Influenza—Novel or Unsubtypable Strain

Signs and Symptoms	Signs and symptoms of infection with novel or unsubtypable influenza may be similar to seasonal flu (typical symptoms of fever, cough, sore throat, myalgias) or may be more or less severe.
Incubation	The incubation period for seasonal influenza is typically 1–4 days, but can range from 1–7 days. The incubation period for novel influenza viruses is estimated as 2-10 days.
Source of Infection	Caused by influenza virus, which could be spread person-to-person, from infected animals or their droppings/environment, or from contact with influenza-contaminated surfaces.
Case classification	***Suspected:*** A case meeting the clinical criteria, pending laboratory confirmation. Any case of human infection with an influenza A virus that is different from currently circulating human influenza H1 and H3 viruses is classified as a suspected case until the confirmation process is complete. ***Probable:*** A case meeting the clinical criteria and epidemiologically linked to a confirmed novel influenza case, but for which no confirmatory laboratory testing for influenza virus infection has been performed or test results are inconclusive for a novel influenza A virus infection. ***Confirmed****:* A case of human infection with a novel influenza A virus confirmed by CDC's influenza laboratory or using methods agreed upon by CDC and CSTE.
Differential diagnosis	Seasonal flu, other viral, bacterial and fungal etiologies. Note: sometimes a commercial flu test will yield an unsubtypable result due to low viral titer or other issues even though the patient is infected with seasonal strain (testing at Washington State Public Health Laboratories [PHL] can determine whether an unsubtypable result commercially is due to seasonal flu or due to novel virus).
Treatment	Antiviral treatment, which is most effective if started within 48 hours of onset. Antiviral prophylaxis may also be considered for exposed contacts.
Laboratory	**Clinicians should collect nasopharyngeal swab for testing at PHL.** Contact Communicable Disease Epidemiology (CDE) to arrange for testing. PHL has CDC reagents that can identify novel influenza (not available at commercial labs). For specimens that are unsubtypable commercially, testing at PHL is needed to determine whether the infection is due to seasonal flu vs. novel flu.
Public Health investigation	Contact CDE **immediately** (206-418-5500) regarding suspected novel influenza infections and specimens that are unsubtypable commercially. Provide exposure history, symptoms and risks for considering novel influenza as etiology (for example, recent exposure to influenza-infected animals such as during an avian flu event, recent travel to area with active avian flu transmission with exposure to a bird market, contact with known novel influenza case etc.) Personnel using personal protective equipment should obtain nasopharyngeal, nasal, and throat specimens using synthetic swabs and viral transport medium. Facilitate the transport of specimens to the Washington State Public Health Laboratories for testing. Contact CDE to arrange testing. Specimen submission instructions and form: https://www.doh.wa.gov/Portals/1/Documents/pubs/301-018-InfluenzaTestingPHL.pdf https://www.medialab.com/dv/dl.aspx?d=1615463&dh=e4b87&u=69790&uh=0e2a1 If there is high suspicion of novel influenza, ensure appropriate infection control practices (including airborne precautions) are implemented while testing is pending. See https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm Consider placing patient on antiviral treatment while awaiting testing results, and consider beginning antiviral prophylaxis for contacts if suspicion of novel influenza is high. For confirmed cases, perform an investigation to assess case's source and transmission from the case.

Influenza - Novel or Unsubtypable Strain

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance

1. To detect emerging threats such as avian and other novel influenza strains.
2. To determine the clinical severity, epidemiology, and communicability of novel influenza viruses.

