How to prevent, recognize and diagnose infection with the swine-origin Influenza A (H1N1) virus in humans*

Infecção pelo vírus Influenza A (H1N1) de origem suína: como reconhecer, diagnosticar e prevenir

Alcyone Artioli Machado

Abstract

In March of 2009, a flu epidemic began in Mexico. Shortly thereafter, similar cases appeared in other countries, alerting authorities to the risk of a pandemic. This article details the principal signs and symptoms of infection with the swine-origin Influenza A (H1N1) virus. In addition, the measures to be taken in suspected or confirmed cases are addressed, as are the procedures to follow in relation to contacts. Furthermore, the drugs used in the prophylaxis against and the treatment of infection with the H1N1 virus are described.

Keywords: Influenza A virus, H1N1 subtype; Influenza A virus; Disease outbreaks.

Resumo

Em março de 2009, houve o início de uma epidemia de gripe no México que, em pouco tempo, levou ao surgimento de casos semelhantes em outros países, alertando as autoridades sanitárias para o risco de uma pandemia. Neste artigo, descrevemos os principais sinais e sintomas da infecção pelo vírus Influenza A (H1N1) de origem suína, as medidas a serem tomadas para os casos suspeitos ou confirmados e como proceder em relação aos contactantes. Comentamos também quais drogas são utilizadas para o tratamento e profilaxia.

Descritores: Vírus da Influenza A subtipo H1N1; Vírus da Influenza A; Surtos de doenças.

In early April of 2009, the global media announced the occurrence of cases of flu caused by a new variant of the Influenza A virus. Within one month after the report of the first case, the scientific literature had provided information on the new virus, as well as the description of 642 cases of infection with the new variant (Influenza A H1N1 virus, initially designated swine-origin Influenza A) identified in the United States.[1] According to the World Health Organization (WHO), 4,379 cases of infection with the aforementioned virus had been reported, in 29 countries, by 7:30 AM (4:30 AM Brasília time) on 10 May 2009.[2]

In Mexico, where the epidemic reputedly started, 1,626 cases were reported and there were 45 deaths. In the United States, there were 2,254 cases confirmed in laboratory and 2 deaths in the state of Texas. In Canada, 280 cases were confirmed through laboratory testing and there was 1 death. In Costa Rica, 8 cases were confirmed through laboratory testing and there was 1 death. In addition, cases were confirmed through laboratory testing (n), although there were no deaths, in the following countries (n of cases): Germany (11); Argentina (1); Australia (1); Austria (1); Colombia (1); South Korea (3); Denmark (1); El Salvador (2); Spain (93); France (12); Guatemala (1); the Netherlands (3); Hong Kong (1); Ireland (1); Israel (7); Italy (9); Japan (4); New Zealand (7); Panama (3); Poland (1); Portugal (1); Sweden (1); Switzerland (1); and the United Kingdom (39).[2]

* Study carried out in the Infectious Diseases Division of the Department of Clinical Medicine, University of São Paulo at Ribeirão Preto School of Medicine, Ribeirão Preto, Brazil.
Correspondence to: Alcyone Artioli Machado. Divisão de Moléstias Infecciosas, Departamento de Clínica Médica, Faculdade de Medicina de Ribeirão Preto-USP, Av. Bandeirantes, 3900, Campus Universitário USP, CEP 14049-900, Ribeirão Preto, SP, Brasil.
Tel 55 16 3633-0436. E-mail: aamachad@fmrp.usp.br
Financial support: None.
Submitted: 11 May 2009. Accepted, after review: 12 May 2009.

infecção pelo Influenza A On 6 May 2009, the Brazilian National Ministry of Health (NMH) received tests to confirm the diagnosis of infection with H1N1, allowing 6 of the suspected cases to be confirmed on 7 May. Three days later, another 20 suspected cases of infection with Influenza A H1N1 were analyzed in Brazil; 18 of those were ruled out and 2 cases were confirmed, totaling 8 cases of Influenza A H1N1 infection in Brazil; 6 were related to international trips and 2 were autochthonous (inside Brazilian territory).[3] The cases were in young Brazilian adults. Two suspected cases were reported in the state of São Paulo, 3 in the state of Rio de Janeiro (2 autochthonous), 1 in the state of Minas Gerais, 1 in the state of Santa Catarina and another in the state of Rio Grande do Sul. Of the confirmed cases, 3 were in individuals who had recently been to Mexico, 1 was in an individual who had recently been to United States and another was in an individual who had recently traveled through various countries in Europe. Seventy individuals who had been in contact with the 3 cases in Rio de Janeiro were, at this writing, under monitoring and asymptomatic.[3] The suspected cases were in the following states (n of cases): São Paulo (6); Rio de Janeiro (2); Minas Gerais (1); Paraná (1); Distrito Federal (3); Santa Catarina (1); Pernambuco (2); Ceará (1); and Rondônia (1). In addition, 25 cases were being monitored in ten states, although 156 cases had been ruled out.[3]

