Influenza D

Last Updated: December 2021

Importance

Influenza D viruses are a group of influenza viruses, apparently maintained in cattle, which were discovered in the last decade. How long these viruses have been circulating is uncertain; however, they have been found in archived samples as old as 2003. Their clinical significance is under investigation. There are some indications that they might cause or contribute to respiratory illnesses in cattle, pigs or other livestock, though experimental infections suggest that, by itself, influenza D does not cause major illness in healthy animals. Serological studies suggest that humans might also be susceptible to infection, and while there are no reports of any human illness to date, the possibility cannot be ruled out.

Etiology

Influenza D viruses are enveloped viruses of the species *influenza D virus*, genus *Deltainfluenzavirus* and family Orthomyxoviridae. They are most closely related to influenza C viruses, sharing approximately 50% amino acid identity and a similar gene structure. Influenza C and D viruses both use a single major envelope protein, the hemagglutinin-esterase-fusion (HEF) glycoprotein, for receptor binding and entry, rather than the separate hemagglutinin and neuraminidase proteins of influenza A and B.

The HEF protein is the major target of neutralizing antibodies against influenza D viruses, and it is the basis for their separation into lineages. The currently recognized lineages include three that were first identified in the U.S. (but also exist in other countries), D/swine/Oklahoma/1334/2011, D/bovine/Oklahoma/660/2013 and a novel group provisionally designated D/bovine/California/0363/2019; two viruses first identified in Japan, D/bovine/Yamagata/10710/2016 and D/bovine/Yamagata/1/2019; and a divergent lineage, first recognized in Europe, that has been designated both D/bovine/France/2986/2012 and D/bovine/Ireland/0077 80/2014. Multiple influenza D viruses can circulate simultaneously, rather than one virus predominating, and they can recombine to generate new variants.

Influenza D viruses should not be confused with viruses of the same name described in the 1950s among people in Russia and Japan, which were later found to be identical with Sendai virus.

Species Affected

Cattle appear to be the primary reservoir hosts for influenza D viruses. As of 2021, these viruses have also been isolated from pigs, and antibodies have been detected in wild boar, sheep, goats, horses, Asian buffalo and dromedary camels. One study found no serological evidence of exposure in 250 serum samples from 25 chicken and turkey farms in North America, while a study from Asia detected nucleic acids at low concentrations in air samples taken on Asian poultry farms. The specificity of the latter finding for poultry is still unclear: in other studies, this group reported finding influenza D nucleic acids at sites where only humans are present. Experimental infections with influenza D have been established in ferrets, guinea pigs and mice.

Whether pigs might maintain influenza D viruses for a time is uncertain, though preliminary evidence (see Morbidity and Mortality) suggests that they do not persist long term under swine modern farming methods. One study found that some viral strains appeared to show host preferences related to transmission in young pigs vs. young colostrum-deprived calves.

Zoonotic potential

Serological studies suggest that influenza D viruses may infect humans, particularly those who are in contact with livestock. There is currently no evidence that these viruses cause any illness in humans; however, it cannot be ruled out.

Geographic Distribution

Influenza D viruses appear to be cosmopolitan. They have been detected in North America, Asia (e.g., China, Japan), several countries in Africa and a number of

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Institute for International Cooperation in Animal Biologics

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- Diagnosis of Animal Disease and Vaccine Evaluation in the Americas
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European countries. Antibodies to these viruses were found in cattle in Argentina, suggesting that they also circulate in South America.

Transmission

Influenza D viruses are likely to be transmitted similarly to other influenza viruses. They are shed in nasal secretions, and in cattle, they have been shown to be transmissible in aerosols over short distances, as well as by direct contact. Some authors have speculated that influenza D viruses might also occur in the intestinal tract, based on one study in experimentally infected mice, and on mass PCR testing of various archived clinical samples, which found nucleic acids in 1 of 8 rectal swabs from goats with severe diarrhea. The latter study's authors noted that this finding, which was not thought to be the cause of the diarrhea, might have resulted from the sick goats swallowing viruses from the respiratory tract. One study found no nucleic acids in rectal swabs from influenza D virus-infected cattle.