B. Legal Reporting Requirements

1. Health care providers: **immediately notifiable to local health jurisdiction**
2. Health care facilities: **immediately notifiable to local health jurisdiction**
3. Laboratories: **immediately notifiable to local health jurisdiction**; specimen submission required – isolate or if not available clinical specimen associated with positive result (2 business days)
4. Veterinarians: animal cases notifiable to Washington State Department of Agriculture. https://app.leg.wa.gov/WAC/default.aspx?cite=16-70
5. Local health jurisdictions: **immediately notifiable to Washington State Department of Health (DOH) Office of Communicable Disease Epidemiology (CDE)**

C. Local Health Jurisdiction Investigation Responsibilities

1. Contact CDE **immediately** regarding suspected novel influenza infections. Determine exposures for the case.
2. Facilitate the transport of specimens to the Washington State Public Health Laboratories (PHL) for testing.
3. Ensure appropriate infection control practices are implemented while testing is pending.
4. For confirmed cases, perform an investigation to assess the source for the case and transmission from the case.
5. Complete the Washington Disease Reporting System (WDRS) novel or unsubtypable flu form https://www.doh.wa.gov/Portals/1/Documents/5100/420-018-ReportForm-InfluenzaNovel.pdf and enter the data into WDRS as influenza novel or unsubtypable.

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic Agent

There are two main types of influenza, influenza A and influenza B. Influenza A viruses are divided into subtypes based on the hemagglutinin (H) and neuraminidase (N) proteins on their surfaces. Influenza A viruses infecting humans have been primarily subtypes H1,

H2, and H3 while influenza A subtypes H1 through H17 can infect birds and other animals such as pigs. There are in addition ten different neuraminidase surface proteins.

Seasonal influenza causes annual winter outbreaks affecting 5-20% of the population. The specific strains of influenza change frequently, necessitating parallel changes in the seasonal influenza vaccine. Since 1977, three types of influenza viruses had been in circulation in humans: influenza A(H3N2), influenza A(H1N1), and influenza B.

Novel influenza virus infections are human infections due to an influenza A virus that is different from currently circulating human influenza viruses, such as an avian or swine influenza virus. In April 2009, a novel influenza A(H1N1) virus was identified in several states and Mexico and caused the first influenza pandemic of the 21st century. This virus is no longer considered "novel" and is circulating as a seasonal strain, replacing the previous influenza A(H1N1) virus. If a novel influenza strain begins to infect humans and is easily transmitted person to person, there is potential for an influenza pandemic. Avian influenza viruses are one possible source of novel influenza strains.

While wild waterfowl shedding the virus are often unaffected by influenza A, domestic poultry infected by the wild birds may be severely affected. In birds, influenza infects both the respiratory and gastrointestinal tracts. As a result, both respiratory and fecal secretions of infected birds carry the virus, which can survive in the environment for weeks to months. Human cases of avian influenza infection, called novel influenza infections, have been associated with a variety of avian influenza strains.

Avian influenza A viruses are designated as highly pathogenic avian influenza (HPAI) or low pathogenicity avian influenza (LPAI) based on molecular characteristics of the virus and the ability of the virus to cause disease and mortality in chickens in a laboratory setting. HPAI and LPAI designations do not refer to the severity of illness in cases of human infection with these viruses; both LPAI and HPAI viruses have caused severe illness in humans.

In 1997, human infections due to avian influenza A(H5N1) virus were identified in Asia. Human infection with H5N1 virus infections have been reported, often resulting in severe pneumonia and greater than 50% mortality. In 2013, human illness due to a novel avian influenza A(H7N9) virus was reported in China. Avian influenza A(H5N1) and A(H7N9) virus infections are primarily transmitted from birds to humans although limited person-to-person transmission has also likely occurred. A small number of other human infections have been reported worldwide including A(H7N2), A(H7N3), A(H7N7), and A(H9N2) novel influenza infections. Worldwide surveillance information on avian influenza is available at: http://www.who.int/influenza/human_animal_interface/en/.

Sporadic human infections with influenza viruses that normally circulate in swine have been reported in the United States (called variant viruses and denoted by adding the letter v to the virus subtype designation). See https://www.cdc.gov/flu/swineflu/variant.htm. Most variant virus infections detected have been associated with exposure to swine at agricultural fairs, but limited person-to-person transmission of this virus has been described.