The flu-causing virus described here contains genes from the human, swine and avian influenza A genes and is characterized by a combination of genes which had never before been identified among the human or swine viruses. There are 16 known subtypes of viral hemagglutinin (HA) and 9 known subtypes of neuraminidase (NA) proteins found on the surface of the influenza A virus, which can recombine in order to create new variations of the flu virus.[4]

Over the last 35 years, more than 50 cases of infection with swine influenza viruses have been documented.[5-9] The identification of the first human infection with the swine influenza A triple reassortant virus (H1) was carried out at the Centers for Disease Control and Prevention (CDC), in December of 2005.[6] However, this seems to be the first flu epidemic related to a virus of such nature.

The mode of human-to-human transmission of the Influenza A virus, including H1N1, is not well known. It seems to occur principally through the dissemination of droplets, and possibly of small-particle droplets, expelled during coughing or sneezing. There is also the potential for transmission through contact with fomites contaminated with respiratory or gastrointestinal material.[10,11] Since cases of diarrhea and vomiting have been described, the potential viral transmission through stool, and subsequent oral-fecal transmission, should be considered and investigated.[1] The virus is not transmitted through the ingestion of pork.[4]

The incubation period of the swine Influenza A H1N1 triple reassortant virus seems to be 2 to 7 days, although further information is still needed. Based on the cases currently described, patients seem to excrete the virus from 24 h before symptom onset up to 5-7 days thereafter or until complete resolution of the symptoms.[1] The period of transmissibility can be longer in children, immunocompromised individuals or individuals with severe diseases.[4,12] The potential of individuals with asymptomatic infection to serve as sources of infection to others remains unknown but merits investigation.

The clinical spectrum of infection with the Influenza A H1N1 virus has yet to be defined. However, among the identified patients, the infection has been found to range from self-limiting disease to more severe manifestations, including respiratory failure and death.[1] The signs and symptoms of infection with the classical swine influenza virus in humans are frequently indistinguishable from those of infection with the human influenza virus.[8]

In the recent report of the 642 cases confirmed in the United States, ages were reported to range from 3 months to 81 years: 40% were between 10 and 18 years of age and only 5% were 51 years of age or older.[1] The most commonly found symptoms were fever (94%), cough (92%) and sore throat (66%). Gastrointestinal symptoms were reported: 25% of the patients presented diarrhea and 25% presented vomiting. Hospitalization was necessary in 36 (9%) of the 399 cases for which hospitalization data were available. In 22 hospitalized patients for whom the relevant data were available, 7 reported having been to Mexico one week before symptom onset, 11 were diagnosed

with pneumonia confirmed through radiology, 8 (36%) required admission to the intensive care unit, and 4 (18%) had respiratory failure and needed mechanical ventilation. There were 2 deaths: one 22 month-old child with neonatal myasthenia gravis and a 33 year-old pregnant woman.

According the NMH, cases are defined as follows[13]:

