence may be seen in **horses** where GETV is endemic, but clinical illness is uncommon. During outbreaks in horses, morbidity up to 40% has been observed.[9]

Mortality in **swine** can be high, especially in neonates. Information on GETV morbidity in swine includes the following:

- In 1964, about 18% of pigs tested on Hainan Island, China, were seropositive for GETV.[2]
- In Japan, seropositivity in pigs has increased in years where equine outbreaks occurred. For instance, prevalence in swine in Ibaraki Prefecture ranged from 0% to 1.6% in 2012-2013, but increased to 29% to 65% in 2014–2015, when GETV occurred at a nearby racetrack.[44]
- In a Japanese wild boar population that has been sampled since 2010, seroprevalence was highest in 2012 (nearly 49%) compared to 2014, 2015, and 2016 (40.4%, 10.3%, and 6.3% respectively).[49]
- A serosurvey of domestic animals from Yunnan Province, China, found that 46% of pigs had antibodies to GETV.[48]

- After GETV was identified in pigs from Guangdong Province, China, in 2018, archived serum samples from sick pigs were tested. No evidence of GETV infection was found in nearly 500 samples collected between 1990 and 2018.[54]
- Following a GETV outbreak on a pig farm in Hunan Province, China, in 2017, seroprevalence was nearly 100%.[8]
- A 2017–2018 analysis of serum from nearly 1200 pigs in 11 Thai provinces showed that about 23% were seropositive for GETV. Nursery pigs (4 to 7 weeks-old) and older pigs (>28 weeks-old) were more likely to be seropositive than finishers (67.9% and 84.5% vs. 14.2%).[55]

How proximity to swine affects GETV in **mosquito** populations has also been investigated.

- In Shanxi Province, China, mosquito pools from dwelling near pigsties were tested for JEV and GETV. Only two of 88 pools were positive for GETV, compared to 16 of 88 positive for JEV.[56]
- A metagenomic analysis of mosquito pools collected from pig farms in the vicinity of Shanghai, China, in 2017 did not detect any sequences from the viral family *Togaviridae*.[57]
- A similar study of mosquito pools collected from animal farms in Yunnan Province, China, in 2018 detected three GETV strains. Two clustered with other Yunnan strains, but GETV-B3/YN was most closely related to AY702913 from South Korea.[58]

ETIOLOGY

CHARACTERISTICS OF TOGAVIRUSES

GETV is an arbovirus belonging to the family *Togaviridae*. Togaviruses are single-stranded RNA viruses that are spherical, uniform, and about 70nm in diameter. They have a lipid envelope (or "toga") surrounding an icosahedral nucleocapsid with glycoprotein spikes.[11] Important components of the virion include:

- Capsid protein (C)
- Envelope ("spike") glycoproteins (E1, E2, and E3 in some alphaviruses); related to viral attachment to the host cell (E2) and release of the viral nucleocapsid into the cytoplasm (E1)
- Nonstructural proteins (NSPs 1–4)
- NSP1 is related to capping and membrane association; NSP2 is related to polyprotein processing and RNA helicase activity; NSP3 mediates various host cell molecule interactions (through its C-terminal hypervariable domain, HVD, and probably other mechanisms that are not completely understood); NSP4 acts as an RNA-dependent RNA polymerase.[11, 35, 59]

The family *Togaviridae* contains two genera, *Alphavirus* and *Rubivirus*. GETV belongs to the genus *Alphavirus,* which contains approximately 30 pathogens of humans and/or animals.[11] The genus *Rubivirus* contains only one species, rubella virus, a pathogen of humans.[6, 9]

Alphaviruses are classified as New World or Old World depending on their suspected origin. Over the last few thousand years, these alphavirus clusters have evolved separately; their main differences are shown in Table 2. GETV is an Old World alphavirus.[60] Alphaviruses are also grouped into eight antigenic complexes based on sequencing and serological cross-reactivity (excluding salmonid strains).[6, 61] GETV is part of the Semliki Forest serocomplex,[9] which includes Ross River virus, Bebaru virus, Sagiyama virus, and Chikungunya virus.