In late 2014 and 2015, influenza A H5 infections were identified in birds in Washington state as well as elsewhere in the nation. Although 48 million birds were depopulated due

to influenza infection and although CDC, USDA and state and local public health collaborated to monitor exposed persons for illness, no human infections with avian influenza were identified. However, CDC still considers it possible that these avian flu viruses may cause human infection resulting in severe disease and recommends that people limit exposure to these viruses, and if exposure must occur, wear personal protective equipment including N-95 respirators, gowns, goggles and gloves and also be monitored for symptoms of illness during exposure and for 10 days after exposure. Animal infections with H7N8 viruses (turkeys) and H7N2 viruses (cats) have also been reported in recent years in the United States. One human infection with cat-associated H7N2 virus has been reported in the United States. See https://www.cdc.gov/flu/avianflu/past-outbreaks.htm

B. Description of Illness

Patients with uncomplicated **seasonal** influenza may have symptoms that include fever, chills, cough, headache, sore throat and other upper respiratory tract symptoms (rhinorrhea), myalgias, arthralgias, fatigue, vomiting, and diarrhea. Symptoms can be minimal.

Persons infected with influenza A(H3N2v) viruses have had symptoms similar to those of seasonal influenza. Compared to seasonal influenza, a high proportion of persons with influenza A(H5N1) and (H7N9) virus infections progress to severe disease including severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure leading to death, though it is possible that milder cases may occur but not come to medical attention. Other cases of novel influenza infection have tended to result in relatively mild illnesses or apparent asymptomatic infection.

C. Reservoirs

Reservoirs for influenza A viruses include humans, swine, poultry, waterfowl, and other birds and mammals. Humans are the primary reservoir for influenza B.

D. Modes of Transmission

Seasonal influenza viruses spread person-to-person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close proximity between source and recipient persons because droplets do not remain suspended in the air and generally travel only a short distance (<6 feet). Other possible routes of influenza transmission are mucosal inoculation from hands touching contaminated surfaces and airborne transmission. The relative contribution of each type of transmission has not been defined but for airborne transmission is thought to be small.

Avian and swine influenza viruses are generally less transmissible from person-to-person than seasonal influenza viruses. These viruses are primarily transmitted from animals to humans directly or through environmental contamination. However, limited person-to-person transmission has been described with these viruses.

E. Incubation Period

The incubation period for **seasonal** influenza is typically 1–4 days, but can range from 1–7 days. The incubation period for novel influenza viruses is estimated as 2-10 days.

F. Period of Communicability

Most healthy adult with **seasonal** influenza are infectious to others beginning from one day before to up to 7 days following illness onset although communicability decreases rapidly 24 hours after fever resolves (without fever reducing medication). Persons who continue to be ill longer than 7 days after illness onset should be considered potentially contagious until symptoms have resolved. Children, especially younger children, can shed virus for 10 or more days. Immunocompromised persons can shed virus for weeks or months. The period of communicability for novel influenza viruses is not well described.

G. Treatment

CDC recommends appropriate antiviral medications for treatment of human infections with avian and swine influenza A viruses based on known or likely resistance patterns. Guidance for specific novel viruses is available at: https://www.cdc.gov/flu/avianflu/novel-av-treatment-guidance.htm

3. CASE DEFINITIONS

A. Case Definition for Novel Influenza Infections (2013)

1. **Clinical Description**: An illness compatible with influenza virus infection (fever >100° F with cough and/or sore throat).
2. **Laboratory criteria for diagnosis:** A human case of infection with an influenza A virus subtype that is different from currently circulating human influenza H1 and H3 viruses. Novel subtypes include, but are not limited to, H2, H5, H7, and H9 subtypes. Influenza A (H1) and (H3) subtypes originating from a non-human species or from genetic reassortment between animal and human viruses are also novel subtypes. Novel subtypes will be detected at state public health laboratories with methods available for detection of currently circulating human influenza viruses (e.g., real-time reverse transcriptase polymerase chain reaction [RT-PCR]). Confirmation that an influenza A virus represents a novel virus will be performed by the influenza laboratory at Centers for Disease Control and Prevention (CDC). Once a novel virus has been identified by CDC, confirmation may be made by public health laboratories following CDC-approved protocols for that specific virus, or by laboratories using an FDA-authorized test specific for detection of that novel influenza virus.
3. **Criteria for epidemiologic linkage:**
    - The patient has had contact with one or more persons who either have or had laboratory-confirmed influenza AND
    - Transmission of the agent by the usual modes of transmission is plausible.