1) Case under monitoring –
   a) Arriving from affected countries, with unmeasured fever and cough, with or without the other symptoms referred to in the definition of a suspected case, or
   b) Having arrived, in the preceding 10 days, from an unaffected country and presenting the symptoms referred to in the definition of a suspected case
2) Suspected case –
   a) Individual presenting sudden high fever (> 38°C) and cough, with or without one or more of the following symptoms: headache, muscle pain, joint pain and breathlessness, and
   b) Presenting symptoms within 10 days after leaving countries in which there were reported cases of Influenza A H1N1 infection, or
   c) Having had, in the last 10 days, close contact with (caring for, living with or having direct contact with respiratory secretions or body fluids of) an individual classified as a suspected case of human infection with the new subtype of Influenza A (H1N1)
3) Probable case –
   Suspected case which presents one of the following additional criteria:
   a) Confirmation, through laboratory testing, of infection with the Influenza A virus, without conclusive laboratory results for infection with a seasonal influenza virus, or
   b) Symptomatic individual presenting a clinical profile consistent with Influenza A H1N1 infection or who died as a result of undetermined acute respiratory infection and who had an epidemiological link (of time, place or exposure) with another probable or confirmed (suspected, according to the WHO) case of infection with Influenza A H1N1
4) Confirmed case –
   Individual with Influenza A H1N1 infection confirmed by a referral laboratory, through real-time reverse transcription-polymerase chain reaction (real-time RT-PCR)
5) Ruled-out case –
   a) Case under monitoring, arriving from an unaffected country and recovering by day 10 after symptom onset, or
   b) Any case under monitoring or suspected case in which another disease has been diagnosed

In order to confirm the diagnosis, collection of clinical samples must be carried out in accordance with the guidelines provided by the NMH.[13] Respiratory secretions must be collected preferably through nasopharyngeal aspirate using a collection flask, since the sample obtained with this technique can concentrate a greater number of cells. If the nasopharynx aspiration technique cannot be used, the nasopharyngeal and oropharyngeal swab is an alternative; only rayon swabs should be used. A cotton swab should not be used, since it interferes with the molecular methods used. Blood and other clinical samples will be used only for monitoring the clinical evolution of the patient or for making the differential diagnosis. The respiratory secretion samples collected must be stored at 4-8°C and sent to one of the *Laboratórios Centrais de Saúde Pública* (LACENs, Central Public Health Laboratories) on the day of collection.

Processing of the respiratory secretion samples collected from suspected cases will be carried out only at referral laboratories, such as the *Instituto Adolfo Lutz* (IAL - Adolfo Lutz Institute), the *Instituto Evandro Chagas* (IEC - Evandro Chagas Institute) and the *Fundação Oswaldo Cruz* (FIOCRUZ, Oswaldo Cruz Foundation), all of which belong to the network of laboratories accredited by the WHO. The respiratory secretion samples should be collected by the third day after symptom onset. If necessary, this period can be extended to a maximum of 7 days after symptom onset. The diagnostic technique recommended by the WHO is RT-PCR. Indirect immunofluorescence is not recommended for the detection of this new subtype of Influenza A. The respiratory secretion samples collected from monitored patients should be stored at the referral laboratories and should be processed only after the case is classified as suspected of

after a new orientation from the epidemiological surveillance. All collecting facilities should send the samples to the LACEN of their state or of the Federal District of Brasília, together with the epidemiological chart properly filled out.[14] The samples should be transported in thermal containers with rigid sides, which maintain the temperature at 4-8°C until arrival at the LACEN. The LACEN must store the samples in boxes specifically designed for the transportation of infectious substances, preferably on dry ice. If dry ice is not available, the sample can be frozen to –70°C and ice packs can be used.

Individuals who experience any of the symptoms and who have been to countries affected by the Influenza A H1N1 virus should immediately seek a public health care facility. There are 52 referral hospitals in Brazil (at least one per state) for the treatment of cases requiring monitoring. In the hospital environment, such cases should be isolated in a private room, with sealed doors and good ventilation. If available in the hospital, isolation should be carried out in a respiratory isolation room with negative pressure and a high-efficiency particulate air filter.[4,13,14] Isolation should be maintained until Influenza A H1N1 infection has been ruled out, or until day 10 after the onset of the symptoms, characterizing the end of the period of transmissibility.[4,13,14] The isolation room entrance should bear an alert sign referring to the Influenza A H1N1 isolation, and access should be restricted to the professionals involved in the treatment, duly trained in the precautionary measures and isolation (respiratory isolation and isolation from contact).[4,13,14] Professionals should wear N95 masks, gloves, goggles, aprons and caps, according to the degree of contact with the patient. Patients suspected of being infected with Influenza A H1N1 must wear surgical masks from the time at which the infection is the first suspected until arrival at the place of isolation.[4,13,14]

Hand hygiene can be carried with an alcohol preparation (in the form of gel or solution), when those are not visibly soiled. Proper hand hygiene is important due to the following factors:

1) The seasonal influenza virus becomes nonviable 30 s after antisepsis of the hands with 70% alcohol.
2) Certain enveloped viruses (e.g., herpes simplex virus, HIV, influenza and respiratory syncytial virus) have been shown to be susceptible to alcohol in vitro.