Table 2. Old World vs. New World Alphaviruses

	New World Cluster	*Old World Cluster*
Representative species	Venezuelan equine encephalitis virus Eastern equine encephalitis virus Western equine encephalitis virus	Sindbis virus, Semliki Forest virus complex (Getah virus, Ross River virus, Bebaru virus, Sagiyama virus, Chikungunya virus), others
Distribution	North America, South America	Asia, Africa, Europe, Australia
Disease	Encephalitis	Fever, rash, polyarthritis, encephalitis (rarely)

CHARACTERISTICS OF GETAH VIRUS

The GETV genome is a single molecule of linear, positive-sense, single-stranded RNA, 11 to 12 kb in size.[11] It undergoes frequent mutation,[1] and biological differences between strains have been demonstrated with cross-neutralization tests.[19] Isolates from the same year tend to be similar,[60] but there does not seem to be geographic clustering of GETV strains.

Genotyping (based on E2) has been used to establish GETV groups.[55, 62]

- Group I is derived from the prototype strain MM2021, isolated in Malaysia in 1955
- Group II includes two isolates from Japan, 1956 (SAGE and SAGE-original)
- Group III includes nearly all strains isolated from mosquitoes, pigs, horses, and other animals since the 1960s
- Group IV includes isolates from the 2000s: Yunnan Province, China, 2015 (YN12031); Far East Russia, 2007 (LEIV16275Mag); and Thailand, 2017 (GETV/SW/Thailand/2017)

Previously, GETV isolates from China and Korea were shown to be similar to a Sagiyama virus isolate from Japan.[36] The NSP1 genes of GETV and Sagiyama virus share high nucleotide identify and their amino acid sequence is the same.[20, 35, 63] Similarly, amino acid sequences of the E1 gene are homologous,[20, 64] and three prime untranslated regions share 94% identity. A recent phylogenetic analysis found that Sagiyama virus belongs to the GETV group.[62] Although it shares biological and serological features with GETV,[63] Sagiyama virus is considered to be a subtype of Ross River virus by the International Committee on Taxonomy of Viruses.[12]

HISTORY IN SWINE

Outbreak in Piglets, Japan,1985[4, 19]

The first documented outbreak of GETV in pigs occurred in 1985 in Kanagawa Prefecture, Japan. Twelve newborn pigs were healthy at birth, but developed depression, tremors, and yellow-brown diarrhea within two to three days. Four died at 3 days-of-age, and four died at 4–5 days-of-age. The remaining four piglets survived but were stunted. The sow showed no signs of disease. No gross or histopathological lesions were seen in necropsied pigs. The isolated virus was identified as a strain of GETV. Interestingly, the authors noted that "…pigs in Japan [were] infected widely with GETV," but disease in pigs was thought to be subclinical prior to this report.

Experimental and Natural Infection in Pregnant Sows, Japan, 1988[5, 7, 65]

In 1988, Izumida *et al*. confirmed that GETV is a cause of reproductive disease in pigs. Five pregnant sows were experimentally infected with the virus; all developed viremia but none showed clinical signs. At 11 to 28 dpi, four sows were laparotomized and fetal viability was assessed. In two sows inoculated early in pregnancy (days 26 and 28), 14 dead fetuses were found. In sows inoculated at 44 or 52 days of pregnancy, no fetal death occurred. GETV was isolated from multiple fetal tissues. In 1988, Shibata *et al.* isolated GETV from dead fetuses in a naturally infected sow in Japan. Further studies confirmed the pathogenicity of GETV in swine. Kumanomido *et al*. infected four adult pigs and four piglets with GETV. Fever and anorexia were seen in all pigs, and two of four piglets developed mild depression and diarrhea.

GETV and JEV Coinfection, Japan, 2014[6, 66]

Tajima *et al.* reported on JEV and GETV coinfection in serum from a single pig. The isolate, GETV/Kochi/01/2005 was most like a Mongolian strain (LEIV17741). JEV and GETV occur in the same geographical areas, share common vectors, and produce similar clinical signs. Because of this, the authors speculated that GETV infection in pigs may be masked by coinfection with JEV.

Outbreak in Piglets and Sows, China, 2017[8]

GETV has circulated in mosquitoes in China since the 1960s; however, the first known outbreak in pigs reportedly occurred at an intensive swine farm (1000 sows) in Hunan Province in 2017 (other reports of porcine infection with GETV from around this time exist but are available in Chinese only).[67, 68] Within five to 10 days of birth, approximately 200 piglets died after becoming febrile and showing signs of neurological disease. More than 150 pregnant sows had stillbirths or delivered fetal mummies. An isolate from an infected piglet (GETV-HuN1) was highly similar to an isolate from Japan (Kochi/01/2005). Seroprevalence was also investigated using 60 post-outbreak and 49 archived swine serum samples, of which 98% and were 33% were positive for GETV, respectively.