Influenza D viruses were reported to be more resistant to inactivation by heat or acid than influenza A, B or C viruses, when suspended in an unspecified liquid. In this study, only influenza D viruses retained some infectivity after exposure to pH 3.0 for 30 minutes, a temperature of 53°C (127°F) for 2 hours, or 57°C (135°F) for an hour. This relative resistance appeared to be conferred by the influenza D HEF protein. The study did not examine the virus's survival on dry surfaces, where its stability could also be influenced by other factors such as the integrity of its envelope.

Disinfection

The disinfectant susceptibility of influenza D viruses has not been published. Influenza A viruses can be destroyed by a wide variety of agents including sodium hypochlorite, 60-95% ethanol, quaternary ammonium compounds, aldehydes (glutaraldehyde, formaldehyde), phenols, acids and iodides. Human influenza A viruses were also found to be susceptible to common household agents including 1% bleach, 10% malt vinegar or 0.01-0.1% dishwashing liquid in water ("washing up liquid"), as well as antimicrobial wipes, although hot water alone (55°C/ 131°F) did not eliminate these viruses rapidly. The higher resistance of influenza D to acid pH suggests that some of these disinfection methods (e.g., 10% malt vinegar) should be tested rather than assuming efficacy; however, their susceptibility to non-pH based disinfectants is likely to be similar.

Heat of 65°C (149°F) for an hour was shown to inactivate influenza D viruses. Ionizing radiation should also be effective.

Incubation Period

Incubation periods of a few days (e.g., 1-3 days, 4 or more days) have been reported in experimentally infected calves and other livestock.

Clinical Signs

Influenza D viruses were originally detected in a herd of pigs with respiratory signs that resembled influenza, and they have since been found in other pigs with similar signs. Experimentally infected 5-week-old pigs and feral pigs did not develop any clinical signs or significant gross lesions, though some animals had a fever and/or mild microscopic lesions in the respiratory tract. However, it is not unusual for a pathogen to be less severe in experimentally infected animals, which are usually in good health, with optimal nutrition and few stressors or coinfections compared to ordinary commercial herds.

Some authors have also suggested that influenza D viruses may contribute to bovine respiratory disease complex (BRDC), a multifactorial disease informally known as "shipping fever." The various respiratory viruses involved in BRDC can predispose cattle to secondary bacterial infections, particularly in the presence of stressors that can reduce immune defenses. Whether influenza D viruses play a significant role in this complex is still not entirely clear: these viruses have been recovered from apparently healthy cattle as well as animals with respiratory signs, and while some researchers find that they are more likely to be present in sick cattle, the opposite has also been reported. Findings in experimentally infected healthy calves included mild upper respiratory signs (e.g., nasal discharge, dry cough) and/or mild nonspecific signs (e.g., lethargy) in some animals, and no clinical signs in others. Somewhat more severe illnesses were seen in 6-week-old, colostrum-deprived gnotobiotic calves. Most of the latter animals had mild to moderate respiratory signs that included coughing, increased respiratory rates and, in some cases abdominal dyspnea with wheezing, though their appetite and attitude remained normal. More severe signs, including pneumonia, occurred in a few gnotobiotic calves that developed secondary bacterial infections. Calves in contact with inoculated animals in this experiment either remained asymptomatic or had mild signs.

The effects of influenza D have not been investigated in other livestock, as of 2021, though some were found to have antibodies. Experimentally infected guinea pigs, mice and ferrets were asymptomatic, though inflammatory changes occurred in the lungs of guinea pigs and mice.

Post Mortem Lesions

Microscopic lesions of tracheal inflammation and rhinitis, occasionally with mild suppurative bronchitis and bronchiolitis, were reported in experimentally infected calves with mild respiratory signs. Colostrum-deprived gnotobiotic 6-week-old calves sometimes also had moderate subacute bronchopneumonia with restricted lesions of interstitial pneumonia in up to 10% of the lung. Secondary bacterial infections caused additional lesions, such as fibrinous and necrotic pleuropneumonia with abscesses.

Diagnostic Tests

Diagnostic testing for influenza D viruses can be complicated by the presence of these viruses in healthy as well as sick animals. RT-PCR tests are commonly used to identify infected animals in research. They are also available in some university and other diagnostic laboratories, sometimes as part of a multiplex PCR assay for respiratory viruses in the BRDC. If necessary, influenza D viruses can be isolated in at least two cell lines, swine testicular (ST) cells and Madin–Darby canine kidney (MDCK) cells.