In home isolation, social contact should be avoided until recovery, or until it is clarified whether the case is indeed one of Influenza A H1N1 infection.[4,13,14] Disposable surgical masks should be used; foods, glasses, towels and personal objects are not to be shared; touching eyes, nose or mouth should be avoided; and hands should be washed frequently with soap and water, especially after coughing or sneezing. The environment should be kept ventilated, and, if possible, the patient should use a separate bathroom, which should be cleaned daily with disinfectants. Furniture must be cleaned with disinfectants, and utensils used by the patient are to be washed with soap and warm water, due to the risk of transmission through contact.

Data on genetic sequencing and functional tests of inhibition of neuraminidase show that the swine-origin Influenza A H1N1 virus is susceptible to both oseltamivir and zanamivir, and is resistant to adamantanes, including amantadine and rimantadine.[1,4,15,16] Therefore, cases that fit the description of suspected, probable or confirmed cases, in individuals ≥ 1 year of age, should be treated with oseltamivir. The treatment with oseltamivir should be initiated within 48 h after symptom onset.[13-15] A dose of 75 mg twice a day for 5 days is recommended for adults. For children weighing less than 40 kg, the total recommended daily doses vary according to weight as follows: < 15 kg , 60 mg; 15-23 kg, 90 mg; and 24-40 kg, 120 mg. For children weighing more than 40 kg, the total recommended daily dose is the same as that recommended for adults (150 mg). In all cases, the oseltamivir should be given twice a day for 5 days.[13,15,16]

In patients with severe gastrointestinal symptoms, oral absorption of oseltamivir can be impaired, although there is no current evidence to suggest the need to increase the dose or the period of use of the antiviral. Patients who vomit within 1 h after medication intake can be given an additional dose of 75 mg.[13]

The use of oseltamivir in children under 1 year of age should be thoroughly evaluated: 12 mg can be used in children under 3 months of age; 20 mg in children from 3 to 5 months of age; and 25 mg in children from 6 and 11 months of

age. In all cases, doses should be administered twice a day, for 5 days.

Clinical support measures should be instituted in parallel with pharmacological treatment, according to medical evaluation of each case.

Additional information on treatment can be obtained on the CDC website.[15,16] The NMH does not currently recommend the prophylactic use of oseltamivir.[13]

Individuals under 18 years of age who are infected or suspected of being infected with the Influenza A (H1N1) virus should not be given aspirin or products which contain aspirin, due to the risk of developing Reye's syndrome. Other antipyretics such as acetaminophen or anti-inflammatory non-steroid drugs can be given in order to control fever.[4,16]

In pregnant women, infection with the Influenza A H1N1 virus results in severe disease. Oseltamivir and zanamivir are category C medications for pregnant women, which indicates that no clinical study has been conducted to evaluate the safety of these drugs in pregnant women. Although some side effects have been reported in pregnant women who used those drugs, the true relationship between the side effects presented and the medications has yet to be established. Pregnancy should not be considered a contraindication to the use of oseltamivir or zanamivir. Due to the systemic activity of oseltamivir, it should be the drug of choice for the treatment of pregnant women. The choice of prophylactic medication is even less clear. Zanamivir can be preferable due to the fact that its systemic absorption is limited, although possible respiratory complications should be considered due to the inhaled administration of the product, especially in women at risk for respiratory problems.[15,16]

The inappropriate and indiscriminate use of those antiviral drugs can mask or attenuate symptoms of other conditions, as well as causing viral resistance to the specific medication used in the treatment of the flu virus.[13]

At this writing, there is no vaccine against this new variant of the influenza A virus, although the development of such a vaccine is projected for the next months.