    A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in a chain of transmission is laboratory confirmed. Laboratory testing for the purposes of case classification should use methods mutually agreed upon by CDC and the Council of State and Territorial Epidemiologists (CSTE). Currently, only viral

isolation, RT-PCR, gene sequencing, or a 4-fold rise in strain-specific serum antibody titers are considered confirmatory.

4. Case Classification

Suspected: A case meeting the clinical criteria, pending laboratory confirmation. Any case of human infection with an influenza A virus that is different from currently circulating human influenza H1 and H3 viruses is classified as a suspected case until the confirmation process is complete.

Probable: A case meeting the clinical criteria and epidemiologically linked to a confirmed case, but for which no confirmatory laboratory testing for influenza virus infection has been performed or test results are inconclusive for a novel influenza A virus infection.

Confirmed: A case of human infection with a novel influenza A virus confirmed by CDC's influenza laboratory or using methods agreed upon by CDC and CSTE as noted in Laboratory Criteria, above.

Note: Once a novel virus is identified by CDC, it will be nationally notifiable until CSTE in consultation with CDC determines that it is no longer necessary to report each case.

4. DIAGNOSIS AND LABORATORY SERVICES

A. Diagnosis

Healthcare providers who clinically suspect a novel influenza virus infection and laboratories that identify an unsubtypable influenza virus specimen using a PCR assay should immediately contact their local health jurisdiction and submit a specimen to the Washington State Public Health Laboratories. Rapid influenza tests should not be used to rule in or rule out avian flu.

B. Tests Available at Washington State Public Health Laboratories (PHL)

PHL uses the RT-PCR assays developed by Centers for Disease Control and Prevention (CDC) to distinguish seasonal influenza viruses from novel influenza viruses. Confirmatory testing for novel influenza viruses and serologic testing for both symptomatic and asymptomatic infections are performed at CDC.

C. Specimen Collection

Airborne precautions are preferred and include placement of patient in a negative air pressure room and appropriate PPE with a respirator (fitted N-95 or Powered Air Purifying Respirator), eye protection, gown, and gloves. If airborne precautions are not possible, institute droplet precautions by placing patient in a private room and instructing staff to wear a surgical mask, eye protection, gown, and gloves. For more information on infection control: https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm

Information regarding testing is available from Centers for Disease Control and Prevention: https://www.cdc.gov/flu/avianflu/severe-potential.htm

Obtain specimens as soon as possible, ideally within 7 days of illness onset. Preferred specimen is nasopharyngeal swab. See: https://www.doh.wa.gov/Portals/1/Documents/pubs/301-018-InfluenzaTestingPHL.pdf

Using appropriate personal protective equipment, collect nasopharyngeal, nasal, and throat swabs using swabs with a synthetic tip, such as Dacron or nylon, and a plastic or wire shaft. Specimens collected with cotton or calcium alginate swabs with wooden shafts will not be tested. Immediately after collection, place the swab or aspirate material into a sterile vial with 2–3 ml of viral transport media; for swab specimens, aseptically break or cut off the end of the swab shaft. The shaft is most easily broken where it is scored. **Close vial tightly** to avoid leakage during transport. Do not let a swab come into contact with reagents used for other tests. If a swab contacts reagents for other tests, a new swab must be submitted. Label vial with patient's name AND a second identifier, specimen source, and date obtained.

Specimen Storage: Optimal testing performance is obtained with freshly-collected specimens stored and shipped refrigerated (2–8°C) that arrive to the WAPHL for processing within 72 hours of collection. If you are unable to ship the specimen for testing within 72 hours of collection, any specimen except serum should be frozen at ≤ -70°C and shipped on dry ice. Serum should be refrigerated. All viral isolates should be frozen at ≤ -70°C prior to shipment.

Note that PHL require all clinical specimens have two patient identifiers, a name and a second identifier (e.g., date of birth) on both the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

Specimens need to be shipped with a completed PHL Virology Submission form which is available at:
https://www.medialab.com/dv/dl.aspx?d=1615463&dh=e4b87&u=69790&uh=0e2a1.