Most serological studies have used hemagglutination inhibition (HI) assays, but virus neutralization can also be employed. The high incidence of seropositive healthy animals complicates serological diagnosis unless rising titers are found.

Treatment

There is no specific treatment for influenza D, but supportive treatment (e.g., good nursing; antibiotics as needed to control secondary bacterial infections) should be helpfu1.

Control

Disease reporting

Influenza D infections appear to be common in livestock and are unlikely to be reportable in most areas; however, veterinarians should remain aware of any national and/or local reporting guidelines.

Prevention

Influenza D infections are common, even in asymptomatic animals, and there do not appear to be any practical, cost-effective measures to exclude these viruses from herds. Good animal husbandry is likely to be helpful in reducing any effects on health. Facilities that must exclude these viruses (e.g., research facilities) can use quarantines and testing on entry, together with strict biosecurity to avoid entry on fomites. The possibility of transmission by people, including temporary nasal carriage, should also be considered.

Morbidity and Mortality

Influenza D viruses seem to be common in cattle, with studies reporting 16-96% seroprevalence in most of the world, and a somewhat lower positivity rate (3-21%) in East Africa and West Africa. More than 90% of the calves in some studies had maternal antibodies to this virus. Many calves seem to be exposed between 6 months and a year, after maternal antibodies decline. Other livestock are less likely to be seropositive, with studies from Europe and North America reporting antibodies to influenza D viruses in < 0.5% to 12% of domestic pigs, 1-9% of small ruminants, 11-16% of horses, < 5% of wild boar in Europe, and 19% of feral swine in four U.S. states. Repeat serological testing of two farrow-to-finish swine herds suggested that, while the virus may sometimes spread to infect a large percentage of the pigs within these herds, it does not seem to persist.

Uncomplicated infections with other influenza viruses (i.e., influenza A, B or C) in their usual hosts tend to be associated with high morbidity, low mortality and rapid recovery, though more severe disease and increased fatalities may be seen in very young, old or debilitated animals. Secondary bacterial infections can exacerbate the clinical signs, prolong recovery and result in complications such as pneumonia. Influenza D infections in livestock appear to be mild or asymptomatic to date, and it is plausible that they will also follow this pattern. One study found that this virus did not enhance illness from secondary infection with *Mannheimia haemolytica*, a common bacterial agent of BRDC, in calves, while a study in mice found it did not increase susceptibility to secondary *Staphylococcus aureus* infections. However, its effect might be more apparent among livestock in the field when stressors are also present.

Public Health

Serological studies suggest that influenza D viruses may infect humans, particularly those who are in contact with livestock. One study found antibodies in 1% of the residents of two urban areas in Canada and Connecticut in 2007-2009. In Florida, 97% seroprevalence was found among 35 cattle-exposed farmers. Two of 11 people not exposed to cattle (18%), including one who had contact with pigs, also had antibodies in this report. A third study found antibodies in 5% of archived serum samples that had been taken from swine veterinarians in 2004. The potential for cross-reactivity with influenza C viruses complicates some of these reports, but a 2019 Italian study that specifically excluded cross-reactivity also detected antibodies in a significant number of archived serum samples. In this study, the lowest rates (5-10%) were seen in 2005–2007, the earliest period examined, followed by a much higher seroprevalence in 2008, then fluctuating annual values between 11% and 46%. There appeared to be a correlation between epidemics in pigs and years of high seroprevalence in humans.

There is currently no evidence linking influenza D viruses to any human illnesses, but this possibility has also not been ruled out. A Scottish study did not find any PCR-positive samples among 3300 archived human respiratory samples from patients visiting Edinburgh hospitals in 2006-2008. During surveillance for various pathogens of swine, influenza D nucleic acids were detected in the nasal passages of one person who worked on a swine farm in Asia. The authors noted that this could reflect nasal carriage rather than active infection. A group that sampled air in an airport and a hospital reported finding nucleic acids in these environments; however, this form of surveillance is known to have a high rate of false positives, and these studies remain to be validated by finding replicating viruses in humans.

Acknowledgements

This factsheet was written by Anna Rovid Spickler, DVM, PhD, Veterinary Specialist from the Center for Food Security and Public Health. The U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) provided funding for this factsheet through a series of cooperative agreements related to the development of resources for initial accreditation training.

The following format can be used to cite this factsheet. Spickler, Anna Rovid. 2021. *Influenza D*. Retrieved from http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php.

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