For questions and further information, one of many options is to consult the United States Department of Agriculture website.[17]

References

1. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans. N Engl J Med. 2009 May 7 [Epub ahead of print].
2. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [updated 2009 May 10; cited 2009 May 12]. Influenza A. (H1N1) – update 24. Available from: http://www.who.int/csr/don/2009_05_10/en/index.html.
3. Gabinete Permanente de Emergências [homepage on the Internet]. Brasília: Ministério da Saúde [updated 2009 May 10; cited 2009 May 12]. Nota à imprensa: Ocorrências de casos humanos de influenza A (H1N1). Available from: http://portal.saude.gov.br/portal/aplicacoes/noticias/default.cfm?pg=dspDetalheNoticia&id_area=124&CO_NOTICIA=10180.
4. Galwankar S, Clem A. Swine influenza A (H1N1) strikes a potential for global disaster. J Emerg Trauma Shock [serial on the Internet] 2009 [cited 2009 May 12];2:99-105. Available from: http://www.onlinejets.org/text.asp?2009/2/2/99/50744.
5. Centers for Disease Control and Prevention (CDC). Swine influenza A (H1N1) infection in two children--Southern California, March-April 2009. MMWR Morb Mortal Wkly Rep. 2009;58(15):400-2.
6. Newman AP, Reisdorf E, Beinemann J, Uyeki TM, Balish A, Shu B, et al. Human case of swine influenza A (H1N1) triple reassortant virus infection, Wisconsin. Emerg Infect Dis. 2008;14(9):1470-2.
7. Olsen CW, Karasin AI, Carman S, Li Y, Bastien N, Ojkic D, et al. Triple reassortant H3N2 influenza A viruses, Canada, 2005. Emerg Infect Dis. 2006;12(7):1132-5.
8. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. Clin Infect Dis. 2007;44(8):1084-8.
9. Adiego Sancho B, Omenaca Teres M, Martinez Cuenca S, Rodrigo Val P, Sanchez Villanueva P, Casas I, et al. Human case of swine influenza A (H1N1), Aragon, Spain, November 2008. Euro Surveill [serial on the Internet] 2009 [cited 2009 May 12];2009;14(7):pii=19120. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19120.
10. Bean B, Moore BM, Sterner B, Peterson LR, Gerding DN, Balfour HH Jr. Survival of influenza viruses on environmental surfaces. J Infect Dis. 1982;146(1):47-51.
11. Boone SA, Gerba CP. The occurrence of influenza A virus on household and day care center fomites. J Infect. 2005;51(2):103-9.
12. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol. 2008;167(7):775-85.
13. Secretaria de Vigilância em Saúde. Gabinete Permanente de Emergências de Saúde Pública [homepage on the Internet]. Brasília: Ministério da Saúde [updated 2009 May 10; cited 2009 May 12]. Emergência de Saúde Pública de Importância Internacional – ESPII. Protocolo de procedimentos para manejo de casos e contatos de Influenza A (H1N1). Versão II. Available from: http://portal.saude.gov.br/portal/arquivos/pdf/influenza_a_h1n1_protocolo_tratamento.pdf.

14. Ministério da Saúde [homepage on the Internet]. Brasília: Ministério da Saúde [updated 2009 May 10; cited 2009 May 12]. Infuenza A (H1N1). Available from: http://portal.saude.gov.br/portal/saude/profissional/area.cfm?id_area=1534.
15. Centers for Disease Control and Prevention. [homepage on the Internet]. Atlanta: U.S. Department of Health and Human Services [updated 2009 May 06; cited 2009 May 12]. Interim Guidance on Antiviral Recommendations for Patients with Novel Influenza A (H1N1) Virus Infection and Their Close Contacts. Available from: http://www.cdc.gov/h1n1flu/recommendations.htm.
16. Centers for Disease Control and Prevention. [homepage on the Internet]. Atlanta: U.S. Department of Health and Human Services [updated 2009 May 10; cited 2009 May 12]. H1N1 Flu Clinical and Public Health Guidance. Epidemiology and Surveillance. Available from: http://www.cdc.gov/h1n1flu/guidance.
17. Newsroom: Questions and Answers [homepage on the Internet]. Washington: U.S. Department of Agriculture [updated 2009 May 07; cited 2009 May 12]. Release No. 0131.09 - Frequently asked questions about H1N1. Available from: http://www.usda.gov/wps/portal/!ut/p/_s.7_0_A/7_0_1OB?contentidonly=true&contentid=2009/04/0131.xml.

About the authors

Alcyone Artioli Machado
Associate Professor. Department of Clinical Medicine, University of São Paulo at Ribeirão Preto School of Medicine, Ribeirão Preto, Brazil.