5. ROUTINE CASE INVESTIGATION

A. Evaluate the Diagnosis

1. Use the full case report form to itemize clinical symptoms, illness severity, and potential exposures to novel viruses, such as travel or animal contact.
2. Facilitate the transport of specimens to PHL for novel influenza testing and for testing of specimens that are unsubtypable commercially.

B. Manage the Case

1. Hospitalized persons with confirmed or suspected seasonal influenza should be placed on droplet precautions for 7 days after illness onset or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer. In some cases, facilities may choose to apply droplet precautions for longer periods based on clinical judgment, such as in the case of young children or severely immunocompromised patients who may shed influenza virus for longer periods of time. Complete infection control recommendations for seasonal influenza are available at:
https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm

   CDC advises that the infections control principles and actions relevant for seasonal influenza are appropriate for the control of influenza A (H3N2v) as well.
https://www.cdc.gov/flu/swineflu/prevention-strategies.htm

More stringent infection control practices are recommended for patients suspected of having other novel influenza viruses such as influenza A(H5N1) or A(H7N9). When these infections are suspected, healthcare facilities should immediately implement airborne, contact and standard precautions. Patients should be placed in an airborne isolation room and healthcare personnel caring for these patients should wear gloves, gowns, eye protection and an N95 or higher respirator for all patient care activities. Prolonged influenza viral shedding in the lower respiratory tract has been documented for critically ill patients with A(H5N1) and A(H7N9) infections.

For infection control guidance novel influenza virus infection see:
https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm

2. Antiviral treatment should be administered according to current CDC guidance.
https://www.cdc.gov/flu/avianflu/novel-av-treatment-guidance.htm
3. Persons with suspected or confirmed novel influenza virus infections who do not require hospitalization should be counseled to stay home and away from other persons in the household and follow respiratory hygiene recommendations (Section 6).

C. Identify Potential Sources of Infection

Inquire about recent travel or exposure to ill persons who have recently traveled, and about exposure to animals such as wild birds, poultry and swine.

D. Identify and Manage Contacts

Contact investigations should be performed for all confirmed cases of novel influenza. Consult with CDE for managing contacts of known or suspect novel influenza cases.

Interim guidance for novel influenza A viruses with the potential to cause severe disease in humans (examples include H5N2, H5N8, and North American H5N1) is available at:
https://www.cdc.gov/flu/avianflu/severe-potential.htm

For exposure to H5N2, H5N8, H5N1 and other novel influenza A viruses identified in North America, interview all persons with potential exposure to avian influenza **during the past 10 days**.

Exposure to avian influenza is defined as:

- Persons having direct contact with infected birds, contact with surfaces contaminated with the body fluids of infected birds (including fecally contaminated surfaces) or being in an enclosed location (for example, hen house) with infected birds.

OR

- Persons who have had contact with a suspect or confirmed human case of novel influenza.

As the incubation of avian influenza is estimated to be 2-10 days, contact with avian influenza infected birds or their environment within the previous 10 days warrants recommendations for symptom monitoring, as below, as well as consideration of antiviral prophylaxis. If the contact with avian-influenza infected birds or swine occurred in Washington, coordination with the Washington State Department of Agriculture is

essential; contact CDE for consultation. CDE can provide form letters and other supportive materials for contacting potentially avian-flu exposed persons and their healthcare providers.