GETV in Samples from Pigs with Suspected CSF, China, 2018[54]
In 2018, kidney samples were collected from two pigs with suspected classical swine fever (CSF) in Guangdong Province, China. The pigs were from herds that had recently experienced signs of CSF and/or high mortality. CSF was detected in both samples, and pseudorabies virus (PRV) was also detected in one. Since the observed rapid cytopathic effect was uncharacteristic of CSF and PRV, further genomic sequencing was performed (LncRNA sequencing). GETV was detected in one sample, and both GETV and PRV (Bartha vaccine strain) were detected in the other. The GETVs isolated were identical, both Group III strains that were highly similar to porcine strain HNJZ-S2 from Henan province (99.7% homology). The GETV isolates also shared 98.6% sequence identity with the equine strain GZ201808. No evidence of GETV infection was found in nearly 500 archived swine serum samples collected between 1990 and 2018.

Additional Reports of GETV in Swine
The GETV strain HNJZ-S1 was isolated from aborted swine fetuses in 2016.[69] Homology of 97.4% to 99.3% was seen compared with other GETV isolates in GenBank. Pathogenicity was verified in mice, pregnant mice, and 3-day-old piglets. At 12 hpi, 10 intranasally-inoculated piglets became febrile, and then developed diarrhea. All piglets died within 18 to 32 hpi.

GETV was isolated during a 2017-2018 seroprevalence study in Thailand. Phylogenetic analysis showed that GETV/SW/Thailand/2017 did not cluster with Group III strains common in East Asia. Rather, it was most like Group IV strains from China (YN12031) and Russia (LEIV16275Mag).[55]
Routine testing on clinical samples from swine farms in Guangxi Province, China, 2018 led to the isolation of GX201808, which was closely related to Group III strains (HuN1, SD17/09, JL1808) from different animals in Hunan, Shandong, and Jilin Provinces, China.[70]

GETV was also isolated from dead pigs on Shaanxi, Hebei, Henan, and Anhui provinces, China. Using RT-PCR, 37 liver and spleen samples (37/801, 4.62%) were positive for GETV, and isolates were more closely related to horse and mosquito strains from Japan than to mosquito- and pig-borne strains found in China and Korea.[71]

IMMUNITY

POST-EXPOSURE
Serum neutralizing antibodies develop by six dpi in pigs, with maximum titers observed at day 14.[5] Following natural infection, horses with titers greater than 1:4 are considered to be resistant to GETV.[9] In serological studies of closely related Sagiyama virus, serum neutralizing antibody titers were higher in naturally infected pigs compared to experimentally infected pigs, likely due to repeat infection.[20]

VACCINES
A live-attenuated trivalent vaccine for protection against GETV, JEV, and porcine parvovirus has been available for swine in Japan since 1993; however, recently sequenced JEV and GETV isolates were not the same as vaccine strains,[66] and vaccine efficacy is unknown. GETV vaccination for sows was mentioned in a non-GETV-related study,[72] but no further information is available.

For horses, an inactivated GETV vaccine has been available since 1979, and a bivalent inactivated vaccine for GETV and JEV has been available since 1997.[73] Vaccination programs at Japanese racehorse training facilities appeared to be effective for many years. However, GETV re-emerged in horses in Japan in 2014,[40] 2015,[42] and 2016.[43]

CROSS-PROTECTION
No information was found on cross-protection for GETV in pigs. High levels of cross-reactivity and cross-protection were seen in mice infected with GETV and Ross River virus.[53]

GAPS IN PREPAREDNESS

GETV is primarily known as an equine pathogen that has caused sporadic, concentrated, non-fatal outbreaks at large horse facilities in Japan. Disease has been identified in swine, but the importance of GETV as a swine pathogen remains unclear. Even in humans, the pathogenesis of alphavirus infection is not clearly understood, and licensed vaccines and targeted anti-viral therapies are lacking.[10] Equine and swine vaccines have been used

in Japan, but their efficacy is questionable. GETV had a wide geographic distribution, it mutates rapidly, and it can be transmitted by many different mosquito species. More information is needed on potential hosts and local vectors to understand the risk to livestock and provide a targeted response if GETV reaches North America.

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