1. If any avian-flu exposed persons are identified in the initial interview as symptomatic with influenza-like illness (check with CDE for CDC guidance on symptoms of concern), arrange for collection of a specimen for testing at PHL (see Section 4 for precautions and specimens). Do not send specimens commercially or rely on rapid influenza tests.
2. If the last exposure to avian influenza (contact with infected birds or surfaces contaminated by infected birds, being in an enclosed environment with infected birds, or contact with a human case) occurred within the previous 10 days, consider prophylaxis (treatment dose). See https://www.cdc.gov/flu/avianflu/guidance-exposed-persons.htm
    a. Adults: Oseltamivir 75mg twice daily for 5 days
    b. Pediatric dosing (use treatment dose): https://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-dosage-duration.pdf
3. Persons who have had contact with influenza-infected birds or other animals in the context of a zoonotic influenza event should be monitored for illness during exposure and for 10 days after exposure in accordance with CDC and USDA procedures. Contact CDE for latest CDC/USDA protocols and for form letters and materials that can be used in communication with the exposed person and healthcare providers. Coordination with Washington State Department of Agriculture is essential and will be arranged through CDE. In general:
    a. Active surveillance is strongly advised, such that the LHJ makes contact with the exposed person daily to confirm illness status. Final contact should be made at day 10 to confirm illness status. In the event of elevated temperature or other symptoms of concern, exposed person should immediately contact LHJ via phone or, if LHJ is unavailable after hours, exposed person should immediately call CDE 24/7 on-call number 206-418-5500. In the event of development of influenza-like illness in an exposed person under monitoring, LHJ should immediately contact CDE.
    b. LHJ should develop a plan for where the patient should go for testing/evaluation in the event of symptoms, and how the patient should be transported to the facility (do not use public or commercial transport such as buses or taxis).
4. Provide instructions for the contact if fever or other symptoms develop:
    a. Call the local health jurisdiction to report the symptoms, or CDE on-call if LHJ is unavailable. (LHJ should immediately notify CDE so that testing at PHL can be arranged.)

b. Call the healthcare facility identified by the local health jurisdiction and ask to be evaluated for possible avian (bird) influenza. Provide the facility with the HCP letter.

c. Travel to the healthcare facility without using public (e.g., bus) or commercial (e.g., taxi) vehicles.

d. Besides travel to the healthcare facility, stay home.

5. Without giving names or identifiers, notify the receiving facility that persons being monitored for avian influenza exposure may seek care at that facility.

a. Confirm that the facility has private room (closed door, private bathroom) where a person could be evaluated, like is done for measles.

b. Confirm that the facility has personnel trained in use of standard, contact, and airborne precautions who could evaluate a patient.

c. Provide hospital with the infection control guidelines: https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm

E. Evaluate the Environment

Environmental investigations may be necessary for the exposure source of persons with novel influenza virus infection. An affected area may need to be disinfected and left without flocks for months. Consult with CDE and the Zoonotic Disease Program regarding the need for an environmental evaluation. Consultation with Washington State Department of Agriculture may occur. Personal protective equipment is necessary for removing birds and cleaning a farm.

6. ROUTINE PREVENTION

A. Vaccine Recommendations:

Routine annual vaccination is recommended for all persons 6 months and older. Annual vaccination is particularly important for persons at increased risk of complications and for persons in contact with those at high risk for complications. https://www.cdc.gov/flu/consumer/vaccinations.htm Seasonal influenza vaccines are not likely to provide significant protection against novel influenza viruses, but will prevent dual infection with the risk of viral reassortment.

B. Routine Prevention Recommendations

General respiratory hygiene measures are recommended at all times, and particularly during periods when respiratory viruses are circulating:

- Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it and then clean your hands;
- Wash your hands with soap and water frequently, especially after you cough or sneeze. Alcohol-based hand cleaners are also effective;
- Try to avoid close contact with people ill with respiratory symptoms;
- If you get sick with respiratory symptoms, stay home the recommended period and limit contact with others to keep from infecting them;

- Avoid touching your eyes, nose or mouth;
- Don a mask when entering a healthcare facility if you are coughing or sneezing.

ACKNOWLEDGEMENTS

We would like to acknowledge the Oregon Department of Human Services for developing the format of this document.

UPDATES

June 2012: The document was reviewed for accuracy. No significant changes were made.

December 2013: The existing guideline for influenza was divided into a guideline for novel influenza and a guideline for influenza-associated death.

June 2015: Updated to include recommendations for evaluating and monitoring human contacts of avian influenza infected birds.

April 2018: Added a cover page, updated to reflect use of Washington Disease Reporting System (WDRS) instead of the Public Health Issues Management System (PHIMS) and web links for management of novel influenza updated given changes to locations of CDC materials.

December 2022: Updated to clarify laboratory reporting requirements given 2023 changes to WAC 246-101-201